# The Obstetric Hematology Manual

Edited by Sue Pavord and Beverley Hunt

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Edited by

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Beverley Hunt Guy's and St. Thomas' NHS Foundation Trust and King's College, London



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### Preface

This book aims to appeal to both those who have already submersed themselves in the field of obstetric haematology and new-comers to the area. Many have already discovered the numerous challenges and dilemmas involved but also have found this area of medicine to be both stimulating and rewarding. Others may be new to the field or have unwittingly found themselves regularly involved in the care of these women. We hope that all will benefit from this manual, which reflects up-to-date clinical management of this complex group of patients as they present in clinical practice.

The impact of haematological disease on fertility, pregnancy and the puerperium can be considerable. Thrombosis and haemorrhage are the leading causes of maternal mortality and a large number of haematological conditions are associated with fetal loss. Advances in fetal maternal medicine and obstetric care has enabled high expectations of fetal survival and maternal wellbeing. However the stakes are high, management can be complex and good outcomes require excellent multidisciplinary team work.

New challenges arise in the light of changing cosmopolitan populations, including rising birth rates and improved survival and fertility from chronic illnesses and life-threatening conditions. Thus in-depth understanding is required to deal with this broad range of disease. We are fortunate to have such a distinguished group of contributors, whose knowledge, experience and opinions are invaluable, particularly in an area where randomised clinical trials are scant and good quality evidence hard to find.

This branch of medicine is gaining increasing recognition as a subspecialist area, with the growth of national and international specialist groups and development of educational courses in the area. Clinical problems have become an important feature in postgraduate examinations, both in hematology and obstetrics. This book is therefore not only an important guide for practitioners in haematology, obstetrics, midwifery, and obstetric anaesthesia but is invaluable for those studying for postgraduate examinations.

Obstetric haematology is immensely rewarding, and we hope this book provides encouragement, particularly for those who are new to the speciality, to view it as both thought-provoking and enjoyable.

Sue Pavord Beverley Hunt

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**Cellular changes** 

# Normal hematological changes during pregnancy and the puerperium

Margaret Ramsay

#### Introduction

There are both subtle and substantial changes in hematological parameters during pregnancy and the puerperium, orchestrated by changes in the hormonal milieu. A thorough understanding of these is important to avoid both over and under-diagnosing abnormalities. Appreciation of the time frame for some of the changes allows sensible planning; this is particularly true when considering thromboprophylaxis.

Some of the quoted reference ranges may differ between centers, depending on laboratory techniques. However, the principles of recognizing physiological changes can still be applied.

#### **Red cells**

During pregnancy, the total blood volume increases by about 1.5 l, mainly to supply the needs of the new vascular bed. Almost 1 liter of blood is contained within the uterus and maternal blood spaces of the placenta. Expansion of plasma volume by 25%–80% is one of the most marked changes, reaching its maximum by mid pregnancy. Red cell mass also increases by 10%– 20% but the net result is that hemoglobin (Hb) concentration falls.<sup>1</sup> Typically, this is by 1–2 g/dL by the late second trimester and stabilizes thereafter. Women who take iron supplements have less pronounced Hb changes, as they increase their red cell mass proportionately more than those without dietary supplements (the increase is approximately 30% over pre-pregnancy values).<sup>1</sup>

It is hard to define a normal reference range for Hb during pregnancy and the limit for diagnosing anemia. The World Health Organization has suggested that anemia is present in pregnancy when Hb concentration is < 11 g/dL. However, large studies in healthy Caucasian women taking iron supplements from mid pregnancy found Hb values in the early third trimester to be 10.4–13.5 g/dL (2.5th–97.5th centiles)<sup>2</sup>. Studies from other ethnic populations have documented lower third trimester Hb concentrations, which may be attributable to the women entering pregnancy with poor iron stores or with dietary deficiencies of iron and folic acid.

Red cell count and hematocrit (Hct) values are likewise lower in pregnancy, but the other red cell indices change little (Table 1.1), although red cells show more variation in size and shape than in the non-pregnant state. There is a small increase in mean cell volume (MCV), of on average 4 fL for iron-replete women, which reaches a maximum at 30–35 weeks gestation and occurs independently of any deficiency of B12 and folate.<sup>2</sup>

Hemoglobin and hematocrit increase after delivery. Significant increases have been documented between measurements taken at 6–8 weeks postpartum and those at 4–6 months postpartum, demonstrating that this length of time is needed to restore them to non-pregnant values.<sup>1</sup>

- Hb concentrations decrease in pregnancy.
- Hb < 10.4 g/dL suggests anemia.
- Hb > 13.5 g/dL is unusual and suggests inadequate plasma volume expansion (which can be associated with pregnancy problems including pre-eclampsia and poor fetal growth).
- MCV is normally slightly increased.
- MCH and MCHC are normally unchanged in pregnancy and do not change with gestation.

Table 1.1 Red cell indices during pregnancy and the puerperium

	Gestation					
Red cell indices	18 weeks	32 weeks	39 weeks	8 weeks postpartum		
Hemoglobin (Hb) g/dL	11.9 (10.6–13.3)	11.9 (10.4–13.5)	12.5 (10.9–14.2)	13.3 (11.9–14.8)		
Red cell count $ imes$ 10 <sup>12</sup> /L	3.93 (3.43–4.49)	3.86 (3.38–4.43)	4.05 (3.54–4.64)	4.44 (3.93–5.00)		
Mean cell volume (MCV) fL	89 (83–96)	91 (85–97)	91 (84–98)	88 (82–94)		
Mean cell hemoglobin (MCH) pg	30 (27–33)	30 (28–33)	30 (28–33)	30 (27–32)		
Mean cell hemoglobin concentration (MCHC) g/dL	34 (33–36)	34 (33–36)	34 (33–36)	34 (33–36)		
Hematocrit	0.35 (0.31–0.39)	0.35 (0.31–0.40)	0.37 (0.32–0.42)	0.39 (0.35–0.44)		
Mann and reference renease (2 Eth. 07 Eth. cont	ilaa) Camanalaaaa	بالمعقم والمتعمنة ببروالمعقم	frame 121			

Mean and reference ranges (2.5th–97.5th centiles). Samples were collected longitudinally from 434 women. Adapted from Ref 2.

#### White cells

White cell count (WBC) is increased in pregnancy<sup>2</sup> with a typical reference range of  $6 \times 10^9-16 \times 10^9/L$ . In the hours after delivery<sup>3</sup>, healthy women have been documented as having WBC  $9 \times 10^9-25 \times 10^9/L$ . By 4 weeks post-delivery, typical WBC ranges are similar to those in healthy non-pregnant women ( $4 \times 10^9-10 \times 10^9/L$ ).

There has been much discussion about the normal ranges for the different types of white cells.<sup>4</sup> Neutrophils contribute most to the overall higher WBC. There is an increase in immature forms and the cytoplasm shows toxic granulation. The count<sup>3,4</sup> is relatively constant throughout gestation  $(3 \times 10^9-10 \times 10^9/L)$ , markedly elevated in the hours after delivery (up to  $23 \times 10^9/L$ ) and back to non-pregnant values by 4 weeks post-partum  $(1.5 \times 10^9-6 \times 10^9/L)$ . Neutrophil chemotaxis and phagocytic activity are depressed, the latter being inhibited by factors present in pregnancy serum. There is also evidence of increased oxidative metabolism in neutrophils during pregnancy.

Lymphocyte count<sup>3,4</sup> decreases during pregnancy through first and second trimesters, increases during the third trimester, but remains low in the early puerperium as compared to normal non-pregnant values. Typical pregnancy range for lymphocyte count is  $1.1 \times 10^9$ – $2.8 \times 10^9$ /L, compared with the non-pregnant reference range  $0.8 \times 10^9$ – $4.0 \times 10^9$ /L. Lymphocyte count is restored to normal range by 4 weeks after delivery. Detailed studies of T and B lymphocyte subsets in peripheral blood and the proliferative responses of these cells to mitogens found more helper and suppressor cells and less killer cells during pregnancy. Lymphocyte proliferation in response to a variety of agents was found to be impaired in pregnancy, suggesting that there is an immunosuppressant factor present in the serum.

Monocyte count is higher in pregnancy, especially in the first trimester, but decreases as gestation advances.<sup>4</sup> Typical values<sup>3,4</sup> in the third trimester are  $0.2 \times 10^9$ – $1.0 \times 10^9$ /L, as compared to non-pregnant values  $0.1 \times 10^9$ – $0.9 \times 10^9$ /L. The monocyte to lymphocyte ratio is markedly increased in pregnancy.

Eosinophil and basophil counts do not change significantly during pregnancy.<sup>3</sup>

Myelocytes and metamyelocytes may be found in the peripheral blood film of healthy women during pregnancy and do not have any pathological significance.

- WBC is elevated in pregnancy, mostly due to neutrophilia.
- Lymphocyte count is lower and monocyte count higher.
- During pregnancy, only WBC  $> 16 \times 10^9$ /L is considered abnormal.
- Soon after delivery, only WBC  $> 25 \times 10^9$ /L is considered abnormal.
- Eosinophil and basophil counts do not change in pregnancy.

#### Platelets

Large cross-sectional studies in pregnancy of healthy women (specifically excluding any with hypertension) have shown that the platelet count decreases during pregnancy, particularly in the third trimester.<sup>5</sup> This is termed "gestational thrombocytopenia." Almost 12% of women in one study<sup>5</sup> were found to have a platelet count of  $< 150 \times 10^9$ /L late in pregnancy. Of these women, 79% had platelet counts  $116 \times 10^9$ –149 ×  $10^9$ /L; none had complications related to thrombocytopenia and none of their babies had severe thrombocytopenia (platelet count  $< 20 \times 10^9$ /L). Thus, it has been recommended that the lower limit of platelet count in late pregnancy should be considered as  $115 \times$  $10^9$ /L. Only 1% of healthy women have platelet counts  $< 100 \times 10^9$ /L.

Platelet size is an indicator of the age of the platelets; young ones are large and they become progressively smaller with age. Platelet volume has a skewed distribution, tailing off at larger volumes. The platelet volume distribution width increases significantly and continuously as gestation advances and the mean platelet volume becomes an insensitive measure of platelet size. Studies suggest that platelet lifespan is shorter in pregnancy. The decrease in platelet count and increase in platelet size in pregnancy suggests that there is hyperdestruction of platelets.

Platelet function, as assessed by the time required for whole blood to occlude a membrane impregnated with either epinephrine or adenosine 5'diphosphate (ADP), has been studied in late pregnancy.<sup>7,8</sup> No correlation was found between platelet count and the "closure times" over a range of platelet counts  $44 \times 10^9$ - $471 \times 10^9$ /L in healthy women.<sup>8</sup> Another study found that the closure times were increased in women with severe pre-eclampsia, although they did not correlate with clinical bleeding problems in these women.<sup>9</sup> In women with gestational thrombocytopenia, platelet closure times are influenced by hemoglobin level, being prolonged when there is both thrombocytopenia and anemia.<sup>7</sup> This is perhaps not surprising, given the contribution of red cells to the hemostatic process, in part due to ADP donation. The increase in fibrinogen during pregnancy helps to maintain platelet function.

#### Summary points

 Platelet count decreases during pregnancy in some patients.

- The lower limit of normal platelet count at term is  $115 \times 10^9$ /L.
- There is evidence of platelet hyperdestruction in pregnancy.
- Platelet closure times are not affected by absolute platelet count in healthy women during pregnancy.
- Platelet closure times are prolonged when there is anemia in addition to a low platelet count.
- The increase in fibrinogen during pregnancy more than compensates for the fall in platelet count.

#### **Coagulation factors**

Screening tests used to assess the coagulation pathways include the activated partial thromboplastin time (APTT), which measures the intrinsic pathway, the prothrombin time (PT), which measures the extrinsic pathway, and the thrombin time (TT) which measures the final common pathway. In pregnancy, the APTT is usually shortened, by up to 4 seconds in the third trimester, largely due to the hormonally influenced increase in factor VIII. No marked changes in PT or TT occur.

Many coagulation factors are increased in pregnancy (Table 1.2). Von Willebrand Factor and Factors VII, VIII, X, and fibrinogen increase substantially as gestation advances. In one longitudinal study,<sup>10</sup> Factor VII activity increased from the range 60%-206% (compared to standard) at the end of the first trimester to 87%-336% by term. The same study, found Factors II and V increased in early pregnancy, but then reduced in the third trimester. Another cross-sectional study found a 29% rise in Factor V from 6-11 weeks' to 36-40 weeks' gestation.<sup>11</sup> Increased levels of coagulation factors are mediated by rising estrogen levels and thought to be due to both increased protein synthesis and enhanced activation by thrombin. Coagulation factors remain elevated in the early puerperium and for assessment of true non-pregnant levels, it is best to sample 8-12 weeks after delivery.

- APTT is usually shortened in pregnancy.
- Von Willebrand factor and factors VII, VIII, X, and fibrinogen increase.
- There is a variable change in factor XI levels.
- Coagulation factor levels remain high in the early postpartum period.

Table 1.2 Coagulation factors during pregnancy and the early puerperium

	6–11	12–16	17–23	24–28	29–35	36–40	3 days
	weeks	weeks	weeks	weeks	weeks	weeks	post-natal
	<i>N</i> = 41	N = 28	<i>N</i> = 10	N = 19	N = 36	N = 23	N = 87
Prothrombin fragments 1 + 2 nmol/l	1.1	1.1	1.3	1.8	2.0	1.9	2.2
	< 2.9	< 1.5	< 2.1	< 3.4	< 3.9	< 3.5	< 4.9
Fibrinogen activity	3.6	3.8	3.6	4.4	4.1	4.2	4.5
g/l	2.5–4.8	2.5–5.1	2.6–4.7	2.9–5.9	2.5–5.8	3.2–5.3	3.1–5.8
Prothrombin activity	153	160	153	172	153	162	169
iu/dl	107–200	111-209	41–265	92–252	100–211	107–217	108–231
Factor V activity	99	101	111	108	111	129	141
u/dL	39–159	39–162	47–175	50–166	43–179	65–194	71–211
Factor VIII activity	107	129	189	187	180	176	192
iu/dl	62–220	82–130	59–159	71–341	31–328	50–302	54–331
Factor IX activity	100	106	96	121	109	114	136
iu/dl	49–151	82–130	74–118	59–183	65–154	79–150	65–207
Factor X activity	125	129	128	159	146	152	162
iu/dl	88–162	78–180	50–206	52–263	81–212	113–191	69–254
Factor XI activity	102	103	86	102	100	92	96
iu/dl	50–154	58–147	58–114	45–162	31–169	36–181	46–146
Factor XII activity	137	160	186	170	178	179	174
iu/dl	70–204	52–268	64–247	54–286	78–278	62–296	86–262
Von Willebrand Antigen iu/dl	137	160	186	170	178	179	174
	70–204	52–268	64–247	54–286	78–278	62–296	86–262
RCo	117	132	128	204	169	240	247
iu/dl	47–258	55–298	50–206	68–360	86–466	100–544	97–630

Mean and 2 standard deviation normal ranges. From a cross sectional study of 239 women, each of whom was only sampled once. Adapted from ref. 11.

RCo: Ristocetin cofactor activity.

Table 1.3 Natural anticoagulant factors during pregnancy and the early puerperium

	6–11	12–16	17–23	24–28	29–35	36–40	3 days
	weeks	weeks	weeks	weeks	weeks	weeks	post-natal
	<i>N</i> = 41	<i>N</i> = 28	<i>N</i> = 10	<i>N</i> = 19	N = 36	N = 23	N = 87
Total Protein S	80	77	66	68	67	58	69
u/dl	34–126	45–109	40–92	38–98	27–106	27–90	37–85
Free Protein S	81	72	64	60	54	57	58
u/dl	47–115	44–101	38–90	34–86	32–76	15–95	29–87
Protein C activity	95	94	101	105	99	94	118
u/dl	65–125	62–125	63–139	73–137	60–137	52–136	78–157
Antithrombin activity	96	100	100	104	104	102	108
u/dl	70–122	72–128	74–126	70–138	68–140	70–133	77–137

Mean and 2 standard deviation normal ranges. From a cross sectional study of 239 women, each of whom was only sampled once. Adapted from ref. 11.

#### **Natural anticoagulants**

There are changes in the balance of the natural anticoagulants during pregnancy and the puerperium (Table 1.3). Levels and activity of Protein C do not change and remain within the same ranges as for nonpregnant women of similar age.<sup>11</sup> There are increased levels and activity of Protein C in the early puerperium. Total and free (i.e. biologically available) Protein S levels decrease progressively through gestation. Ranges for total and free Protein S are lower in the

Number of patients		41	48	47	66	62	48	61 Post-	61 Post-
Weeks		11–15	16–20	21–25	26-30	31–35	36–40	delivery	natal
Fibrin degradation Products µg/ml	Mean	1.07	1.06	1.09	1.13	1.28	1.32	1.66	1.04
Fibrinolytic activity (100/Lysis time)	Mean	7.6	7.4	7.3	5.5	4.5	5.6	6.75	5.75
Lysis time in hours	Mean	13.25	13.5	13.75	18.25	22.25	17.8	14.8	17.4
Antithrombin III:C	Mean	85	90	87	94	87	86	87	92
	Range	49–120	46–133	42–132	47–141	42–132	40–132	48–127	38–147
Antithrombin III:Ag	Mean	93	94	93	97	96	93	95	100
	Range	60–126	56–131	56–130	56–138	59–132	50–136	58–133	64–134
$\alpha_1$ Antitrypsin	Mean	124	136	125	146	149	154	172	77
	Range	66–234	86–214	53–295	85–249	89–250	91–260	84–352	44–135
$\alpha^2$ Macroglobulin	Mean	176	178	170	160	157	153	146	142
	Range	100–309	98–323	92–312	88–294	85–292	85–277	81–265	82–245

 Table 1.4
 Natural anticoagulants and markers of fibrinolysis

Where no units are shown, values are expressed as per cent of standard. Where shown, range is 2.5th–97.5th centile. Samples were collected longitudinally from 72 women. Post-natal samples were collected 2 weeks-12 months following delivery. The post-natal values were found to be similar to those obtained from healthy pre-menopausal women who were not using oral contraceptives. Adapted from ref. 10.

first trimester (34–126 and 47–115 iu/dL, respectively) than in women of similar age, not using oral contraceptives (64–154 and 54–154 iu/dL, respectively).<sup>11</sup> This makes it difficult to diagnose Protein S deficiency in pregnancy. Antithrombin levels and activity are usually stable during pregnancy, fall during labor and rise soon after delivery (Tables 1.3 and 1.4).

Acquired activated Protein C (APC) resistance has been found in pregnancy, in the absence of Factor V Leiden, antiphospholipid antibodies or a prolonged APTT.<sup>11</sup> This has been attributed to high Factor VIII activity and may also be influenced by high Factor V activity and low free Protein S levels. Similar acquired APC resistance has been found in women using oral contraceptives and in association with inflammatory disorders. The changes in APC resistance with gestation preclude use of APC sensitivity ratios as a screening test for Factor V Leiden during pregnancy.

#### Summary points

- Protein C is unchanged in pregnancy.
- Protein S decreases in pregnancy.
- Antithrombin levels decrease during labor.
- There is acquired APC resistance during pregnancy.



Fig. 1.1 Thromboelastograph analyzer.

#### Thromboelastography

Thromboelastography (TEG)(Fig. 1.1) provides an overall assessment of coagulation by measuring the

viscoelastic properties of whole blood as it is induced to clot in a low-shear environment. The parameters derived from the automated TEG equipment define the reaction time to initiation of a clot (R), the clot formation rate ( $\alpha$ ) and time (K), the clot strength or maximum amplitude (MA) and clot lysis (reduction in maximum amplitude after 60 minutes, LY60) (Fig. 1.2). The various parameters are correlated and are affected by the availability of fibrinogen and platelet function. The TEG coagulation index (TEG CI) is derived from R, K, MA, and  $\alpha$ , which has a normal range of -3 (hypocoagulability) to +3 (hypercoagulability).

In healthy late pregnancy, there is increasing hypercoagulability and the TEG CI has been measured in the range -0.6 to +4.3. Within the first 24 hours of delivery, TEG CI values of -0.5 to +3.9 have been found.<sup>12</sup> The highest TEG CI values have been found during active labor. Parameters return to baseline by 4 weeks postpartum<sup>13</sup>(Fig 1.3). No differences have been found in TEG parameters during pregnancy between smokers and non-smokers. Significantly lower TEG CI values were found in a large study of women who took folic acid supplements<sup>14</sup> during the first trimester (-1.22 to +2.87), indicating that they were less hypercoagulable than those who did not take supplements (-1.52 to +2.60).

Studies of TEG in pregnant women with thrombocytopenia are inconclusive to date. The TEG MA correlates with platelet count as well as fibrinogen, but it is as yet unclear whether TEG parameters can be used clinically to predict the safety of regional anesthetic techniques in women with low platelet counts, especially those with pre-eclampsia.<sup>8,9</sup>

#### Summary points

- TEG gives a global assessment of coagulation status.
- TEG CI measurement demonstrates the tendency to hypercoagulability in pregnancy.
- There is insufficient experience with TEG in pregnant women with thrombocytopenia or pre-eclampsia to judge its clinical usefulness.

#### Markers of hemostatic activity

Hemostatic activity can be assessed by measuring markers of both clot formation and clot destruc-

tion.<sup>15</sup> Many have been used in research settings, but the ones that have clinical applications are thrombin-antithrombin complexes (TAT) and prothrombin fragments (F 1+2), which reflect in vivo thrombin formation, plus tests that demonstrate plasmin degradation of fibrin polymer to yield fragments, namely D-dimers and fibrin degradation products (FDP). Exact reference ranges depend on the reagents and testing kits used for the assays. Increased levels of F 1+2 are shown in Table 1.2; by term, levels are approximately four times higher than those from a healthy adult population. Likewise, TAT levels<sup>15</sup> increase with gestation; in early pregnancy the upper limit of normal is similar to the adult range of 2.63  $\mu$ g/L, whereas by term, the upper limit of normal is 18.03 µg/L.

D-dimer levels are very markedly increased in pregnancy, with typical ranges tenfold higher in late pregnancy than in early pregnancy or the non-pregnant state. In one study,<sup>15</sup> where the healthy adult range for D-dimers was  $< 433 \ \mu g/L$ , by mid pregnancy the range was  $< 3000 \ \mu g/L$  and by late pregnancy  $< 5300 \ \mu g/L$ . It is thought that the increase in D-dimers reflects the increase in fibrin during pregnancy, rather than increased fibrinolytic activity.

#### Summary points

- Markers of thrombin production (TAT and F1+2) are elevated in pregnancy.
- D-dimers are tenfold higher in late normal pregnancy than typical levels from healthy non-pregnant women.

#### Fibrinolysis

There is additional hemostatic control exerted by lysis of the fibrin clot. This is achieved by plasmin, created from plasminogen by activators. The fibrin mesh is lyzed to fibrin degradation products, including D-dimers. Tissue plasminogen activator is the most important endothelial cell derived plasminogen activator. There is reduction in the activity of the fibrinolytic system during pregnancy, mostly due to increased levels of plasminogen activator inhibitors (PAI-1 and PAI-2), which are produced by the placenta. PAI-1 is also produced by platelets and endothelium. There is an exponential



Fig. 1.2 Thromboelastograph trace (a) pregnant (b) non-pregnant, showing shortened R and K times and increased maximum amplitude in pregnancy.

increase in PAI-1 with gestation, from typical values  $< 50 \ \mu g/L$  in early pregnancy and the nonpregnant state, to values 50–300  $\mu$ g/L at term.<sup>15</sup> Old studies of fibrinolytic mechanisms in pregnancy and the puerperium demonstrated that levels of plasminogen activator decline through pregnancy, reach their lowest levels during labor and increase soon after delivery.<sup>16</sup> The discovery of PAI-1 and PAI-2 provides the explanation for these changes, which lead to maximum suppression of fibrinolysis during labor.

There are a number of inhibitors of plasmin, including  $\alpha_2$  antiplasmin, antithrombin,  $\alpha_1$  antitrypsin,  $\alpha_2$  macroglobulin and C<sub>1</sub>-esterase inhibitor. Levels of  $\alpha_1$  antitrypsin and  $\alpha_2$  macroglobulin increase after delivery (Table 1.4), as do Factor VIII and fibrinogen





Fig. 1.3 Interval plot of maximum amplitude vs. weeks' postpartum after normal delivery.

activities (Table 1.2); this is an acute phase reaction, similar to that seen after surgery. There are also increased levels of thrombin activatable fibrinolysis inhibitor (TAFI) in pregnancy, which inhibits fibrinolysis by various mechanisms.<sup>17</sup> Overall, although fibrinolytic activity increases after delivery, it takes at least 6 weeks to be completely restored to normal non-pregnant levels.

Clot lysis time is prolonged in pregnancy (Table 1.4), particularly in the third trimester. In one study,<sup>17</sup> the median and interquartile range for clot lysis time was 98 (90–111) minutes in the first trimester, 110 (99–124) minutes in the second trimester and 127 (107–171) minutes in the third trimester, but 92 (80–99) minutes in the first 24 hours after delivery of the placenta.

Increased circulating FDP levels (Table 1.4) and D-dimers<sup>15</sup> are found during pregnancy despite systemic suppression of fibrinolysis. It is thought that there is increased fibrin generation and degradation locally in the placental circulation. Differences have been found in hemostatic and fibrinolytic processes

in blood samples from venous placental blood and from forearm blood<sup>10</sup>. It is also possible that clearance of FDP and D-dimers may be altered in pregnancy. Overall, there is a low level of intravascular coagulation, demonstrable from as early as 11–15 weeks gestation.<sup>10</sup> Levels of FDP, D-dimers and soluble fibrin remain high after delivery for at least the first week.

- Fibrinolysis is suppressed during pregnancy and especially during labor.
- PAI-1 from endothelial cells is increased in pregnancy.
- PAI-2 is produced in the placenta.
- Various factors continue to suppress fibrinolysis soon after delivery.
- Raised FDP and D-dimers indicate clot formation and destruction, possibly locally in the placental circulation.

#### Homocysteine

Homocysteine levels fall in early pregnancy and are significantly reduced compared to the non-pregnant state, in all three trimesters.<sup>18</sup> This appears to be multifactorial and related to the hormonal changes

in pregnancy, physiological hemodilution, increased renal clearance of homocysteine, folic acid supplementation and enhanced remethylation of homocysteine due to increased demands for methionine by the fetus.

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#### **Cellular changes**

### **Hematinic deficiencies**

Jane Strong

#### Introduction

Deficiency of any of the vitamins and minerals essential for normal erythropoiesis (hematinics) may be associated with defective erythropoiesis and anemia. Hematinics include iron, copper, cobalt, vitamins A,  $B_{12}$ ,  $B_6$ , C, E, folic acid, riboflavin, and nicotinic acid.

Iron, folate, and vitamin  $B_{12}$  deficiency are the most common hematinic deficiencies. These are the focus of this chapter.

#### Iron deficiency

#### Epidemiology

Iron deficiency anemia is the most common health problem that women face worldwide. It affects about 20% of the world's population and is a significant cause of morbidity and mortality. Of anemias diagnosed in pregnancy, 75% are due to iron deficiency.

On a worldwide perspective, the deficiency in iron reflects poor nutrition resulting from widespread economic and social deprivation. Many women have depleted or borderline iron stores due to menstruation and the demands of previous pregnancies, and few women enter into pregnancy with sufficient iron stores. Combined with the increased iron demands in pregnancy due to the expansion in red cell mass and the requirements of the developing fetus, many women become iron deficient.

Worldwide, iron deficiency anemia in pregnancy affects about 50% of women. In developing countries the prevalence is 56% and in developed countries 18%. The majority of these women are already anemic prior to pregnancy. Prevalence studies in the United States reveal iron store depletion in about 10% of women of reproductive age, with anemia present in 5%. The iron deficiency anemia rates in pregnancy increase with each trimester – starting with 9% in the first trimester, 14% in the second, and 37% in the third.

It is of note that it takes 2 years of normal dietary iron to replace the iron lost with each pregnancy. More than 500 mg of storage iron are required to avoid iron deficiency in pregnancy. This amount of storage iron is present in only 20% of women with 40% having no storage iron at the start of pregnancy.

#### Pathogenesis

#### Iron homeostasis

Dietary elemental iron is absorbed from the duodenum and jejunum. The typical western diet will contain 15 mg/day iron. The recommended daily allowance of iron for pregnancy is 30 mg/day.

The dietary bioavailability of iron depends on the iron content of the food and its form. Heme iron, derived from meat is more readily absorbed than non-heme iron. Absorption is facilitated by reducing agents such as vitamin C, hence the recommendation to take iron supplements with orange juice or ascorbic acid tablets. Absorption is inhibited by phytates in cereals, tannins in tea and polyphenols in some vegetables.

Only approximately 10% of dietary iron is absorbed. This increases in pregnancy and triples from the first to the third trimester peaking after 30 weeks.

The iron requirements of a pregnancy, labor, and delivery are approximately 1240 mg (see Table 2.1).

Iron requirements in pregnancy rise sharply from 1-2 mg/day in the first trimester to 4 mg/day in the second trimester and peaking at 6 mg a day in the third trimester. Lactation requires 0.5-1.0 mg/day of iron.

Table 2.1 Iron requirements for pregnancy, labor, and delivery

Source of increased iron requirement	Iron demand
Increase in red cell mass	450 mg
Fetus and placenta	300 mg
Increase in basal maternal requirements	240 mg
Blood loss at delivery (normal vaginal delivery)	250 mg
Iron requirements for pregnancy, labor, and delivery	1240 mg

Absorption is regulated by the gastrointestinal tract and is dependent on iron stores. In normal pregnancy a physiological hypervolemia occurs and this results in a modified response to blood loss. The plasma volume increases from 6 weeks gestation by 50%. The red cell mass has a slower rate of expansion. By term, it has increased by 25%, but this is dependent on iron status.

Iron is required for the red cell expansion and ferritin levels show a marked decline between 12 and 25 weeks. This results in a physiological reduction in hemoglobin concentration that is maximal at 32 weeks. Hemoglobin concentrations return to normal within 1 week in the postpartum period in iron-replete women.

The increase in blood volume helps to compensate for blood loss at delivery. A blood loss of 1000 ml can be tolerated without a significant drop in hemoglobin. Provided the blood loss at delivery does not exceed 25% of the pre-delivery blood volume, there is no further increase in blood volume. The plasma volume decreases as a result of diuresis, the hematocrit increases, and the blood volume returns to nonpregnant values.

# The placental regulation of iron transfer to the fetus

The apical surface of the placental syncytiotrophoblast has transferrin receptors that trap maternal transferrin by endocytosis, and the iron is bound to halotransferrin within the placental cell. Iron is released, bound to ferritin within the placenta, and then actively transported to the fetus initially as fetal apotransferrin and then as holotransferrin in the fetal circulation.

If maternal iron decreases, the placental tranferrin receptors increase and conversely placental iron uptake is inhibited by placental synthesis of ferritin. Transfer of iron to the fetus occurs predominantly in the last 4 weeks of pregnancy. Two-thirds of fetal iron is found in the fetal hemoglobin, the rest in the fetal liver.

Maternal iron deficiency anemia affects both mother and fetus. Iron-dependent enzymes in every cell are affected and there are neuromuscular, gastrointestinal, and epithelial consequences that can influence fetal mortality, growth, and programing.

#### **Diagnosis of iron deficiency**

Iron deficiency develops sequentially, with storage iron becoming depleted initially. This is followed by a fall in the amount of iron available for erythropoiesis. Subsequently, the peripheral blood hemoglobin drops and, with that, there is a fall in the delivery of oxygen to peripheral tissues, and the patient develops clinical symptoms and signs.

Each phase in the development of symptomatic iron deficiency anemia has various hallmarks outlined below.

#### Decrease in storage iron

Tissue and bone marrow iron become deplete first. Bone marrow samples can be specifically stained to look for iron. Without iron supplementation, 80% of women are deplete of iron stores at term with no stainable iron in their bone marrow samples. Although this is a rapid and reliable method of assessing iron stores, the invasive nature of the test means it is rarely done to diagnose iron deficiency as there are several reliable non-invasive tests. Bone marrow examination is generally reserved for severe anemias when the cause cannot be determined by other means and when there is evidence of marrow failure.

Serum ferritin levels fall early in the development of iron deficiency. This is one of the first abnormal laboratory tests. Ferritin levels are not affected by recent ingestion of iron, but they are an acute phase reactant rising if there is active infection or inflammation.

Transferrin levels increase early in the development of iron deficiency, but are rarely available as a laboratory measure. This transporter protein increases in an attempt to deliver more iron to the tissues.

#### Decrease in iron for erythropoiesis

Serum transferrin receptors are transmembrane proteins present in all cells. They bind transferrin-bound iron and transport it to the cell interior. Receptors increase as the iron supply decreases. Small amounts of transferrin receptors circulate in the plasma in amounts proportional to the total. These soluble transferrin receptors can be measured by immunological techniques. This test is reported as being 100% specific in identifying iron deficiency in pregnancy and has significant advantages over ferritin and transferrin saturation.

Once tissue iron deficiency is established, serum transferrin receptors increase in proportion to the degree of iron deficiency. Serum transferrin receptor level changes occur before a reduction in the mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) in red cells and also before the rise in free erythrocyte protoporphyrin.

A reduction in MCV and MCHC are seen at an early stage in the development of iron deficiency in the non-pregnant state, but these are a poor indicator of iron deficiency that develops during pregnancy. The increased drive to erythropoiesis resulting in the physiological increase in red cell mass means that there are a higher proportion of young large red cells and this can mask the effect of iron deficiency on red cell MCV. A normal MCV does not exclude iron deficiency and the red cell indices in established iron deficient women in pregnancy may be normochromic normocytic.

Iron replete pregnancies are associated with a physiological increase in red cell size – usually around 4fL (femtoliters –  $10^{-15}L$ ).

Free erythrocyte protoporphyrin increases as iron for erythropoiesis reduces. Iron addition to the porphyrin ring is the last step in heme biosynthesis. When iron is low, free protoporphyrin increases. Zinc competes with iron and, if iron is unavailable, zinc protoporphyrin levels increase and these can also be measured. Both free erythrocyte and zinc protoporphyrin increase in situations of acute infection or inflammation. These measurements are also elevated in lead poisoning.

#### Decrease in peripheral hemoglobin

Anemia is defined as a hemoglobin level at least two standard deviations below the median value for a healthy matched population. The World Health organization defines anemia in pregnancy as a hemoglobin below 11 g/dL. Some define a different cut-off in the second trimester – the United States Centers for Disease Control (US CDC) use a value of 10.5 g/dL.

The maternal blood volume expands in the first and second trimesters – the plasma volume expansion is

increased by 50% and the red cell mass by 18%–25% depending on iron status. These physiological changes cause a dilutional decrease in hemoglobin and hematocrit. Increased hemoglobin in the second trimester may represent poor maternal blood volume expansion and is associated with maternal and fetal morbidity. A hematocrit above 43% has been associated with a four-fold increased risk of fetal growth retardation.

Iron deficiency is often diagnosed retrospectively after a good hemoglobin response to a therapeutic trial of iron supplements. In populations where there is a possibility of thalassemia that can present with full blood count features similar to iron deficiency, iron therapy should only be started after iron deficiency is confirmed with a measure of iron stores such as ferritin.

#### **Clinical signs and symptoms**

Patients with iron deficiency are often asymptomatic, but symptoms may occur without an anemia. Irondependent enzymes in every cell are affected and there are neuromuscular, gastrointestinal and epithelial consequences. Prior to the development of an anemia, the signs and symptoms of iron deficiency are non-specific and include reduced exercise tolerance and tiredness.

Severe iron deficiency is associated with pallor, glossitis, angular chelitis, nail ridging, and when severe nail spooning – koilonychia. Dsyphagia can develop if a post-cricoid web occurs. Iron deficiency can also affect cellular immunity and phagocytosis, with women being increasingly susceptible to infection. Pica can occur in as many as 50% of patients as a symptom of severe iron deficiency and can take different forms – craving for earth, clay, starch, and ice. It improves with iron replacement (Tables 2.2, 2.3, 2.4).

Table 2.2	Clinical	signs	and	symptoms	of iron	deficiency
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	Symptoms	Signs
lron deficiency without anemia	Irritability Poor concentration Tiredness and fatigue Reduced exercise tolerance	None
Iron deficiency with anemia	Tiredness and fatigue Reduced exercise tolerance Shortness of breath on exercise Palpitations Headache Dysphagia Pica	Pallor Glossitis Angular chelitis Koilonychia

#### Table 2.3 Effects of iron deficiency

	Mother	Fetus and pregnancy outcome	Neonate, infant, and older
Effects of iron deficiency	See Table 2.2 above Decreased cognitive function Tissue enzyme malfunction Effects on neuromuscular transmission	<ul> <li>Hb≤9 g/dL - increased risk of:</li> <li>Prematurity (doubles risk)</li> <li>Small for gestational age</li> <li>Spontaneous abortion</li> </ul>	Lower Apgar scores Low iron stores in newborn associated with growth restriction, neurological and mental impairment
		Low ferritin: Placental hypertrophy – increase in angiogenesis	Increased placenta:fetal ratio is a predictor of cardiovascular disease and diabetes in adult life

Table 2.4 Laboratory investigations in iron deficiency

Laboratory test and normal non-pregnant female range	Normal – pregnancy	Iron deficiency without anemia – iron store depletion	lron deficiency with anemia – Mild – severe
Bone marrow reticuloendothelial iron 2+ – 3+	2+-3+ Difficult to maintain by third trimester without iron	None	None
Serum iron 60–150 mcg/dL	>60 mcg/dL progressive fall over pre-pregnancy values	Borderline low	low
Transferrin 200–400 mg/dL	Progressive rise over pre-pregnancy values – within normal range	Borderline high	Raised
Saturation SI/TIBC: 20%–50%	Progressive fall within normal range	Normal	Low
Plasma or serum ferritin 40–200 $\mu$ g/L	Decreases within normal range between 12th and 25th week (hemodilution)	<40	<20 (mild)-<10 (severe)
Soluble transferrin receptors 2.9–8.3 mg/L	First trimester -2.6-6.7 mg/L Second and third trimester - 25% increase (increased erythropoiesis)	Increased	Increased
Red cell indices and red cell morphology	MCV can rise: average 4–6 fL	Normal	Mild hypochromia and microcytosis
Erythrocyte protoporphyrin 30–70 ng/mL	Progressive rise, usually within normal range	30–70	>100 - 200
Hemoglobin 12–15 g/dL	>11 first and third trimesters >10.5 second trimester	Normal	9–12 (mild), 6–7(severe)
Other tissue changes	None	None	Nail/epithelial changes

#### **Management options**

#### Iron

Iron is available in a variety of forms – dietary, tablet, and liquid, intravenous and intramuscular.

#### **Dietary iron**

In pregnancy it is recommended that iron consumption is increased by 15 mg/day to a daily recommended allowance of 30 mg/day. Women will often find it difficult to increase dietary iron sufficiently, but these recommended amounts are met by most prenatal vitamin formulations.

Dietary iron is predominantly in the reduced ferric form (Fe<sup>3+</sup>) and this is poorly soluble above a pH of 3. It is poorly absorbed at the duodenal pH of 7– 8. The oxidized ferrous form of iron (Fe<sup>2+</sup>) is more soluble at the duodenal pH and hence more easily absorbed.

Heme dietary sources of iron – meat, fish, and poultry have a much greater bioavailability than nonheme vegetable sources. Iron bioavailability from heme sources is approximately 30% vs. 10% for nonheme sources.

#### Table 2.5 Iron absorption

Enhanced iron absorption	Reduced iron iron absorption
Ascorbic acid	Phytates in bran, oats, rye, and fiber
Heme iron	Tannins in tea
Oxidized, ferrous form of iron (Fe <sup>2+</sup> )	Polyphenols in some vegetables High dietary calcium content

Intraluminal factors in the gastrointestinal tract also affect absorption (Table 2.5).

#### Tablet and liquid iron

Iron can be given to supplement dietary iron and maintain iron stores at a time of marked increased iron demand. Most studies report that this approach decreases the prevalence of iron deficiency anemia at delivery. This may help anemia in infancy, but it is unclear whether iron supplementation in wellnourished non-anemic women improves birth outcome.

It can be given selectively based on a measure of iron stores or routinely. The need for iron supplementation in Western countries is debatable, but the practice is recommended in the developing world. The World Health Organization (WHO) recommend universal oral iron supplementation with 60 mg elemental iron daily for 6 months in pregnancy in areas where the prevalence of iron deficiency is less than 40%. The supplementation is continued for 3 months postpartum in areas where the prevalence is greater than 40%. The Center for Disease Control and prevention recommends supplementation with 30 mg elemental iron daily as does the American College of Obstetricians and Gynecologists.

Universal supplementation is considered practical and cost effective by some. The debate is ongoing. A recent Cochrane database library review demonstrated no definite advantage to mother or fetus with routine iron or iron and folate supplementation.<sup>1</sup>

Women with iron deficiency anemia should receive iron supplements of 30–120 mg elemental iron until the anemia is corrected and there has been time for iron stores to replenish. Oral iron is an effective, cheap, and safe way of replacing iron, provided there is compliance.

There are a large number of oral iron-containing preparations and they often come combined with other vitamins and minerals. As a general principle, enteric coated or slow release formulations should be avoided as the iron is released beyond the duodenum and proximal jejunum where it is maximally absorbed. Women should be counseled regarding diet and the factors that can inhibit iron absorption. Iron salts should ideally not be given with food because the phytates, tannins, and phosphates within the diet can bind iron preventing its absorption. Antacids should also be avoided around the ingestion of iron and ideally ascorbic acid should be taken to enhance absorption.

The iron preparation of choice is based on effectiveness and minimal side effects. The three ferrous salts available are ferrous fumurate, ferrous gluconate, and ferrous sulphate. They each contain differing quantities of elemental iron:

- ferrous fumarate 65 mg elemental (ferrous) iron per 200 mg tablet
- ferrous sulphate 60 mg elemental iron per 300 mg tablet
- ferrous sulphate, dried 65 mg elemental iron per 200 mg tablet
- ferrous gluconate 35 mg elemental iron per 300 mg tablet.

The recommended oral dose of elemental iron for the treatment of iron deficiency is 100–200 mg daily. Ferrous sulphate 200 mg three times daily provides 195 mg elemental iron and, on this treatment, regimen the hemoglobin should rise 2 g/dL over 3–4 weeks. Once the hemoglobin has normalized, the treatment should be continued for a further 3 months to replenish the iron stores.

Side effects are experienced in 10%–20% of patients at treatment doses. Iron salts irritate the gastrointestinal tract and can cause nausea, vomiting, epigastric discomfort, and altered bowel habit (constipation or diarrhea). There appears to be a clear dose relationship with the upper gastrointestinal symptoms, but this is less clear with the altered bowel habit.

If side effects occur, an iron preparation containing a smaller dose of iron can be tried. Liquid preparations can be useful, allowing patients to titrate their dose to a level where side effects are acceptable. Iron can be taken with meals, but this will decrease the amount absorbed.

#### **Parenteral iron**

Parenteral iron therapy is available as iron dextran or sucrose. It is reserved for patients unable to tolerate oral iron or where compliance is in doubt or in patients where there is a level of bleeding that exceeds the ability of the GI tract to absorb iron or there is malabsorption. It should be noted that parenteral administration does not produce a faster response than correctly taken oral iron that is absorbed adequately. It merely ensures compliance. First trimester administration is not recommended.

There are currently two well-established preparations approved for use in the UK:

- iron dextran (Cosmofer<sup>®</sup>) a complex of ferric hydroxide with dextran containing 50 mg of elemental iron/ml that can be given either intramuscularly or intravenously;
- iron sucrose (Venofer<sup>®</sup>) a complex of ferric hydroxide with sucrose containing 20 mg of elemental iron/ml that is approved for intravenous use.

Dose is calculated according to body weight and iron deficit. Cosmofer<sup>®</sup> has the advantage of being licensed for administration as a single total dose infusion. Anaphylactoid reactions can occur with parental iron preparations and a test dose is recommended prior to the first dose. Cardiopulmonary resuscitation facilities should be available with injectable 1:1000 adrenaline solution, antihistamines, and corticosteroids.

Iron dextran has safety issues related to anaphylaxis. The high molecular weight dextran moiety is thought to share antigens with gastrointestinal organisms. Much of the reported experience with this drug is in hemodialysis patients. The safety of intravenous iron dextran has been reviewed in 573 hemodialysis patients:<sup>2</sup>

- 4.7% had an adverse reaction.
- Ten patients (1.7%) had reactions classified as anaphylactoid including cardiac arrest in 0.2%, chest pain1%, and hypotension 0.5%.
- There were no deaths.
- Only in 4 of the 10 with anaphylactoid reactions did these occur during the test dose administration, emphasizing the need for vigilance.
- Drug allergies were strong predictors for reactions.

The iron dextran SPC report severe anaphylactoid reactions as being very rare <1/10000.

Iron sucrose appears to be safe even amongst those with a prior history of sensitivity to iron dextran. Again, the experience comes from hemodialysis patients. A group of 665 patients including 80 with previous iron preparation intolerance experienced no adverse reactions to iron sucrose.<sup>3</sup>

The next generation of parenteral iron has recently become available:

 Ferric carboxymaltose (Ferinject<sup>®</sup>) – contains 50 mg of elemental iron/ml that can be given intravenously.

Dose is also calculated according to body weight and iron deficit. It is contraindicated in the first trimester of pregnancy. Clinical data on pregnant women are not currently available and the SPC advises a careful risk/benefit evaluation prior to use in pregnancy. The appeal of this new product includes significantly reduced infusion times and no requirement for a test dose. Adverse events from pooled data from 10 multicenter trials involving 2800 patients reported no serious or life-threatening hypersensitivity (anaphylactic) events, but as with other parenteral iron preparations the SPC warns that facilities for cardiopulmonary resuscitation must be available.

#### Intramuscular iron

Iron administration given by deep intramuscular injection into the gluteal muscle. This route is often painful, can stain the skin and the mobilization of iron from intramuscular sites is slow and often incomplete. There have been difficulties in sourcing the intramuscular preparation and its administration has become less popular.

#### Erythropoietin

Recombinant human erythropoietin is widely used for anemia associated with chronic renal failure, malignancy, and cytotoxic chemotherapy. It has been used in difficult anemia cases in pregnancy. The widest experience is with Jehovah's witnesses. It does not cross the placenta, but carries a risk of hypertension and thrombosis. Currently, its role in the treatment of maternal anemia or to increase the yield in autologous or salvage techniques in pregnancy is not well established. The usual dose is of 50–200 IU/kg subcutaneously two to three times weekly, usually along with supplemental iron. Trials of intravenous iron with

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Treatment option	Indication	Dose	Advantages	Disadvantages
Oral iron	Standard treatment	30–120 mg elemental iron/day until anemia corrected and stores replenished	Cheap Easy to administer	Low bioavailability Poorly tolerated Frequent side effects Often poor compliance
Intravenous iron	Non-compliance or intolerance	Calculated according to body weight and iron deficit	Fast Efficient Ensures compliance Reduced need for blood transfusions	Anaphylactoid reactions (see text)
Intramuscular iron	Non-compliance or intolerance	Calculated according to body weight and iron deficit	Ensures compliance Reduced need for blood transfusions	Pain, abscess, skin pigmentation at injection site Difficult to source product
Erythropoietin	Specialist sub-groups of patients	50–200 IU/kg sc 2–3 times/week	Useful adjunct in difficult cases and where blood transfusion prohibited (e.g., Jehovah's witnesses)	Hypertension Pure red cell aplasia Clinical benefit and cost-effectiveness not well established
Blood transfusion	Emergency treatment in acute hemorrhage	Assessment based on volume lost and hemoglobin	Fast rise in hemoglobin	Risks of infection, contamination, reaction, antibody formation

Table 2.6 Summary of treatment options in iron deficiency

or without recombinant erythropoietin conclude that intravenous iron therapy is the first-line treatment in resistant iron deficiency anemia but that erythropoietin may be considered in severe anemia requiring rapid correction in patients who do not respond to intravenous iron alone. The hemoglobin rise with combination therapy is quicker than with parenteral iron alone. Median duration of therapy in the combined treatment group was 18 days vs. 25 days in the group treated with i.v. iron alone. It has also been used effectively in the setting of postpartum anemia.<sup>4,5</sup> Further assessment of clinical benefit and costeffectiveness is required.

#### **Blood transfusion**

Blood transfusion should be avoided if possible. Transfusion should be reserved for acute hemorrhage. In chronic iron deficiency, transfusion is not indicated. There are circumstances when women with severe iron deficiency are not detected until just prior to delivery and there is not enough time for iron in any form to raise the hemoglobin. Transfusion may be required in these circumstances and this is regrettable as it reflects lack of antenatal surveillance and action.

Transfusion has many known risks, including transmission of viruses and bacteria, immunomodulation and increase of post-operative infections, morbidity, and mortality. The possibility of transmitting prions is an increasing concern. Furthermore, confidential reporting systems indicate that human error resulting in incorrect blood being transfused is still the commonest serious hazard of transfusion.

Top-up transfusions are inappropriate especially in a patient group that are young, essentially well and undergoing a physiological process known to be demanding on iron stores. Transfusion remains the emergency treatment for acute hemorrhage.

To reduce transfusion in this group of patients, anemia prevention strategies during pregnancy and peripartum are required, including antepartum screening, monitoring, and iron supplementation and treatment when necessary, to optimize pre-delivery hemoglobins. There should also be strategies to minimize parturition hemorrhage.

Despite the high incidence and burden of disease associated with iron deficiency, good-quality studies evaluating clinical, maternal, and neonatal effects of iron administration in pregnant women with anemia are lacking.<sup>6</sup> (Tables 2.6, 2.7).

#### **Prevention strategies**

#### Iron supplementation for all

Iron supplementation is a controversial issue in pregnancy. Despite the precarious and often depleted iron stores during and after pregnancy, iron

	Formulations available	Elemental iron content	Prophylactic dose	Treatment dose
Oral iron – tablets Oral iron – syrups Oral iron – over-the- counter preparations	Ferrous fumarate Ferrous sulphate Ferrous sulphate, dried Ferrous gluconate Ferrous fumurate – ferasamal Sodium Feredetate – sytron Spatone – iron rich water straight from source	65 mg/200 mg tablet 60 mg /300 mg tablet 65 mg /200 mg tablet 35 mg /300 mg tablet 45 mg/5 mL 27.5 mg/5 mL 5 mg/10 mL sachet 26% to 40% bioavailability compared to an average 5%–20% from food and 3% –10% from iron pills	1 tablet daily 1 tablet daily 1 tablet daily 2 tablets daily 5 mL 3 x daily 5 mL 3 x daily 1 sachet daily	1 tablet twice daily 1 tablet 2–3 x daily 1 tablet 2–3 x daily 4–6 tablets daily in divided doses 10–20 mL twice daily 10 mL 3 x daily 2 sachets daily
Intravenous iron	Iron dextran (Cosmofer <sup>®</sup> ) – a complex of ferric hydroxide with dextran Iron sucrose (Venofer <sup>®</sup> ) – a complex of ferric hydroxide with sucrose	50 mg of elemental iron/ml 20 mg of elemental iron/ml	N/A	Calculated according to body weight and iron deficit: consult product literature
Intramuscular iron	Iron dextran (Cosmofer <sup>®</sup> ) – a complex of ferric hydroxide with dextran	50 mg of elemental iron/ml	N/A	Calculated according to body weight and iron deficit: consult product literature

Table 2.7         Summary of the iron formulations availa	b	le	e
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supplementation in non-anemic women has not been shown to improve pregnancy outcome.

The Cochrane library database has reviewed the effects of routine oral iron supplementation with or without folic acid during pregnancy. Forty trials with a total of 12 706 women were reviewed. Iron supplementation with or without folic acid does reduce the number of women with a hemoglobin less than 10 g/dL in late pregnancy, at delivery and 6 weeks postpartum, but there are no clear conclusions regarding clinical outcomes for mother, fetus, or neonate.<sup>1</sup>

Routine iron and folic acid supplementation is recommended by international organizations in areas where there is a high prevalence of anemia.

Selective iron supplementation is the approach adopted in most industrialized countries. Assessment of iron stores, usually with a ferritin level in the first trimester, identifies women with low or depleted iron stores and these women are the ones given iron supplements. In the United States the Centers for Diseases Control and Prevention and the American College of Obstetricians and Gynecologists recommend routine iron supplementation with lower doses of elemental iron (30 mg/day) as a primary prevention intervention.

There are several concerns about iron supplementation in iron-replete women. These include hemoconcentration leading to impaired placental circulation and fetal growth, the production of free radicals, and oxidative damage and the risk of iron overload in women with hemochromatosis. Iron-replete women given iron do not increase their hemoglobin levels, and hemoglobin concentration in these women is a reflection on the degree of plasma volume increase. Ineffective plasma volume expansion is predictive of poor pregnancy outcome.

Claims that iron causes a variety of chronic diseases and birth defects have not been substantiated. Accidental ingestion of iron supplements by children is a potential hazard, however. Although most fatal cases involve ingestion of 2-10 g of iron, as little as 1-2 g can cause death in young children. Women should be made aware of this and advised to keep iron tablets well out of the reach of young children.

#### Screening for iron deficiency

In industrialized countries screening of women for iron deficiency anemia is done by measuring the hemoglobin concentration at booking, 28 weeks and again at 36 weeks if the 28-week blood result is abnormal. Practice does vary in different countries.

For many clinicians it is difficult to accept that in well-nourished populations the extra requirements of pregnancy are not met by a normal mixed diet. The hemodilution, which occurs in healthy pregnancy, has encouraged the acceptance of abnormally low hemoglobin levels as being physiological.

It is my personal opinion, based on experience in the UK, that iron store depletion without anemia is not well identified. Women rarely have routine first trimester ferritin measurements, which are then acted on to prevent the development of anemia. By the time an anemia is established in pregnancy, it is more difficult to correct and replenish stores as the iron requirements continue to escalate. Either ferritin screening and selective supplementation needs improvement or universal supplementation should be adopted as a practical and cost effective approach. Controlled trials do not demonstrate any obvious benefit of iron supplementation, but indirect associations such as general maternal wellbeing, reduced fetal placental ratio, preterm deliveries, postpartum hemorrhage, and recovery from blood loss at delivery have not been looked at in an objective manner.

#### Postpartum anemia

Postpartum anemia is defined as a Hb value less than 10 g/dL and an acute or severe anemia corresponds to Hb less than 8 g/dL. The prevalence of postpartum anemia varies from 4% to 27%. In industrialized countries, iron stores are depleted in approximately one-third to one-half of parturients.

The physiological hemodilution that occurs in pregnancy protects the mother from blood loss at delivery, but the 5% of deliveries that have a blood loss greater than 1 litre can result in a symptomatic anemia and an increased risk of blood transfusion.

At the present time, there is no consensus on the management of postpartum anemia, and clinical practice varies. Treatment currently consists of oral iron therapy and blood transfusions.

The Cochrane library database has reviewed the treatment for women with postpartum iron deficiency and concluded that there is some limited evidence of favorable outcomes for treatment of postpartum anemia with erythropoietin. Some of the studies suggest improved lactation with this approach. Laboratory hematological parameters improve, but it is not clear how this relates to clinical outcomes. Six randomized controlled trials were reviewed involving 411 women. All the trials involved erythropoietin. The authors state that further high-quality trials assessing the treatment of post partum anemia with iron supple-

mentation (e.g., intravenous administration of iron) and blood transfusions are needed.<sup>4</sup>

#### Summary – key points

Reference ranges in pregnancy are different from the non-pregnant adult female population, but are rarely quoted on laboratory reports.

Hemoglobin levels fall in pregnancy as a result of a physiological increase in plasma volume that is greater than the pregnancy-associated increase in red cell mass.

Iron stores are exhausted by the end of pregnancy in the majority of women unless iron is given.

Iron deficiency accounts for over 90% of anemia during pregnancy, therefore iron should be the mainstay of therapy.

Anemia affects quality of life and virtually all organs.

Maternal anemia influences mortality, fetal growth, premature death in utero, and fetal programing.

Anemia is screened for in pregnancy at booking, 28weeks and possibly 36 weeks (if the 28-week test result is low). The frequency of testing is dependent on the country of care – France, for example, carries out a hemoglobin level at every pregnancy visit.

Anemia screening is primarily done by measuring the hemoglobin. Further investigation is usually a ferritin level or a trial of iron.

All tests assessing iron status have to be assessed in the light of gestational changes.

Oral iron is the usual first-line treatment in iron deficiency.

Parenteral forms of iron are of use if there is nontolerance or non-compliance of oral iron.

Blood transfusion should not be given as top-ups for iron deficiency anemia.

Peripartum transfusions are often inappropriate (in 2004 one series put the rate at 32%).

The prevalence of postpartum anemia varies between 4% and 27%.

Iron stores are depleted in 33%–50% of parturients in industrialized countries (Fig. 2.1)

### Folate deficiency

#### Epidemiology

Folate deficiency has a prevalence of less than 5% in developed countries and a very low prevalence where



Fig. 2.1 Algorithm summarizing the management of ante-natal hemoglobin level – haematology in pregnancy, chapter in Midwife's Guide to Antenatal Investigations, A Sullivan, L Kean, A Cryer.

there is food fortification with folic acid. Worldwide folate deficiency is far more common and may complicate one-third of pregnancies. It is a reflection of nutritional status.

#### Pathogenesis

Folate is a water-soluble B vitamin. It cannot be synthesized by humans, but is found in a wide variety of food sources, including leafy green vegetables, liver, citrus fruits, nuts, bread, and dairy produce. Folate is heat labile and it is often lost in the cooking process. It is absorbed mainly in the jejunum and then taken up by the liver. Folate stores last several months.

There are various disorders and factors that cause or exacerbate folate deficiency including malabsorption, hemolysis (particularly congenital red cell disorders and hemoglobinopathies), myeloproliferative disorders, and anticonvulsants.

#### Diagnosis

#### Full blood count and blood film

B12 and/or folate deficiency cause a megaloblastic anemia. This is usually suspected by the presence of macrocytic red cells. Megaloblastic erythropoiesis requires a bone marrow to demonstrate large developing red cells with nuclear cytoplasmic asynchrony and giant metamyelocytes. In practice, this is rarely necessary. In pregnancy, interpretation of MCV can be more difficult due to the physiological increase in red cell size and the increased likelihood of an additional iron deficiency anemia that may reduce the MCV. Blood film examination can provide useful diagnostic clues. Features suggestive of a megaloblastic anemia include hyper-segmented neutrophil nuclei (more than five segments), oval macrocytes and mild leukopenia, and thrombocytopenia in severe cases. If iron deficiency co-exists with a megaloblastic anemia, the blood film will be dimorphic with a mixture of large and small red cells (macrocytic and microcytic cells).

#### Hematinic assays

Red cell folate assays give an indication of overall body tissue levels and are better than serum folate levels that are affected by recent diet and fluctuate significantly from day to day. Even so, red cell folate does not have good sensitivity or specificity in pregnancy. Serum and red cell folate levels are lower in smokers. Red cell folate levels may show a slight downward trend in pregnancy, but recover by 6 weeks postpartum. Normal references in pregnancy have not been established and standard adult reference ranges quoted on laboratory reports are not applicable in pregnancy.<sup>7</sup>

#### Homocysteine levels

Homocysteine is the precursor to methionine in the remethylation cycle and increases in B12 or folate deficiency, as both are required as cofactors. This indirect measurement is a sensitive marker for folate deficiency. Throughout pregnancy, plasma homocysteine levels are lower than non-pregnant controls. The lowest levels are in the second trimester but may rise slightly in the third trimester. Normal references in pregnancy have not been established and standard adult reference ranges quoted on laboratory reports are not applicable in pregnancy.<sup>7</sup>

#### Bone marrow

Megaloblastic erythropoiesis is demonstrated by the finding of large erythroblasts and giant abnormally shaped metamyelocytes. Although this is a rapid and reliable method of assessment, the invasive nature of the test means it is rarely done to diagnose folate deficiency as there are several reliable non invasive tests. Bone marrow examination is generally reserved for patients with pancytopenia.

#### Management

#### Prophylaxis of folate deficiency

Mild folate deficiency can be associated with neural tube defects. Folic acid supplementation at a dose of 400  $\mu$ g/day is recommended 3 months prior to conception and throughout the first trimester. Periconceptual folic acid reduces the incidence of neural tube defects by 70%. If women have had a child affected by a neural tube defect, the recommendation is for a higher dose of folic acid periconceptually – at least 5 mg/day.

Folate deficiency is also an independent risk factor for thrombosis.

Folate prophylaxis is required in those with an increased red cell turnover seen in inherited and acquired red cell disorders and also for those on anticonvulsants. Currently, doses of 5 mg/day are used for these indications (Table 2.8).

#### Table 2.8 Folate requirements

	Folate supply	Folate demand/ requirement
Typical Western diet	250 µg/day	
Average daily requirements (non-pregnant)		100 μg/day
Average daily requirements (pregnant)		400 µg/day increased folate metabolism transfer of folate from the mother to the fetus (approximately 800 µg at term).
Puerperium		100 μg/day from 6 weeks postpartum 25 μg/day in breast milk <sup>7</sup>

#### Treatment of folate deficiency

Proven folate deficiency should be treated with folic acid 5 mg three times a day. Dietary history should be taken and advice given. Deficiency of B12 should be excluded as folic acid in these doses can improve the anemia of B12 deficiency, masking the underlying B12 deficiency and thereby potentially exacerbating a neurological deterioration.

#### Treatment of hyperhomocysteinemia

This is based on increasing folate, vitamin B6, and vitamin B12 levels. Doses used in treatment are usually 1–5 mg folic acid, 10 mg vitamin B6, and 0.4–1 mg vitamin B12.

#### **Prevention strategies**

#### Folate food fortification

The addition of folic acid to bread has been considered in government committees for years. The fortification of the nation's food supply with vitamins and minerals dates back to the post-second world war era. The British population at this time had significantly poor nutrition and, as a consequence, diseases due to vitamin deficiencies such as rickets.

In the US, the Food and Drug Administration have made folic acid food fortification mandatory since 1998. All enriched flour, pasta, rice, and other grain products contain 140  $\mu$ g of folic acid per 100 grams. This strategy has reduced the incidence of neural tube defects by 20% from 37.8 per100 000 live births in 1998 to 30.5 per 100 000 live births currently.<sup>8</sup> There are concerns that, in the effort to reduce the neural tube defects, other patient groups may have suffered from the increased levels of folate in the diet. Folic acid supplementation is potentially harmful in B12 deficiency, where it can mask the anemia leading to delayed treatment and risk of neuropsychiatric symptoms such as peripheral neuropathy, mood changes, dementia type syndromes, and posterolateral spinal cord demyelination (subacute combined degeneration of the cord). There are also concerns that high intakes of folic acid may speed up the progression of certain cancers.

A major objection against folic acid fortification in the UK is that it requires mass supplementing the population at large to treat a relatively small target group of young mothers and that this group should be targeted by other means. It is estimated that, by adding folic acid to bread, spina bifida is prevented in 120 babies in the UK every year. For every baby saved, half a million people, male and female, will have to take the added folic acid.

## Implementing periconceptual folic acid supplementation

Neural tube closure is complete 4 weeks after conception, when many women are not aware that they are pregnant and will not have initiated folic acid supplements. Women need to be made aware of the recommendation for folic acid so that they may start it early when attempting to conceive.

#### Summary

Periconceptual folic acid is advised to reduce the incidence of neural tube defects. Ideally, it should be started 3 months prior to conception and continued throughout the first trimester. The dose is 400  $\mu$ g daily unless there has been a previously affected child in which case the dose should be at least 5 mg/daily.

Folate prophylaxis should be considered in at risk groups such as those on anticonvulsants and with chronic hereditary or acquired red cell disorders.

Folate stores can be depleted within months and women need education on diet to ensure recommended folate consumption.
# **B12 deficiency**

# Epidemiology

Deficiency of B12 in pregnancy is rare. It is usually associated with infertility. B12 plays a key role in the development of new tissue; thus women who are deficient may not ovulate, or a fertilized egg may not develop, resulting in miscarriage

The most common cause of B12 deficiency in the general population is pernicious anemia and this is rare in women of childbearing years. Pernicious anemia usually begins after the age of 40 years. Pernicious anemia is due to lack of intrinsic factor that is required to bind B12 in the stomach prior to absorption in the terminal ileum. Other causes of B12 deficiency include ileal resection, partial gastric resection, Crohn's disease, tropical sprue.

Dietary deficiency can occur and is most often seen in vegans who do not eat animal products. Even vegans, however, obtain B12 from bacteria synthesis in the gastrointestinal tract or on legumes and in marmite.

Maternal cobalamin stores are around 3 mg and the daily dietary requirement is approximately 3 ug/day. The developing fetus requires 50 ug/day. It takes about 5 years for a deficiency of B12 to manifest itself clinically because of the stores.<sup>9</sup>

## Pathogenesis

Vitamin B12, also known as cobalamin, is present in animal-derived foodstuffs such as meat, milk and eggs. It is required for methionine synthesis and the conversion of methylmalonyl CoA to succinyl CoA. It is involved in myelin synthesis, protein and DNA synthesis, and fatty acid degradation.

Inadequate B12 levels leads to hyperhomocysteinemia and this in itself can be associated with obstetric complications. Small subsets of women with recurrent miscarriages have been found to have elevated homocysteine and is hoped that treatment with vitamins will reduce levels and prevent pregnancy loss. Low levels of vitamin B12 have also been found in women with children with neural tube defects. It is unknown, however, whether vitamin B12 status affects the incidence of neural tube defects. Meta-analyses have suggested an association, but methodological differences in the studies mean it is difficult to draw this conclusion.

There is a correlation between maternal and neonatal B12 levels. Whilst persistent deficiency can lead to infertility, mild B12 deficiency can be compatible with Table 2.9 Features of B12 and folate deficiency

	Folate deficiency	B12 deficiency
Symptoms	Anemia Very occasionally neuropsychiatric symptoms	Gradually progressive symptoms and signs of anemia Neuropsychiatric symptoms inc. dementia
Signs	Neural tube defects Vascular disease (associated with high levels of homocysteine)	Mild jaundice may be present Glossitis Angular stomatitis purpura due to thrombocytopenia Subacute combined degeneration of the cord Rarely optic atrophy

a normal pregnancy outcome but a low B12 level in the baby especially if the baby is breastfed. This usually becomes apparent at about the age of 6 months when the infant fails to thrive, has regression of development and anemia. Prompt recognition and treatment with B12 will limit neurological damage.

# Diagnosis

See Table 2.9 for clinical signs and symptoms of B12 deficiency.

# Full blood count and blood film

Megaloblastic anemia is the hallmark of B12 deficiency. Blood film examination can be useful. See above, under diagnosis of folate deficiency.

## Hematinic assays

B12 assays give an indication of overall body tissue levels. B12 levels fall in pregnancy, but this is not thought to represent a true tissue deficiency. It is likely to be a consequence of increasing maternal plasma volume and transfer to the fetus. The physiological reduction can be 30%–50% during pregnancy. Levels tend to be lower in smokers. The levels return to normal rapidly after delivery without supplementation. Levels greater than 130 ng/ml may be considered normal but levels with less than 130 ng/ml with macrocytosis and/or neurological symptoms should be considered for B12 treatment.

B12 levels can be falsely lowered by folate deficiency that resolves with folate treatment.

# Homocysteine and methylmalonic acid levels

Homocysteine is the precursor to methionine in the remethylation cycle and increases if B12 and/or folate are deficient as both are required as cofactors. Methylmalonic acid is the precursor for the conversion of methylmalonyl-CoA to succinyl CoA. It increases if there is a deficiency of cobalamin, but it is not affected by folate stores.

This indirect measurement is a sensitive marker for B12 deficiency in the non-pregnant setting. In pregnancy, however, there is a poor correlation between serum B12 and no correlation between urinary methymalonic acid and serum B12. Normal references in pregnancy have not been established and standard adult reference ranges quoted on laboratory reports are not applicable in pregnancy.

## Auto-antibodies

Intrinsic factor antibodies can be helpful in the diagnosis of pernicious anemia if the results are positive. Antibodies to intrinsic factor are found in 70% of patients with pernicious anemia. These antibodies can cross the placenta and cause intrinsic factor deficiency in the fetus. Antiparietal antibodies are non-specific and not very sensitive in diagnosing pernicious anemia. They are no longer recommended.

## Schilling test

This test has been used classically to diagnose pernicious anemia. It is contradicted in pregnancy because of the radiation risks.

## Trial of B12

A therapeutic trial of B12 can confirm the diagnosis. A reticulocytosis occurs within 3–4 days and peaks at day 6–7. The hemoglobin concentration rises within 10 days and usually returns to normal within 8 weeks. Hyper-segmented neutrophils disappear at around 10–14 days.

In patients with severe anemia, hypokalemia can occur as potassium is used in the production of new red cells. This requires monitoring and potassium supplementation if necessary.

Neurological abnormalities are slower to improve and can take months.

## Bone marrow

Megaloblastic erythropoiesis is demonstrated by the finding of large erythroblasts and giant abnormally shaped metamyelocytes. Although this is a rapid and reliable method of assessment, the invasive nature of the test means it rarely done to diagnose B12 deficiency as there are several reliable non-invasive tests. Bone marrow examination is generally reserved for patients with pancytopenia.

## Management

Most mechanisms of B12 deficiency are absorptive and treatment is generally parenteral. Hydroxycobalamin or cyanocobalamin 1 mg is given three times a week for 2 weeks and then every 3 months. Neurological involvement may require higher doses.

Oral B12 can be given if dietary deficiency is the etiology. There is literature supporting the use of high dose cobalamin 1-2 mg/day in patients with impaired intrinsic factor function. There is a second less efficient cobalamin transport system that does not require intrinsic factor. This type of treatment requires very good patient compliance and monitoring of cobalamin levels.

## Dilemmas

# B12 assays are often coupled with folate assays

Often unrequested B12 results are generated because of the coupling of these tests. This can lead to difficulties as the B12 level is almost always low in the pregnant population but the quoted reference range on the laboratory report is that of a non pregnant population. This can lead to many phone calls, referrals, and concerns. Ideally, B12 assays should not be carried out unless a specific request, based on clinical grounds, has been made.

## Summary

B12 deficiency is rare in pregnancy and vitamin B12 levels should be interpreted with caution. B12 levels fall in pregnancy by up to 50% in the third trimester. The reference ranges quoted on reports are for non-pregnant populations.

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## **Cellular changes**

# Inherited red cell disorders

Emma Welch and Josh Wright

# Introduction

The hemoglobinopathies are common genetic disorders. They may result in significant morbidity and mortality, affecting all age groups and genders. This chapter will concentrate on sickle cell disease and thalassemia. The abnormalities of hemoglobin can be of two kinds.

Structural: such as in sickle cell disease, where a single nucleotide change in the  $\beta$ -globin gene leads to the substitution of valine for glutamine at position 6 on the  $\beta$ -globin chain.

Or

*Disorders resulting from unbalanced globin chain production*: the thalassemias, the globin chains produced are structurally normal, but reduced in quantity.

# Ante- and neonatal screening for hemoglobin disorders

# Rationale

Ante-natal screening aims to allow informed reproductive choice by identifying couples, at risk of an affected infant, at an early stage in pregnancy. Options include pre-natal diagnosis with either termination or continuation of affected pregnancies.

It has long been known that morbidity and mortality in children with sickle cell disease is high in the first 5 years of life. The protective effects of high levels of HbF in the newborn decline over the first 4–6 months of life, thereafter much of the mortality is due to pneumococcal septicemia and acute splenic sequestration. Successful antibiotic prophylaxis, vaccination and education programs have all but eliminated these problems<sup>2</sup> and are perhaps the single most important step in the improved survival of sickle cell disease. Since these severe complications are often the presenting features of sickle cell disease, a screening program is required to identify at-risk couples and/or affected newborns.

In  $\beta$  thalassemia major the failure of  $\beta$  globin chain production results in a severe transfusion-dependent anemia, which is manifest as HbF levels reduce in the first few months of life. From this point on, the management of thalassemia is based upon regular transfusion and iron chelation to reduce the risk of organ damage, particularly cardiac. Care of the patient with thalassemia involves collaboration of hematologists, endocrinologists, diabetologists, cardiologists, with occasional input from other specialities such as hepatology. With appropriate care and good compliance, life expectancy may be normal; however, early cardiac death is common in those who do not comply with iron chelation.

Neonatal screening for inherited disease is only undertaken if:

- 1. it is common in a particular population;
- 2. there is a cost-effective reliable screening strategy;
- 3. detection of disease leads to improvements in care/survival.

# NHS sickle and thalassemia screening – an example of a linked ante-natal and neonatal program

The newborn program screens all births in England, with samples collected by heel prick onto a Guthrie card. The regional screening laboratories generally use high performance liquid chromatography (HPLC) to detect the presence of significant variant hemoglobins; second-line confirmation is performed by iso-electric focusing. The program has close links with Child

*The Obstetric Hematology Manual*, ed. Sue Pavord and Beverley Hunt. Published by Cambridge University Press. © Cambridge University Press 2010.

**Fig. 3.1** Distribution of α thalassemia (taken from Barbara Bain, *Hemoglobinopathy Diagnosis*). Reproduced with permission.



Table 3.1 Outcomes for neonatal screening	g
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Hemoglobin results	Diagnostic possibilities
Sickle disorders	
FS	Sickle cell disease 81% Sickle cell β0 thalassemia 17% Sickle HPFH 2%
FSC	Hemoglobin SC disease
FSA HbS> HbA	Sickle <b>β</b> + thalassemia ?transfusion
Other significant disorders	
Fonly	Possible β thalassemia major Prematurity Homozygous HPFH
FE	Homozygous hemoglobin E Hemoglobin E β thalassemia Hemoglobin E HPFH
FA plus Hb Bart's Barts>20% A	Hemoglobin H disease $\alpha$ thalassemia carrier
HPFH, Hereditary persistence	of fetal hemoglobin.

Health, to allow appropriate referral of those requiring further follow-up, and the antenatal laboratories to highlight mothers at risk of an affected child. The main aim of the program is the detection of children with sickling disorders, those at risk of thalassemia major will be highlighted for further investigation (see Table 3.1). With the aim of the antenatal program being choice, there is considerable time pressure to obtain results of the patient and partner and to counsel and arrange antenatal diagnostic procedure if required. Since termination is one option, early diagnosis is crucial and a target for identification of at risk couples is set at 10 weeks.

All couples at risk of having an affected child should be offered pre-natal diagnosis, although many will decline. Prenatal diagnosis is usually by chorionic villous sampling between 10 and 12 weeks' gestation. The fetal loss rate is approximately 1%. Alternatively, amniocentesis may be performed at 15 weeks or more with a miscarriage rate 0.5%–1%.

If prenatal testing results confirm a fetus affected with a major hemoglobin disorder, then a couple need counseling about living with a child affected by hemoglobinopathy. The earlier a diagnosis of a hemoglobinopathy is made, the higher the likelihood that termination is acceptable. In a study examining at prenatal testing in thalassemia amongst British Pakistanis, 70% accepted prenatal diagnosis if offered in the first trimester, with over 90% of pregnancies being terminated. However, if testing was offered in the second trimester, only 40% of couples accepted prenatal testing with fewer affected pregnancies terminated.<sup>1</sup> Antenatal screening for hemoglobin disorders is universal in areas of high prevalence and, where prevalence is low, the selection for screening is on the basis of family origin using an ethnicity questionnaire and red cell indices (see screening algorithms: Figs. 3.2 and 3.3).

## Sickling disorders in pregnancy

The sickling disorders are a group of inherited chronic hemolytic anemias with clinical manifestations occurring as a result of the polymerization of hemoglobin S. The disorders in which sickling occurs are:

 Homozygous sickle cell disease – HbSS. The most common and generally the most severe.

## Compound heterozygous states

- Hemoglobin SC disease
- Hemoglobin Sβ Thalassemia
- Hemoglobin SD Punjab
- Hemoglobin SO Arab
- Hemoglobin SLepore Boston.

Carriage of hemoglobin S is not associated with significant disease and its only significance in pregnancy is in terms of genetic counseling and the need for partner testing.

## Pathogenesis

The clinical manifestations in sickle cell disease are as a result of many interacting pathological processes including:

- polymerization of HbS;
- hemolysis and nitric oxide depletion;
- vaso-occlusion.

## Polymerization of HbS

HbS forms insoluble polymers at low oxygen tensions. The polymers interact with red cell membrane proteins causing progressive damage ultimately leading to the formation of the typical sickled blood cell.

## Hemolysis

Sickle cell disease is characterized by chronic intravascular and extravascular hemolysis, red cell lifespan is shortened from 120 days to 16–20 days. This chronic hemolysis leads to the liberation of free hemoglobin which mops up nitric oxide released from the vascular endothelium. This, in turn, leads to endothelial activation and vasoconstriction, providing ideal conditions for adherence of cellular blood components.

## Vaso-occlusion

The combination of poorly deformable red blood cells, increased viscosity, endothelial activation, and vasoconstriction causes ongoing vaso-occlusion in the microvasculature. The process is further exacerbated by leukocytosis, platelet activation, and increased levels of pro-inflammatory cytokines. Vaso-occlusion leads to both the acute complications of sickle cell disease such as painful crises as well as chronic organ damage, including cardiac and renal impairment seen in older patients.<sup>2,3</sup>

## Contraception

There are few data to guide contraceptive choice for women with sickle cell disorders. What is certain is that the risks of pregnancy in sickle cell disease far outweigh the risks of contraception. The condition is listed as a relative contraindication for some combined oral contraceptive preparations based upon the theoretically greater risk of thromboembolism in sickle cell disease. There is little evidence to support this, particularly with the lower dose pills, which are commonly prescribed. Progesterone-only contraceptives are also safe, indeed limited data suggests they are associated with a favorable change in hematological parameters such as reduction in hemolytic rate and increased HbF. Levonorgestrol implants and intrauterine systems are safe and have a low failure rate. Copper-containing intrauterine devices have been felt to be contraindicated because of infection, and possibly heavier menstrual loss.

In general, sickle patients should be offered the full range of contraceptives available and counseled about the risks and benefits of each method.

# Maternal and fetal complications of pregnancy

Much of the published information on pregnancy in sickle cell disorders relates to homozygous (SS) sickle cell disease. This, and  $S\beta^0$  thalassemia, are, in general, the most severe forms. Patients with milder sickle conditions such as SC disease and  $S\beta^+$  thalassemia can also have complicated pregnancies though the risks are lower. All patients with sickling disorders should be









jointly managed by an obstetrician and a hematologist with interest and experience in these diseases. Since these pregnancies are high risk, patients will require frequent review by the multidisciplinary team.

Twin and multiple birth pregnancies are associated with a higher rate of serious complications.

## Problem-free pregnancies

Despite the potential complications, more than onequarter of these pregnancies occur without problems.

#### Table 3.2

Maternal risks
Increased mortality
Painful crisis
Infection
Chest syndrome
Hypertension & pre eclampsis
Worsening anaemia
Increased cesarian rate
Thrombosis

#### Table 3.3

Fetal/neonatal risks
Miscarriage
Increased perinatal mortality
Intrauterine growth retardation and low birth weight
Premature delivery
Increased cesarean rate

## Maternal mortality

Maternal mortality rates are known to be increased in sickling disorders. Prior to the 1970s, 30%–40% of women with sickle cell disease did not survive pregnancy, prompting obstetricians to question whether the maternal risks of pregnancy were justified. Recent decades have seen a marked improvement, currently mortality has been shown to be 1%–2% in studies from USA and Europe.<sup>4,5</sup> In Africa, maternal mortality rates are between 7% and 12%, probably as a result of a lack of ante-natal care. In Benin, one of the least developed countries in Africa, an active pre-natal program reduced mortality to 1.8%, comparable to the West.<sup>6</sup> Mortality and morbidity rates have been found to be similar in both HbSS and HbSC pregnancies.

In the triennial "Confidential Enquiries into Maternal Deaths in the UK" there were five deaths between 1982 to 1999 associated with sickling conditions. These were due to pneumonia, multi-organ failure following placental abruption in SS disease, acute chest crisis in SS disease, septicemia in SB thalassemia and sickle crisis with multi-organ failure in SC disease. From 1999 to 2005 there were four deaths in women with sickling disorders, but not all directly associated with their hemoglobinopathy. One woman with SC disease died of thromboembolism. another with SS disease and myocardial fibrosis died whilst having a fit and a painful crisis, another woman also died during an epileptic fit, and finally a woman with SC disease died of an amniotic fluid embolism.

The recent NCEPOD report ("A Sickle Crisis?" July 2008) highlights difficulties with death certification and autopsy in sickle cell disorders. Few pathologists have significant experience and non-specialist sickle clinicians are in a similar position. It is recommended that pathologists with appropriate experience perform such autopsies, though there are now national guidelines for autopsy in sickle cell disease. Clinicopathological correlation is crucial, for example, in differentiating sickle chest from pneumonia or whether thrombosis is likely to have been in situ or embolic. Notwithstanding this proviso, the reports into maternal death illustrate the importance of multidisciplinary management and, in several cases, suggest a lack of awareness of the nature and difficulty of sickle cell pregnancy.

These women may have complex co-existing medical problems which can make the management of their pregnancy even more challenging.

## Perinatal mortality

The last 30 years or so have seen marked improvements in fetal outcomes as a consequence of joint obstetric/ hematology care. Peri-natal mortality was reported to be as high as 50%–80% prior to the 1970s. More recent studies in USA and Europe have reported a peri-natal mortality rate of between 1-8%,<sup>5</sup> even in Benin rates are between 12% and 19%.<sup>6</sup> Howard *et al.* reported a peri-natal death rate of 60 per 1000 in the period 1991– 1993 in UK centers, five times higher than the general obstetric population at this time.<sup>5</sup>

## Miscarriage

There is known to be an increased risk of miscarriage in the sickling disorders. This has previously been reported at between 19% and 24%. A recent study in Jamaica found a miscarriage rate of 36% in sickle pregnancies and 10% in controls. This is higher than previously documented. <sup>7</sup>

## Premature deliveries

Since the 1970s it has been known that women with sickling disorders are more likely to have premature deliveries. This has been reported at an average of between 34.1 to 38.5 weeks' gestation. In a recent Jamaican study the mean gestational age was found to be 37.0 weeks compared with 38.7 weeks in controls. In African Americans the mean gestational age was 37 weeks. Infants born to SS mothers are twice as likely to be preterm compared to Hb SC mothers.<sup>7</sup>

## Fetal intrauterine growth retardation

Intrauterine growth retardation is a well-documented complication of sickle cell pregnancy. This is thought to arise as a consequence of maternal anemia and impaired placental function resulting from vaso-occlusion in uteroplacental circulation. Histological studies have shown placental infarction with abruptions and villous edema.

Of infants born to mothers with sickle cell anemia, 77% have a birth weight below the 50th centile, with 21% below the 10th centile. Neonates born to mothers with Hb SS disease are significantly smaller than babies born to mothers with Hb SC disease.<sup>4–7</sup>

## Infections

Patients with sickle cell disease have a complex immune defect. In addition to hyposplenism, there are data suggesting subtle changes in leukocyte function, opsonization and complement pathways. Urinary tract infections are increased in normal pregnancies and can lead to pyelonephritis and premature labor. There may be a further increase in risk in sickle pregnancy.

Other common sites of infection include chest and bone. Common pathogens include *Pneumococcus, Salmonella, E. Coli and Mycoplasma*. Infection is a common precipitant of painful crises.

## Hypertension

Pregnancy-induced hypertension and pre-eclampsia complicate one-third of pregnancies in sickle cell disease. There is an association between hypertension with proteinuria and simultaneous sickling complications.<sup>4</sup>

## Thrombotic risk

Pregnancy labor and the puerperium are associated with complex changes of the hemostatic enzyme systems. Thrombotic risk is increased in normal pregnancy. To further complicate this situation, it has long been recognized that steady state sickle cell disease is associated with evidence of platelet and coagulation activation. Furthermore, changes in the levels of the naturally occurring anticoagulants and endothelial activation also have the potential to increase the risk of thrombosis in sickle cell pregnancy.

Despite these biochemical changes, the role of thrombosis in sickle cell disease has been difficult to establish. The pregnant patient with sickle cell disease should be regarded as at high risk of venous thromboembolism. Pulmonary embolism is difficult to diagnose in this setting, but should be considered within the differential of a patient presenting with dyspnea and chest pain.

# General management of sickle cell pregnancy

## Preconception

- Discuss maternal and fetal risks of pregnancy and counsel about availability of pre-natal diagnosis.
- Partner screening.
- Folic acid supplements.
- Review medications, with assessment of risks vs. benefits for individual drugs. Stop hydroxycarbamide 3 months before conception and discuss potential need for transfusion.

## At booking

- Discussion of pregnancy and associated risks.
- Early involvement of a hematologist with expertise in the hemoglobinopathies.
- Review by an obstetrician experienced in the care of women with hemoglobinopathies.

- Early booking appointment and establishment of a planned schedule of care between obstetrician and hematologist.
- FBC, Hb electrophoresis/ HPLC, U&E plus full red cell phenotype. Check ferritin and folate status.
- Ensure partner screening.
- Discussion of pre-natal diagnosis, if appropriate
- Folic acid 5 mg daily, continued throughout pregnancy.
- Take full history particularly frequency and management of crises, transfusions, previous pregnancies, evidence of chronic organ damage, which may contribute to risk.
- Review medication penicillin, folic acid, hydroxycarbamide, iron chelators, analgesic usage.
- Stress the importance of early presentation if unwell.
- Education about the signs and symptoms of infection.
- Ante-natal screening for Hepatitis B, C and HIV, given likely transfusion history.
- Echocardiogram to assess left ventricular function and pulmonary pressures if evidence of iron overload or cardiorespiratory symptoms/signs.
- Ultrasound to assess viability and confirm gestation.

# Throughout pregnancy

- Continued health education.
- Continue folic acid 5 mg.
- Iron supplementation if ferritin low.
- Regular FBC checks every 4 weeks and U&E every 8 weeks.
- Serial ultrasound scans from 20 weeks to assess fetal growth/placental function.
- Monthly mid-stream urine culture.
- Low threshold for admission especially if limb, bone, abdominal, chest pain after 28 weeks.
- 24-hour admission policy and contact numbers.
- Appropriate plan for use of analgesia in pregnancy. Avoid non-steroidal anti-inflammatory drugs after 34 weeks.
- Involve obstetric anesthetist to discuss management in labor.
- Prompt treatment of emesis to avoid dehydration.
- Transfuse only after discussion with a hematologist.

- Watch closely for features of acute chest syndrome. Seek advice from obstetrician, hematologist and anesthetist. Chest crises are most likely to occur during late third trimester and postpartum.
- If admitted during pregnancy, use low molecular weight heparin for thrombopropylaxis and compression stockings.

# Painful crisis in pregnancy

- The majority of severe crises occur in the third trimester often, at the time of delivery, often the complications of sickle cell disease precipitate labor rather than labor precipitating sickling complications.
- 30%–80% of women with Hb SS pregnancies have crises.
- 30% of women with HbSC have crises in pregnancy. SC disease is generally a milder condition when not pregnant but patients may present with pain and other sickle complications in the third trimester.
- Labor and early puerperium are risk periods for development of pain. This becomes more likely in the presence of infection, dehydration or acidosis.
- Sickle patients have a renal concentrating defect from early childhood and pass large volumes of dilute urine. Attention to hydration status is therefore crucial.
- Crises in pregnancy may present as abdominal pain which can be difficult to distinguish from obstetric complications.
- The risk of thromboembolism increases in pregnancy.

## Management

- Admit to obstetric or hematology ward as per local protocol. In the final trimester with the high risk of obstetric problems, the obstetric setting is most appropriate.
- Inform relevant staff (hematologist/obstetrician).
- Ensure rest and warmth.
- Give oxygen if hypoxic on monitoring of O<sub>2</sub> saturation.
- Ensure adequate hydration oral or intravenous fluids 3–4 liters. Strict fluid balance essential.
- Pain relief take account of previous analgesic history. Use paracetamol, non-steroidals if

pregnancy less than 34 weeks but subcutaneous opiates are often necessary.

- Pethidine is not recommended for the treatment of sickle pain. Morpine, diamorphine or oxycodone are appropriate but intravenous use should be discouraged.
- Use linear analog scale to assess pain control. Patient-controlled analgesia or subcutaneous pumps are occasionally required.
- Regular assessment of sedation and conscious level if on strong opiates. The recent NCEPOD report highlights deficiencies in the care and monitoring of patients on opiate analgesics.
- Investigations FBC, reticulocytes, U&Es, group and screen, pulse oximetry and arterial blood gases if appropriate.
- Microbiology urine culture, blood cultures and throat swabs.
- Consider chest X-ray if chest involvement.
- Antibiotics are not routinely required unless evidence of infection, low grade fever <38 °C is common in painful crisis even in the absence of infection.
- Low molecular weight heparin thromboprophylaxis and compression stockings.
- Discuss indication for transfusion or exchange transfusion with hematologist.
- Chest physiotherapy including incentive spirometry will reduce the risk of a subsequent chest syndrome in patients with rib pain.

# Acute chest syndrome (ACS)

This condition remains one of the most common causes of death in sickle cell disease. It is characterized by pulmonary infiltrates on the chest X-ray, chest pain, shortness of breath and fever. Not surprisingly, those unfamiliar with sickle cell disease frequently diagnose a chest infection and manage with antibiotics alone. Despite the radiological appearances (which may lag behind clinical signs), this is predominantly a vascular event and responds well to blood transfusion.

# Management of chest crises in pregnancy

- Inform consultant obstetric and hematology staff on admission.
- Continuous monitoring of O<sub>2</sub> saturation and supplemental oxygen.

- Investigations CXR, blood gases on air, pulse oximetry, FBC, reticulocytes.
- Broad spectrum antibiotics should include a macrolide.
- Bronchodilators.
- iv fluids.
- Transfusion, either exchange or top up, should be considered in hypoxemia (SaO<sub>2</sub><5% lower than patient's steady-state level), deteriorating clinical status or progressive multi-lobe involvement.
- The timing of transfusion rather than the volume is critical (i.e. early in disease course).

The key to appropriate transfusion in ACS is the timing rather than the volume of blood used or the target %HbS. In most cases early top-up or partial exchange transfusion is the optimal approach. In the United States, The National ACS study group showed simple top-up transfusion was performed in 68% of patients using an average of 3.2 units of packed cells. This appeared to be as effective as an exchange transfusion. In the absence of a randomized controlled trial a sensible approach is to use simple top-up transfusion, aiming for a hemoglobin of no more than 9-10 g/dL, in patients with relatively mild episodes or those with severe anemia, e.g. <5 g/dL and to use exchange transfusion in the more severe cases. Again, the timing of exchange transfusion is crucial. It is preferable to perform a limited manual partial exchange urgently rather than waiting for several hours or overnight until staff are available to perform an automated exchange.

## Labor and delivery

- Aim to achieve a vaginal delivery, no need to schedule delivery.
- Keep warm.
- Maintain good hydration commence iv fluids at time of admission in labor at rate 1 L/8 hours to maintain good urine output. Strict fluid balance.
- Check full blood count, blood group, and antibody screen.
- Continuous pulse oximetry. May need supplemental oxygen.
- Continuous CTG monitoring throughout labor
- Epidural analgesia is pain relief of choice.
- Avoid prolonged labor, not more than 12 hours and prolonged rupture of membranes, which increase the risk of infection and dehydration.

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- If operative delivery necessary, discuss with hematologist. Regional (rather than general) anesthesia reduces the likelihood of sickle crisis and post-op acute chest syndrome.
- Thromboprophylaxis with low molecular weight heparin and graduated compression stockings.
- Alert pediatricians.

# Postpartum

## Baby

• Monitor for signs of respiratory depression if opiates have been used intrapartum.

## Mother

- Maintain hydration and oxygenation. Watch for signs of painful or chest crises.
- 4-hourly observations for 24 hours post-delivery.
- Low threshold for the use of antibiotics particularly after operative delivery.
- Check FBC day 1 post-delivery.
- Mobilize early and continue thromboprophylaxis until discharge.
- No contraindication to breastfeeding.
- Give appropriate contraceptive advice prior to discharge.
- Ensure patient has follow-up both for post-natal check and with hemoglobinopathy team.

# Dilemmas

# **Operative deliveries**

To section or not? The management of labor in patients with sickling disorders varies widely from unit to unit. There are risks and benefits of planned vs. spontaneous labor. Many units offer a planned induction at 38 weeks. There is, however, no evidence to support this approach and in general spontaneous labor is preferred. Induction leads to a higher cesarean section rate, with its own complications plus the implication that future pregnancies will need a trial of scar and be associated with a risk of subsequent operative delivery. Elective Cesarean is not usually advised in sickling disorders. They are associated with a 30% increase in maternal morbidity, significantly higher than when emergency section is performed in spontaneous labor for obstetric reasons. If operative delivery is felt necessary then the patient's condition should be optimized preanesthetic. Particular attention needs to be paid to hydration and oxygenation. The procedure may be undertaken without transfusion support. However, if felt necessary, then simple top-up transfusion is adequate.

Post-operative chest physiotherapy including incentive spirometry may reduce the risk of chest syndrome.

# Hydroxycarbamide

Many patients with sickle cell disease are routinely managed with hydroxycarbamide. This agent induces hemoglobin F and also acts as a nitrous oxide donor. Hydroxycarbamide has been found to reduce the occurrence of painful and chest crises and may also prolong life. It has been found to be teratogenic in animal studies. Males and females on hydroxycarbamide should therefore be counseled about the importance of using contraception whilst on the drug. They should be asked to stop hydroxycarbamide at least 3 months before trying to conceive. However, case series have been published showing that hydroxycarbamide can be taken throughout pregnancy without complication. If conception occurs accidentally whilst on hydroxycarbamide, the drug should be stopped.

# Prophylactic transfusion

The role of transfusion in sickle cell disease in pregnancy is controversial though it is generally accepted that transfusion is not required as part of the management of uncomplicated sickle pregnancy.

The rationale is to reduce the amount of circulating hemoglobin S thereby improving oxygenation and placental function. A single randomized control trial in 1980s concluded that routine prophylactic transfusion from the onset of pregnancy does not alter the outcome for the fetus; however, the numbers involved in this study are small and it should therefore be interpreted with caution.<sup>8</sup> A retrospective study of the use of red cell transfusion in the UK noted a trend towards fewer sickling complications in third trimester and puerperium.<sup>4</sup> There was no evidence that transfusion improved fetal growth or outcome. A further study compared a restricted transfusion policy (not transfusing blood unless the hemoglobin fell below 6 g/dl) vs. a prophylactic transfusion policy (transfusing if hemoglobin fell below 10 g/dl). They found similar rates of crises and other complications in both groups.

The risk of alloimmunization was found to be 10%–20%, this rate can be reduced but not completely abolished by the use of phenotypically matched blood.<sup>4</sup> These antibodies have potential to produce hemolytic disease of the newborn and may cause difficulty in provision of compatible units for future transfusions. All women should have a group and full phenotype at booking visit to screen for antibodies present.

In conclusion, transfusion should be reserved for high-risk pregnancies. This would include twin pregnancies, women with previous poor obstetric history, chest crises, recurrent pain, and severe anemia.

## Summary

The key to successful outcome of sickle pregnancy lies in the close interaction between obstetric teams and hematologists. Close monitoring, awareness of risks and complications is essential. The majority of pregnancies have a successful outcome. Where possible, pregnancy should be allowed to proceed with minimal intervention there being little evidence that transfusion or operative delivery are of any benefit in the majority of cases.

## Thalassemia and pregnancy

In the past, thalassemia major was associated with a high mortality rate in the first decade of life. Over recent years outcomes have improved, with children surviving into adult life in good health, leading normal lives, and able to have families of their own.

The mainstay of management is regular transfusions with concurrent iron chelation to reduce iron overload. The most common cause of death is cardiac failure due to siderosis, although iron overload can also occur in the endocrine glands, pancreas, and liver. Many patients develop growth failure, central hypogonadism, and diabetes.

## Pathogenesis

The thalassemias are almost always autosomal recessive disorders caused by mutations or deletions in the  $\alpha$  or  $\beta$  globin genes leading to diminished or absent production of one or more globin chains. The other globin chain is produced in relative excess and precipitates within erythroid precursors causing chronic hemolysis and ineffective erythropoiesis.

## $\alpha$ thalassemia

Four  $\alpha$  globin genes are inherited as a pair from each parent. A normal individual is annotated thus  $(\alpha\alpha/\alpha\alpha)$ . The more  $\alpha$  genes deleted, the more severe the condition (Table 3.4).

Alpha thalassemias are the commonest single gene disorders worldwide. Approximate frequencies and types of carriage are illustrated in Fig. 3.1.

# $\alpha$ thalassemia carrier ( $\alpha \alpha$ /-), ( $\alpha$ -/ $\alpha$ -) or (- $\alpha$ / $\alpha \alpha$ )

Carriers of  $\alpha$  thalassemia are asymptomatic and are usually first detected at ante natal screening. Their hemoglobin is in the normal range or minimally decreased with low mean cell volume (MCV) and mean cell hemoglobin (MCH).

## Hemoglobin H disease $(-/-\alpha)$

Those affected by hemoglobin H disease have three non-functioning alpha genes. The hemoglobin is commonly in the range 8–9 g/dl with microcytic, hypochromic red cell indices, and splenomegaly. HbH disease is a mild form of thalassemia intermedia, those affected rarely need transfusion. The anemia may worsen in pregnancy and with infection. The condition is diagnosed by the presence of an HbH peak on the HPLC trace and typical "Golf ball" cells on supravital staining.

## Hemoglobin Bart's hydrops (–/–)

A complete absence of  $\alpha$  chains is incompatible with life and results in the unopposed  $\gamma$  chains forming tetramers called hemoglobin Bart's. This is a common cause of stillbirth in areas with a high frequency of  $(-/\alpha\alpha)$  such as SE Asia and the Eastern Mediterranean. The fetus is stillborn at 34–40 weeks or dies soon after birth. The Hb Bart's binds oxygen poorly impairing tissue oxygenation. The fetus appears edematous and jaundiced with massive hepatosplenomegaly and ascites.

Couples at risk of a child with Bart's Hydrops should be picked up by ante-natal screening programs and offered ante-natal diagnosis. If found to have an affected infant, termination should be offered.

Table 3.4	Effects of	alpha	gene	deletion
Table 3.4	Effects of	<sup>:</sup> alpha	gene	deletior

Genotpye	Outcome	Effect
<b>α</b> α/ <b>α</b> α	Normal	Normal
-α/αα	Heterozygous α+ thalassemia trait	Frequently silent or slight decrease in MCV/MCH
-α/-α	Homozygous $\alpha$ +	MCH<25 pg
<b>-/α</b> α	Heterozygous α0 thalassemia trait	MCH<25 pg
-/-α	Hemoglobin H disease	Hb 8–9 g/dL
-/-	Hemoglobin Bart's Hydrops	Death in utero
MCV, mean cell volume, MCH, mean cell hemoglobin.		

# β Thalassemia carrier

Asymptomatic and diagnosed at ante-natal screening or during investigation of microcytic, hypochromic indices. The hemoglobin is rarely less than 10 g/dl. Hemoglobin A2 is raised. Iron replacement need not be given unless a deficiency state is proven by reduced serum ferritin.

# β Thalassemia intermedia

A range of interacting genetic lesions may lead to a thalassemic phenotype of varying severity. Some will be asymptomatic whilst others require intermittent transfusion. The hemoglobin is usually 10-12 g/dl, but can be as low as 5-6 g/dl in severe forms. Hepatosplenomegaly may be present.

## β Thalassemia major

This is the inheritance of severe abnormalities in both  $\beta$  globin genes. Onset of symptoms of anemia occurs as fetal hemoglobin levels decline in the first few months of life. Patients are transfusion dependent. If not treated with transfusion, extramedullary hematopoeisis occurs leading to characteristic skeletal deformities and hepatosplenomegaly. Morbidity and mortality in this condition is now caused by transfusional iron overload (Table 3.5).

## Management

Carriers of  $\alpha$  and  $\beta$  thalassemia and those with hemoglobin H disease or other mild forms of thalassemia intermedia can be managed as a normal pregnancy. Anemia may worsen during pregnancy because of the normal physiological changes. Oral iron supplements should be given where there is a reduced Table 3.5 Effects of iron overload

# Common problems due to iron overload with relevance to pregnancy

- Central hypogonadism- may require referral to assisted conception unit
- Diabetes or impaired glucose tolerance
- Cardiac siderosis
- Small stature
- endocrine dysfunction, for example, hypothyroidism

ferritin, but not for microcytosis and hypochromia alone.

It is important to identify couples at risk of a baby affected by hemoglobin Bart's. This should be picked up by the ante-natal screening program and parents offered counseling, education and pre-natal diagnosis. The mother may also develop "mirror syndrome" a severe pre-eclampsia, and delivery of a hydropic fetus and placenta can cause obstetric difficulties.

 $\beta$  thalassemia major and severe forms of intermedia are clinically significant in pregnancy and require careful multidisciplinary management.

## Fertility

Because of the effects of iron overload, transfused patients often have hypogonadotrophic hypogonadism, many patients are on hormone replacement therapies but this does not restore fertility. The Standards for the Clinical Care of Children and Adults with Thalassemia in the UK  $^{9,10}$  state that:

- Iron chelation should be optimized from childhood to reduce the risk of infertility.
- Where there is clinical or biochemical evidence of pubertal or hormone disturbance, management by an endocrinologist is required.
- Early referral for discussion of fertility issues should be offered. This should be to a clinic experienced in treating patients with thalassemia.
- Couples may be infertile for a number of reasons including those unrelated to thalassemia and a range of investigations may be necessary.
- Induction of ovulation or spermatogenesis may be required for patients with central hypogonadism. This needs to be done in a center with experience of such patients to minimize the risk of hyperstimulation syndrome and multiple births.
- It is imperative that a couple are given the opportunity to discuss the risk of having a child

#### Risks to women with thalassemia in pregnancy

- Pregnancy causes a 30%–50% increase in cardiac output, thus patients with significant cardiac siderosis are at risk of decompensation and death
- Transfusion requirements increase in pregnancy
- Risk of accelerating pre-existing diabetic retinopathy or nephropathy
- Worsening osteoporosis
- High incidence of gestational diabetes
- High incidence of operative delivery

Table 3.6 Risks to women of thalassemia in pregnancy

with thalassemia or other major hemoglobin disorder, e.g. sickle cell conditions if partner is a sickle carrier. The partner must be tested and if they carry thalassemia or variant hemoglobin counseled about options and offered pre-natal diagnosis.

## Preconception

Careful preassessment of a woman with thalassemia considering pregnancy is required.

- Full cardiology assessment including echocardiogram, T2\*MRI quantification of cardiac iron (where available) as well as assessment by a cardiologist
- Endocrinological assessment including glucose tolerance test. Optimize diabetic control if known to be diabetic
- Iron chelation should be optimized before pregnancy considered. For well-controlled patients with evidence of normal pituitary function, it may be reasonable to stop chelation for natural conception.
- Folic acid should be started prior to conception until the end of pregnancy.
- Review rubella status, HIV, Hepatitis C status prior to pregnancy.
- Discuss smoking and alcohol consumption.
- Partner screening and risk assessment for thalassemia
- Review medication ACE inhibitors should be changed (Tables 3.6, 3.7).

### **Management of pregnancy**

- Early booking appointment.
- FBC, group and save and full antibody screen at booking.
- U&Es and LFTS at booking.

#### Risks to the baby

- Possibility of a major hemoglobin disorder (depending on partner carrier status)
- Diabetes is associated with a four fold increased risk of fetal anomaly and threefold increased risk of peri-natal mortality
- Increased risk of chromosomal non-dysjunction, related to maternal iron overload
- Increased risks of multiple pregnancies secondary to fertility procedures
- Sudden maternal death in late pregnancy

Table 3.7 Risks to the baby of thalassemia

- Regular FBCs throughout pregnancy. Transfusion requirements are likely to increase.
- Close involvement by obstetrician (experienced in hemoglobinopathy), consultant hematologist and cardiologist.
- Review all medications.
- Start folic acid before pregnancy and continue throughout.
- Continue penicillin prophylaxis (if splenectomized) throughout pregnancy.
- Calcium and vitamin D supplements are advisable if bone density already reduced prior to pregnancy.
- Stop ACE inhibitors and bisphosphonates.
- Stop iron chelators prior to ovarian stimulation and pregnancy. Rate of iron accumulation during pregnancy is surprisingly low.
- Increased risk of thrombosis in splenectomized patients.
- Thromboprophylaxis whilst an inpatient and during labor and puerperium.
- Discuss mode of delivery in advance consider cardiac problems and possible bony abnormalities of pelvis to assess suitability for vaginal delivery.
- Discuss contraception post-delivery.

## Medical problems in pregnancy

### **Bone problems**

- Transfusion-dependent thalassemics show very high rates of osteoporosis and osteopenia which may be exacerbated by pregnancy.
- During pregnancy bisphosphonates need to be stopped but vitamin D and calcium supplements may be continued.
- Patients should be advised against smoking and alcohol and encouraged to take regular exercise.

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• Patients with back pain should be told this may worsen in pregnancy and appropriate analgesia discussed.

### Liver complications

- Common problem in thalassemia due to viral infections, iron overload, biliary problems secondary to gallstones, and drug toxicity.
- In North America 14% of the thalassemic population are hepatitis C RNA positive.
- Vertical transmission of hepatitis C does occur but is rare – upper estimates are 6%, but this increases to 14%–17% where there is co-infection with HIV.

## **Endocrine problems**

- The incidence of Type 1 Diabetes Mellitus in thalassemia major is 6%–8% these patients need to be managed as per standard recommendations for diabetes in pregnancy.
- Glucose tolerance should be assessed throughout pregnancy.
- Treated hypothyroidism is present in 9% but up to 75% have evidence of thyroid dysfunction.
- Any patient with endocrine dysfunction should be regularly assessed by a consultant endocrinologist.

# Dilemmas

## Iron chelation during pregnancy

- Iron chelation should be maximized prior to pregnancy. Where possible, a low cardiac iron load should be shown by T2\*MR.
- It is advised that chelation agents are withheld during pregnancy.
- There are case reports of women receiving iron chelators throughout pregnancy without teratogenic effects. Recommencement of chelation could be considered for patients felt to be at high risk of cardiac death.
- Vitamin C should also be stopped due to a risk of precipitating cardiac damage.
- Serum ferritin levels may remain stable in pregnancy, with no more than a 10% increase after delivery despite cessation of iron chelation. This may be due to the hemodilution effect or fetal consumption of iron.
- Women should be encouraged to resume iron chelation after delivery.

• Desferrioxamine is safe to use whilst breast feeding. Deferiprone and deferasirox should not be used until breastfeeding ceases.

### Transfusion

- Transfusion requirements will increase in pregnancy.
- Patients who are not normally transfusion dependent, e.g. β thalassemia intermedia or hemoglobin H disease may require transfusion in pregnancy or post-delivery.
- Maintain hemoglobin over 10 g/dl in thalassemia major.
- It is reasonable to observe patients with thalassemia intermedia, provided there is no cardiac dysfunction and serial ultrasound shows normal fetal growth, transfusion may be avoided.
- Alloimmunization to minor blood antigens, which may lead to increased difficulties in cross-matching blood and risk of hemolytic disease of the newborn in the fetus.
- Risk of transmission of blood-borne viral infections via transfusion.

## Delivery

- Mode of delivery needs to take account of pre-existing cardiac problems.
- There is a high rate of Cesarean section in thalassemic patients. In the majority of patients this is due to cephalo-pelvic disproportion resulting from the small stature of thalassemic patients and normal growth of the fetus.
- In the absence of contraindications, labor may proceed normally.

## **Cardiac problems**

- The most common cause of death in thalassemic patients is cardiac failure secondary to iron deposition in the myocardium.
- Patients with poor compliance with iron chelators and a ferritin above 2500 µg/l are more likely to develop cardiac problems, pregnancy should be delayed in such patients until chelation status is acceptable.
- Cardiac arrythmias, cardiac failure and sudden death can occur in a previously well patient and those without grossly elevated ferritins.
- Cardiac T2\* MRI is the investigation of choice to quantify cardiac iron and assess myocardial

function, though is only available in a few UK centers. Cardiac T2\* levels less than 20 milliseconds correlate with left ventricular dysfunction. Further aggressive chelation prior to pregnancy should be undertaken in such cases.

- Cardiovascular changes in pregnancy, anemia, increase in plasma volume and increased cardiac output can aggravate or precipitate cardiac failure.
- Severely impaired left ventricular function during periods of stress maybe evident long before the onset of cardiac failure and is a contraindication to pregnancy.

## Summary

Multidisciplinary care is essential to the management of this complex group of patients.

Prior to conception efforts need to be made to maximize chelation and assess organ and endocrine function so that the patient can be counseled accurately.

From assessment of risk (e.g. cardiac, endocrine) through to induction of ovulation and management of established pregnancy it is vital to maintain good communication between the various specialist teams.

## **Red cell membrane disorders**

Hereditary spherocytosis refers to a group of disorders characterized by spherical erythrocytes of increased osmotic fragility. There are a variety of molecular lesions which are typically inherited in an autosomal dominant manner and result in defects in the protein structure and interaction between various red cell membrane components, leading to loss of membrane surface area and reduced deformability. These cells have a reduced lifespan, resulting in a hemolytic anemia. Hereditary spherocytosis occurs in all ethnic and racial groups and there is considerable heterogeneity reflecting the wide range of molecular lesions. Diagnosis is made by the typical blood film appearances, most patients have anemia, with hemoglobin between 9-12 g/dL associated with a reticulocytosis and other biochemical evidence of hemolysis, such as reduced haptoglobin, raised LDH and bilirubin. Approximately 10% of patients may have a more severe anemia (6-8 g/dL). The diagnosis can be confirmed by an incubated osmotic fragility test or flow cytometry. Many patients lead normal lives and indeed the diagnosis may be an incidental finding.

For the most part, there are few implications for pregnancy and the outcome is good. Some experience

anemia greater would be expected from the expanded plasma volume due to higher hemolytic rate. Folate requirements are increased in any hemolytic anemia and patients known to have HS should be encouraged to take pre-conception folic acid supplements and continue these through their pregnancy. In the more severe cases transfusion may be required on an intermittent basis.

A cord sample should be taken for hemoglobin and bilirubin levels. Neonates who have inherited HS themselves may require transfusion, but it is worthy of note that the degree of anemia at this stage does not correlate with the hemoglobin level in later life.

Elliptocytosis has no significant implications for pregnancy, though folate supplementation throughout is prudent. Hereditary pyropoikilocytosis is a related condition and is associated with typical blood film appearances and a more severe degree of anemia. In addition to folate supplementation, such patients may require transfusion. The need for intervention with transfusion in all red cell membrane disorders should be judged individually and based upon hemoglobin level, symptoms and assessments of fetal wellbeing.

# Glucose-6-phosphate dehydrogenase deficiency

Deficiencies in red cell enzymes often lead to shortened red cell lifespan. G6PD deficiency was the first of such abnormalities to be discovered and is the most common. The presence of G6PD is crucial to protect the red cell from oxidative damage. The deficiency is X linked. Despite the mode of inheritance, females may have clinical manifestations and be susceptible to hemolysis. Because of X chromosome inactivation, heterozygotes have two populations of red cells, one normal and one G6PD deficient.

The prevalence of G6PD deficiency varies considerably being rare in Northern European populations to frequencies of 20% in parts of Southern Europe, Africa, and Asia. A large number of mutations within the gene for G6PD may result in a deficient phenotype. The majority cause mild deficiency and only result in significant hemolysis in "stress" situations such as infection and as a complication of certain drugs. Rarely individuals have a more severe chronic non-spherocytic hemolytic anemia. Hemolysis is characterized by the presence of denatured hemoglobin within the red cell, which can be seen on supravital staining (Heinz bodies). Diagnosis may be made using G6PD deficiency screening tests available in the majority of hematology laboratories or by direct quantification, which is available in certain centers and used to confirm positive screens. For the most part, mild deficiency has little effect on the pregnancy.

## Antenatal management

- Determine history of hemolytic episodes and precipitating factors.
- FBC, blood film for characteristic red cell changes, serum folate, G6PD assay if not previously tested. Reticulocyte count, LDH, and bilirubin. Heinz body preparation is helpful during active hemolysis.
- Advise against oxidant drugs (see BNF) and consumption of fresh or lightly cooked broad (fava) beans. If a drug is felt to be indicated and there is no alternative, then the risks and benefits must be taken into account. G6PD deficiency is heterogenous, patients with a significant history of hemolytic crises or chronic hemolysis are more likely to react adversely than those with a milder phenotype.
- Check folate status and prescribe folic acid 5 mg daily for all patients with chronic hemolysis.
- Patients should be made aware of the symptoms and signs of acute hemolytic anemia. Hemolysis is usually self-limiting, as reticulocytes have higher enzyme activity. However, red cell transfusion may be required in severe cases. Occasionally, renal failure can complicate acute severe intravascular hemolysis and should be treated as required.
- Caution with all drugs prescribed to the mother to ensure there is no associated risk of hemolysis.

# Management of the neonate

Neonatal erythrocytes have an increased susceptibility to oxidative hemolysis. Immaturity of hepatic enzyme systems may enhance the risk of jaundice, G6PD deficiency has rarely been described as a cause of Kernicterus. Hemolysis is usually self limiting but exchange transfusion may be required for those cases with severe jaundice.

- A cord sample should be taken at birth for hemoglobin and bilirubin. G6PD assays should also be performed, although this may be difficult to interpret.
- Phytomenadione (a fat soluble preparation of vitamin K) can be administered to the baby in accordance with normal procedures. (Water soluble preparations of the vitamin K should be avoided in view of the possible risk of hemolysis in newborns, though the evidence for this is conflicting.)
- Observe over the first 4 days of life for jaundice. Hemolysis is usually self limiting but exchange transfusion using G6PD screened blood may be required in selected cases.

# **Breast feeding**

• The mother should be advised that certain drugs may be excreted in breast milk and may trigger hemolysis in a G6PD deficient baby.

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Section 1 Chapter

## **Cellular changes**

# Maternal autoimmune cytopenias

Hamish Lyall and Bethan Myers



Autoimmune conditions are characterized by the production of antibodies against self-antigens (autoantibodies). Since these conditions often occur during the second and third decades of life, they may occur during, or predating pregnancy. In these circumstances, the additional considerations of both the effect of pregnancy on the disease, and the disease (and its treatment) on the pregnancy need to be taken into account.

It is recognized that pregnancy may influence the course of maternal autoimmune diseases. This can result in remissions, relapses, or new presentations of these disorders. The pathogenesis of this phenomenon is likely to be related to the hormonal and complex immunological changes that occur during pregnancy. Immunological changes in pregnancy are necessary to prevent rejection of the fetus, which expresses both paternal as well as maternal antigens. Placental immunology, and modulation of the systemic immune response, have been identified as important mechanisms of this immune tolerance. It is probable that these features have a significant influence on autoimmune hematological disorders that occur during pregnancy.

In this chapter, three auto-immune hematological conditions that may complicate pregnancy: immune/idiopathic thrombocytopenic purpura (ITP), autoimmune hemolytic anemia (AIHA), and autoimmune neutropenia (AIN) are discussed. They are characterized by the development of an autoantibody specific for a surface antigen on the platelet, erythrocyte, or neutrophil. Premature cellular destruction occurs, by reticuloendothelial phagocytosis, T lymphocyte cytotoxicity, or complement mediated cell lysis. To date, the relationship between these immune mechanisms and the immunological changes in pregnancy is not fully understood.

Cytopenias occur when the enhanced clearance of the platelet, erythrocyte or neutrophil from the peripheral blood is greater than the bone marrow's ability to produce new cells. ITP is by far the most frequently seen condition. AIN and AIHA rarely occur in pregnancy and few cases are reported in published literature. The three conditions usually occur in isolation but occasionally may be seen together, e.g. Evans syndrome (ITP and AIHA).

About two-thirds of cases present prior to pregnancy with the diagnosis already established, but the remaining third present during pregnancy, either as an incidental finding or less commonly in the symptomatic state. For many women, pregnancy is the first time that a full blood count (FBC) is performed. Careful evaluation of any abnormal result is required before an immune cytopenia can be diagnosed.

The majority of autoantibodies implicated in these disorders are of the IgG subtype, and hence are able to cross the placenta. Consideration therefore, needs to be given not just to the implications for the mother, but also for the developing fetus, and after delivery, the neonate.

Management is difficult because, where treatment is required, there are no agents which are universally efficacious and all carry the potential for adverse effects. As with all therapies in pregnancy, the benefits of treatment compared with the relative risks to mother and baby have to be considered. A multidisciplinary approach, combining expertise from obstetricians, hematologists, anesthetists, and neonatologists is required for optimal care.

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# Idiopathic/immune thrombocytopenic purpura (ITP)

## Introduction

ITP is usually a chronic condition in adults, often occurring in young women, and can be challenging to diagnose and manage in pregnancy. Although it is principally mediated by autoantibodies, the development of specific assays as a diagnostic tool has, to date, proved unsuccessful. Therefore, the diagnosis is predominantly one of exclusion with frequent difficulty in excluding alternative causes of thrombocytopenia. Fortuitously, the risk of major hemorrhagic complications is low. Successful management requires maintaining adequate platelet counts for pregnancy and delivery whilst minimizing the risks of treatmentrelated side effects for mother and baby. Potential risks of fetal thrombocytopenia need to be appreciated and measures taken to prevent hemorrhagic complications at delivery.

## Epidemiology

The annual incidence, of acute and chronic ITP in adults, from population-based studies is estimated as  $2-4 \text{ per } 100\,000$ , when defined using a platelet count of less than  $100 \times 10^9$ /L. These incidence figures are similar for Europe and the USA.<sup>1</sup> In keeping with other immune disorders, it is more common in women than men (F:M 1.7–1.9:1), and frequently occurs during the reproductive years, occurring in all ethnic groups. The incidence in pregnancy has been estimated at 0.1–1 per 1000 pregnancies,<sup>1,2</sup> accounting for about 3%<sup>3</sup> of cases of thrombocytopenia in pregnancy. Approximately two-thirds of cases of ITP already have an established diagnosis prior to pregnancy, allowing the opportunity for pre-pregnancy counseling and planning for a future pregnancy.

## Pathogenesis

Thrombocytopenia is predominantly caused by autoantibodies specific for platelet glycoproteins binding to platelets in the maternal circulation. This results in immune mediated platelet destruction. The immune dysregulation which permits autoantibody formation is still the subject of much research. More recently it has been found that, in addition to increased destruction of platelets, there is also suppression of megakaryopoiesis in the bone marrow. Therapeutic agents targeting this phenomenon are now licensed for use in the non-pregnant setting. There is usually no apparent stimulus for the autoantibody production; however, occasionally a history of recent viral illness or drug exposure can be implicated. ITP usually occurs in isolation but may occur with other immune cytopenias or be secondary to a systemic autoimmune condition, e.g. SLE. The spleen has an important role in ITP, being both a major source of antibody production and the predominant site for destruction of antibody-bound platelets. The antibodies are of the IgG subtype and therefore able to cross the placenta and potentially cause thrombocytopenia in the fetus/neonate.

## Diagnosis

### Thrombocytopenia in pregnancy

The reference range for platelet counts outwith pregnancy is 150–400  $\times$  10<sup>9</sup>/L. During pregnancy there is a general trend downwards in platelet count, especially in the last trimester, resulting in a fall of around 10% from the pre-pregnancy level.<sup>4,5</sup> This is thought to be due to accelerated destruction of platelets and normal physiological dilutional effects. For the majority of women this will not result in the platelet count falling below the normal laboratory range. However, if the pre-pregnancy platelet count lies at the lower end of the normal range, or if there is a more severe drop in counts, thrombocytopenia occurs. The finding of mild thrombocytopenia in pregnancy is common, with approximately 8%–10% of women having a platelet count below the laboratory normal range.<sup>4</sup>

Since the diagnosis of ITP is one of exclusion (when presenting during pregnancy), alternative diagnoses must be considered and excluded where possible. The principal differential diagnoses of thrombocytopenia in pregnancy are discussed below and are summarized in Table 4.1.

### Gestational thrombocytopenia

The majority of cases of thrombocytopenia in pregnancy (74%) are attributable to gestational thrombocytopenia (incidental thrombocytopenia) of pregnancy.<sup>5</sup> This is a benign condition and represents no bleeding risk to mother or fetus. It probably reflects the extreme end of the normal physiological effect described above. It typically occurs in the third trimester and usually results in a mild thrombocytopenia. Platelet counts below  $70 \times 10^9/L$ 

Thrombocytopenic condition	Pathogenesis of thrombocytopenia	Diagnostic characteristics
Gestational thrombocytopenia	Physiological dilution Accelerated destruction	Third trimester, plts $>70 \times 10^9/L$ Incidental finding, no features of other disease
HIP/ Pre-eclampsia/eclampsia	Peripheral consumption	Unwell patient clinical features – hypertension, proteinuria, neurological signs/symptoms
Micoangiopathic hemolytic anemias (MAHA) – TTP, HUS, HELLP syndrome	Mechanical destruction and peripheral consumption (accumulation of micro-thrombi in small vessels)	Unwell patient. Clinical features – neurological signs, fever, renal impairment, deranged LFTs, hemolysis
ITP	Immune mediated peripheral consumption and occasional bone marrow suppression	Absence of other causes of thrombocytopenia Diagnosis of exclusion
Hereditary thrombocytopenia	Bone marrow underproduction	Family history Somatic abnormalities Abnormal blood film
Leukemia/lymphoma	Bone marrow infiltration	Lymphadenopathy, hepatosplenomegaly, Other FBC abnormalities
Pseudothrombocytopenia	EDTA artefact	Platelet clumping seen on blood film
Viral infection	Multifactorial	Recent viral illness. Risk factors
Drugs	Multifactorial	Timing of drug exposure
HIP. Hypertension in pregnancy TTP. Th	rombotic Thrombocytopenic purpura HUS. Her	nolytic uremic syndrome. HELLP: Hemolysis with

Table 4.1 Causes of thrombocytopenia in pregnancy

HIP: Hypertension in pregnancy, TTP: Thrombotic Thrombocytopenic purpura, HUS: Hemolytic uremic syndrome, HELLP: Hemolysis with elevated liver enzymes and low platelets, ITP: Immune thrombocytopenic purpura

should alert the physician to consider alternative diagnoses, although in rare cases the diagnosis has been subsequently confirmed in women with counts as low as  $50 \times 10^9$ /L.<sup>6</sup> Gestational thrombocytopenia is not immune mediated and therefore poses no risk to the fetus. A platelet count that has been normal before pregnancy, and normal in the first and second trimesters is useful in helping make the diagnosis. The FBC returns to normal within a few weeks of delivery. It may cause diagnostic difficulty with ITP when there are no pre-pregnancy counts.

#### Hypertensive disorders

Hypertensive disorders of pregnancy complicate between 12%–22% of pregnancies, and are a common cause of thrombocytopenia in pregnancy, accounting for approximately 20% of cases. "Gestational hypertension," which includes "hypertension in pregnancy" (HIP), pre-eclampsia and eclampsia, is responsible for the vast majority of these. Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and Hemolysis, Elevated Liver Enzymes and Low Platelets (HELLP) syndrome can share similar features with pre-eclampsia, and distinguishing between these conditions is sometimes problematic. Together, these rarer microangiopathic hemolytic anemia (MAHA) conditions cause less than 1% of pregnancy-related thrombocytopenia. Management of these conditions is described in Chapters 17 and 18. Hypertensive disorders may be associated with the disseminated intravascular coagulation (DIC), which will contribute to further platelet reduction.

#### Constitutional thrombocytopenia

Hereditary causes of thrombocytopenia are rare, accounting for less than 1% of cases. This includes MYH-9 disorders characterized by giant platelets on the blood film and Dohle body inclusions in neutrophils. Of these, the May Hegglin anomaly is the most likely to be encountered in pregnancy. Rarely, hereditary bone marrow failure syndromes such as Fanconi's anemia may present with an isolated thrombocytopenia in pregnancy. These diagnoses may be suspected if there is a family history of thrombocytopenia, unexplained thrombocytopenia in more than two first-degree relatives, or physical abnormalities suggestive of the disorder.

#### **Drugs and infections**

Thrombocytopenia is a frequently occurring side effect of many medications. Heparin induced thrombocytopenia, a potentially life-threatening condition, may occur rarely with unfractionated heparin use in pregnancy, but to date has not been described with low molecular weight heparin therapy in pregnancy. As with the non-pregnant setting, viral infection is an important cause of thrombocytopenia. Whilst this occurs as a transient phenomenon with many viruses, specific consideration should be given to hepatitis and HIV infection, particularly if risk factors are present. Thrombocytopenia in this setting is likely to be multifactorial with both an immune and non-immune pathogenesis. Diagnosing these infections early in pregnancy may allow treatment to be initiated, reducing the risk of related complications and vertical transmission.

#### **Others**

Hematological malignancies can present in pregnancy and the initial feature may be isolated thrombocytopenia. Occasionally, a bone marrow examination may be required to exclude these.

Laboratory artifact from EDTA present in the sample tubes may account for some cases of apparent thrombocytopenia. Examination of the blood film is essential to exclude this possibility.

There are no specific diagnostic tests for ITP. Although platelet glycoprotein specific antibodies can be detected in the majority of cases, this test lacks the sensitivity and specificity to be of clinical use. Diagnostic parameters for ITP in pregnancy are: thrombocytopenia with a past history of ITP, or a platelet count during pregnancy of less than  $70 \times 10^9$ /L with other causes excluded. Mild thrombocytopenia presenting in the first or second trimesters may also represent ITP, but this is not clinically significant for the mother since no treatment is required. In all cases, a careful history and examination of the blood film are critical to the evaluation of thrombocytopenia and diagnosing ITP in pregnancy. The important clinical and laboratory points for diagnosis are discussed below and listed inTable 4.2.

#### History

- Where there is a preceding history of ITP, check diagnosis for accuracy.
- Documented response to corticosteroids or intravenous immunoglobulin (IVIG) is usually diagnostic of ITP. In addition, this information is valuable for deciding on future treatment.

- Previous pregnancy experience and any documented blood counts both during and outside of pregnancy are very useful.
- Neonatal platelet counts from previous successful pregnancies should be noted.
- Note any illnesses associated with ITP (e.g. SLE), or the occurrence of other autoimmune disorders in the patient.
- A family history of thrombocytopenia may suggest a hereditary disorder.
- Identify any risk factors for HIV and viral hepatitis, and include the relevant tests.
- Any current medications should be considered for the possibility of drug-induced thrombocytopenia.

#### **Clinical examination**

- Clinical examination is occasionally of value.
- The presence of purpura or mucosal bleeding should be sought.
- Splenomegaly and/or lymphadenopathy are not characteristic of ITP.
- Physical abnormalities may suggest a hereditary disorder.

#### Laboratory assessment

- **FBC**: Incidental finding of thrombocytopenia should prompt a recheck of the FBC.
- **Blood film** is essential to exclude alternative diagnoses:
- (a) Spurious thrombocytopenia is caused either by EDTA artifact (causing platelet clumps – if present, repeat count in citrate sample) or platelet satellitism. Both are readily seen on the film.
- (b) Check erythroid and leukocyte morphology and confirm within normal limits. Abnormal red cell (e.g. fragmentation) or white cell morphology suggests alternative diagnosis.
- (c) Check platelet morphology. Giant platelets may be seen in ITP but, if this is the dominant finding, consider a MYH-9 disorder and examine the neutrophils for Döhle bodies. Giant platelets and thrombocytopenia may also be seen with Bernard Soulier disease, but a lifelong history of abnormal bleeding would be expected. Abnormally small platelets may be seen with hereditary thrombocytopenia and bone marrow failure

	Specific point to elicit	Relevance
Current history	ls patient hemorrhagic? Viral illness/ risk factors for HIV or hepatitis	Thrombocytopenia genuine. Indication for treatment Viral cause for thrombocytopenia; Check serology
Family history	Family history of unexplained thrombocytopenia	Consider hereditary causes
Past medical history	Known ITP	ITP likely cause thrombocytopenia. ? previous response to steroids or immunoglobulin
	SLE, thyroid or other autoimmune disorders	ITP likely cause thrombocytopenia. Possibility of SLE related complications
Past obstetric history	History of pre-eclampsia or previous thrombocytopenia in pregnancy Previous baby with neonatal thrombocytopenia	Increased likelihood of recurrence Establish cause
		ITP likely. If not, consider possibility of neonatal alloimmune thrombocytopenia (NAIT)(see chapter 5A) May predict risk future neonatal thrombocytopenia
Clinical examination	Mucocutaneous bleeding Lymphadenopathy, hepatosplenomegaly	Thrombocytopenia genuine; indication for treatment Possible leukemia/lymphoma Not consistent with ITP
Laboratory assessment	Platelets: clumping present? Giant platelets Normal red cell and white cell numbers and normal morphology Schistocytes/red cell fragments LFTs abnormal coagulation screen abnormal	Pseudothrombocytopenia; repeat FBC in citrate Check platelet count by alternative method. Consider MYH-9 disorders Consistent with gestational thrombocytopenia or ITP Consider MAHA Consistent with HELLP syndrome Consider DIC, hypertensive disorders of pregnancy

#### Table 4.2 Evaluation of suspected ITP

syndromes. Automated platelet counts may be erroneous if they are performed on an analyzer that relies on impedence counting and if the platelets are very large. This should be suspected if the film appearances differ significantly from the analyzer result. An alternative method of platelet measurement available on some analyzers (e.g. flow cytometry platelet count) may give a more accurate measurement.

Some analyzers are able to measure reticulated platelets and this percentage increases significantly in ITP.

• Other **routine investigations** which should be performed are listed in Table 4.2.

#### Bone marrow examination

- A bone marrow examination can confirm the presence of normal megakaryocytes, normal hematopoiesis, and the absence of bone marrow infiltration.
- This is not necessary for younger patients where there are no other clinical or laboratory features to

suggest bone marrow failure or infiltration (BSCH guidelines 2003).

- Consider performing a bone marrow examination in cases that do not respond to standard treatments.
- NB: bone marrow examination will not differentiate between ITP and gestational thrombocytopenia or other consumptive causes, which constitute the main differential diagnoses, only confirming that thrombocytopenia is due to peripheral consumption.

#### Management

The aim of management of ITP in pregnancy is not to achieve a sustained normal platelet count but simply to maintain a platelet count which is adequate to avoid hemorrhagic complications during pregnancy, delivery and immediately postpartum. This conservative approach minimizes the risks of maternal and fetal exposure to therapeutic agents. There are no universally accepted criteria for "safe" platelet counts in pregnancy. It is advisable that members of the team involved in managing these cases (obstetricians,

Table 4.3 Suggested platelet thresholds for intervention

Intervention	Platelet count
Ante-natal, no invasive procedure planned	$>20 \times 10^{9}/L$
Vaginal delivery	$>40 \times 10^{9}/L$
Operative or instrumental delivery	$>50 \times 10^{9}/L$
Epidural anesthesia	$>80 \times 10^{9}$ /L

hematologists, anesthetists) agree a consensus for minimum accepted platelet thresholds. Generally, these can be low in the antenatal period if the patient is not hemorrhagic. Thresholds typically need to be higher for delivery. Suggested platelet thresholds for ITP are stipulated in Table 4.3.

#### Monitoring during pregnancy

Platelet counts in women with ITP need to be closely monitored through pregnancy: in general, monthly in the first and second trimesters, 2-weekly in the third, and weekly near term, although the frequency of monitoring will depend on the rate of change as well as absolute values.

#### Treatment

There are two decisions to be made in treating ITP in pregnancy: when to treat and what treatment to give. The majority of women will not require therapy throughout the whole duration of the ante-natal period.<sup>7,8</sup> Only women with very low platelet counts  $(<20 \times 10^{9}/L)$  or who are hemorrhagic will require treatment at this stage. By contrast, treatment is often required to raise the platelet count prior to delivery. The two treatment options for the initial management of ITP usually considered are corticosteroids and intraveous immunoglobulin (IVIG); anti-D immunoglobulin appears to have equivalent efficacy to IVIG, and could be considered as an alternative in non-splenectomized Rhesus positive patients.9 The characteristics of these agents are summarized in Table 4.4a, 4.4b and 4.4c. The choice of which agent to use requires discussion with the individual about the relative risks and benefits of each treatment. Some authorities advocate first-line therapy with IVIG rather than corticosteroids. Currently, there is little experience of using Anti D in pregnancy for ITP; however, it is widely used in Rhesus D negative women for the prevention of hemolytic disease of the newborn (HDN). It should be noted that the dose for ITP is substantially higher than for HDN and this may result in an

#### Table 4.4a Corticosteroids

Advantage	Disadvantage	
<ul> <li>Oral therapy</li> <li>Most experience</li> <li>Can be used for extended periods if prolonged platelet count rise is required</li> <li>Dose can be tapered to minimum required for desired effect.</li> <li>Not a blood product</li> <li>Inexpensive</li> </ul>	<ul> <li>Risk of gestational diabetes mellitus</li> <li>Immunosuppressive</li> <li>Slow response 3–7 days for first response, maximal response 2–3 weeks</li> <li>Risk of osteoporosis with prolonged therapy</li> <li>Risk of hypertension</li> <li>Possible adverse effects on fetus at high doses (but 90% metabolized)</li> </ul>	

Table 4.4b Intravenous immunoglobulin (IVIG)

Advantage	Disadvantage
<ul> <li>Established therapy</li> <li>Response to treatment is rapid (6–72 hours)</li> <li>No corticosteroid side effects</li> <li>Low risk to fetus</li> </ul>	<ul> <li>Intravenous therapy with long duration of administration</li> <li>Pooled plasma product therefore potential risk of pathogen transmission for mother and fetus</li> <li>Transient response (&lt;1 month)</li> <li>Risk of infusional reactions</li> <li>Risk of aseptic meningitis</li> <li>Headache common</li> <li>Exponsive</li> </ul>

Table 4.4c Anti D immunoglobulin

Advantage	Disadvantage
<ul> <li>Short administration period (3–15 min)</li> <li>Good reported efficacy</li> <li>Non-immunosuppressive</li> <li>No corticosteroid side effects</li> </ul>	<ul> <li>Limited experience in pregnancy</li> <li>Transient response &lt; 1 month</li> <li>Occasionally may induce significant hemolysis</li> <li>Pooled plasma product therefore potential risk of pathogen transmission for mother and fetus</li> <li>Crosses the placenta. Fetus may be at risk of hemolysis</li> <li>Only available to patients who are Rh positive (approx. 90% of individuals)</li> </ul>

increased risk of neonatal hemolysis. Currently, there are no anti D preparations licensed in the UK for the treatment of ITP. Patients with contraindications to corticosteroids (diabetes mellitus, concurrent infections, history of steroid psychosis) should be managed with IVIG or Anti D alone.

No efficacy if prior

splenectomy

**Fig. 4.1** Algorithm for initial ITP therapy \*IVIG 0.4 g/kg for 5 days or 1 g/kg for 2 days

Anti D 50–70 mcg/kg single dose Consider methylprednisolone 1 g IV in addition to IVIG or Anti D.

\*\* Reassess earlier if obstetric indications that might need early delivery



The choice of therapy depends on the following factors:

- the speed with which a platelet increment is required;
- the length of time for which a rise needs to be sustained;
- which therapy carries the least potential risk for a given individual.

A suggested algorithm for initial therapy is shown in Fig. 4.1. This algorithm is only suitable for uncomplicated cases. Suggested management for various scenarios are listed below.

#### Patients with moderate/severe thrombocytopenia ( $<20 \times 10^9/L$ )

• Prednisolone 20 mg/day<sup>10</sup> (it is common practice to use less than the 1 mg/kg to avoid adverse effects).

Patients with very severe thrombocytopenia ( $\leq$ 10 $\times$  10<sup>9</sup> /L) significant major bleeding:

- requires treatment to raise the platelet count urgently;
- IVIG +/- high dose corticosteroids (usually 60 mg daily);
- consider platelet transfusions if significant bleeding.

#### Patients with life-threatening bleeding

- platelet transfusion + ;
- IVIG + IV methyl-prednisolone;

Where possible, the dose of prednisolone should be promptly reduced to the minimum effective dose. Unless hemorrhage is a major feature, prolonged therapy (>6 weeks) with high doses of prednisolone is considered to carry too high a risk of adverse events for the mother. The response to IVIG or anti D is often transient. Patients receiving these treatments may require repeat infusions. The addition of methylprednisolone 1 g intravenously is used to speed up/improve the response as compared to standard prednisolone in difficult or refractory cases.

It is not always possible to achieve the desired platelet count in individuals with ITP. Many patients (35% in one series) diagnosed with ITP in pregnancy will not respond to corticosteroids or IVIG. In addition, response to platelet transfusions are transient with poor increments as circulating antibody rapidly clears transfused platelets.

#### Management of refractory cases

- In considering other therapeutic options the balance of risks need to be considered between treatment-related toxic effects vs. risk of major bleeding with prolonged severe thrombocytopenia. In many circumstances it may be preferable or necessary to accept the increased hemorrhagic risk of significant thrombocytopenia rather than use more aggressive therapies.
- **Splenectomy**: this procedure has a well established, though diminishing, role in ITP. It can generally be performed safely in pregnancy but carries the risks of general surgery and of fetal loss. Where possible, it should be performed in the second trimester. This avoids the risks of teratogenicity associated with drugs in the first trimester. In the third trimester the gravid uterus may make splenectomy technically more demanding, although laparoscopic splenectomy may make the procedure more feasible.
- Tranexamic acid: this is an antifibrinolytic, normally avoided in pregnancy because of concerns that it may increase thrombotic risk. Reproductive animal studies do not indicate risk to the fetus, but there are no adequate and well-controlled studies done on pregnant women (category B). It could be considered in the refractory patient with ongoing symptoms, after the first trimester.
- Azathioprine is used as a second-line agent, and has been given safely in pregnancy, but there is insufficient evidence to currently advocate its routine use in this setting. It has a slow onset of action (about 8 weeks), which also reduces its utility.

• **Rituximab**: this agent is an anti-CD20 monoclonal antibody, which is increasingly used to treat non-pregnancy related ITP. However, there is insufficient evidence regarding safety and efficacy to advocate its use during pregnancy. The manufacturer currently recommends avoiding pregnancy for 1 year following treatment.

Other agents, which are useful outside pregnancy, such as androgen analogs (e.g. danazol), and cytotoxic agents such as cyclophosphamide or vinca alkaloids, are contraindicated in pregnancy.

#### General measures – the following should be avoided:

- aspirin and non-steroidal medication;
- intramuscular injections;
- strenuous activity.

## Planning for delivery

Consideration of potential maternal and neonatal thrombocytopenia is required in addition to any obstetric factors that may be present when planning delivery.

#### **Maternal considerations**

The principal concern is hemorrhage. This may be during delivery or postpartum. Postpartum hemorrhage is of particular concern due to the sharp fall in procoagulant factors that occurs at this time. As discussed above, there is no universally agreed safe platelet count; however, hemorrhage caused by thrombocytopenia occurring at a platelet count  $>50 \times 10^9$ /L would be considered unusual.

Epidural analgesia is of particular concern, as even a small increase in venous hemorrhage could have the potential for spinal cord compression. The risk is considered to be greatest at the time of insertion and withdrawal of the catheter. There is controversy over the safe threshold for epidural anesthesia; there is some evidence to suggest that a platelet count of  $50 \times 10^9$ /L is adequate (based on British Society of Haematology guidelines), however anesthetic practice is to use a threshold of at least  $80 \times 10^9$ /L, in experienced hands (based on BCSH and anesthetic guidelines). A predelivery anesthetic consultation is helpful to discuss alternative analgesia during labor. The role of spinal anesthetic is more difficult. This procedure may allow a cesarean section to be performed without the need for a general anesthetic. A decision may be taken that the risks of a single pass spinal needle could be less than those of a general anesthetic in some situations and, if an experienced obstetric anesthetist is available, a cut-off of  $50 \times 10^9$ /L is suggested.

Chronic immunosuppression antenatally for ITP may increase the risks of postpartum sepsis.

### **Neonatal considerations**

The principal neonatal risk is intracranial hemorrhage due to severe thrombocytopenia and birth trauma. This is rare (<1% of ITP cases), although potentially devastating when it occurs. The overall incidence of thrombocytopenia in neonates born to mothers with ITP is reported in various studies as 14%–37.5%.<sup>8,11,12</sup> However, only approximately 5% of babies born to mothers with ITP will have platelet counts <20 ×  $10^9$ /L, with a further 5% having counts between 20 ×  $10^9$ -50 ×  $10^9$ /L.<sup>8,13</sup>

Unfortunately, predicting which babies may be affected or directly assessing the fetal platelet count is difficult. No correlation has been established with the severity of maternal ITP or levels of circulating antibody. Although there are no reliable predictors of its occurrence or severity, neonatal thrombocytopenia is more likely if:

- there is a previous sibling with thrombocytopenia.<sup>13</sup>
- the mother has had a splenectomy prior to this pregnancy (although not all studies confirmed this finding).
- severe maternal ITP.<sup>13,14</sup>

Where babies have been born previously with severe thrombocytopenia, testing for paternal platelet antigen incompatibility to exclude Neonatal alloimmune thrombocytopenia (NAIT) is required.

There is currently little role for the routine measuring of fetal platelet counts by percutaneous umbilical blood sampling (PUBS) in ITP. Studies evaluating this technique have estimated the procedure-related risk to be greater than the risk of preventing neonatal hemorrhage. Platelet counts taken from fetal scalp samples are prone to erroneously low results, and carry the risk of scalp hematoma, and are therefore best avoided.

### Mode of delivery

Concerns regarding potential neonatal thrombocytopenia and birth trauma have previously led some clinicians to recommend cesarean section. There is currently no evidence that cesarean section reduces the incidence of intracranial hemorrhage in susceptible babies compared with an uncomplicated vaginal delivery. This is true for congenital bleeding disorders as well as ITP. For this reason it is recommended that the mode of delivery is determined by obstetric indications rather than ITP. However, vaginal delivery that is augmented by ventouse or rotational forceps does carry an increased risk of head trauma to the neonate and where possible should be avoided. Induction of labor at the time of maximal platelet count may be required if platelet count rises are very transient with therapy. The exact mode and timing of delivery has many patient-specific variables and therefore an individualized plan with multidisciplinary input is advised.

# Management of labor when platelet count has not been corrected

In these cases a pragmatic approach needs to be taken. Experiences suggest that normal delivery can occur without excess hemorrhage, reassuringly, even at very low platelet counts. It is advisable to have platelet transfusions available on standby and to proceed with delivery. If time allows, high dose IVIG (1 g/kg) may be used. Epidural anesthesia should be avoided as should non-steroidal anti-inflammatory (NSAIDs) drugs for postpartum pain relief.

### Postpartum – neonatal care

The neonatal team should be alerted prior to delivery. A cord platelet count should be measured at birth. If the platelet count is normal, further neonatal platelet counts are not required. If thrombocytopenia is present, this should be confirmed on a capillary or venous sample. Intramuscular injections are best avoided, if severe thrombocytopenia is present, and vitamin K given orally.

Further alternate-daily FBC measurements over the next week are required to ensure that the neonate is not at risk of hemorrhage. The nadir platelet count is usually between days 2 and 5.

Babies with severe thrombocytopenia of  $<20 \times 10^9/L$  or clinical hemorrhage require treatment with IVIG. Life-threatening complications should be treated with immediate platelet transfusions and IVIG. Consideration should be given to using HPA

1a 5b negative platelets if available until NAIT is excluded.

Babies with severe thrombocytopenia should have a cranial ultrasound to assess for evidence of intracranial hemorrhage.

## Prenatal counseling

Women who have an established diagnosis of ITP may request pre-natal counseling before deciding whether to embark on a pregnancy. There are few predictors of outcome that can be used to assess risk. While pregnancy should not be discouraged, it is suggested that the following points should be discussed:

- Circulating antiplatelet antibodies may still be present in the maternal blood. This is particularly relevant for women who have had a splenectomy. In these circumstances the ITP may appear in remission with normal platelet counts. However, this is primarily due to an inability to clear platelet–antibody complexes rather than a cessation of antibody production. These women will still be at risk of neonatal thrombocytopenia or hemorrhagic complications in utero.
- ITP may relapse or worsen during pregnancy.
- If treatment of ITP is required it will carry both maternal and fetal risks.
- There is an increased risk of hemorrhage at delivery, but the risk is small even if the platelet count is low.
- Epidural anesthesia may not be possible.
- Although it is not possible to accurately predict if a neonate will be affected, the risk is high if a sibling had thrombocytopenia, or mother had undergone splenectomy.
- Maternal death or serious adverse outcomes for mothers with ITP are rare.
- The risk of intracranial hemorrhage for the fetus/neonate is very low.

## Autoimmune neutropenia (AIN)

## Introduction

Neutropenia is a common finding in routine FBC testing, and is defined as an absolute neutrophil count (ANC) of  $<1.5 \times 10^9$ /L (or < 1.2 for some ethnic groups – see below). The majority of cases are mild, transient, and no specific etiology is determined. By contrast, AIN is a rare disorder and can cause severe neutropenia associated with recurrent infection.<sup>15</sup> It may occur in isolation or in conjunction with ITP or AIHA. Many cases in adults are secondary, associated with collagen vascular disorders, rheumatoid conditions, and SLE. Primary AIN is predominantly a disease of childhood. The main complication of this condition is recurrent infection, which occurs if the neutropenia is severe (ANC <  $0.5 \times 10^9$ /L). Diagnosis can be problematic as laboratory investigation of neutropenia is limited, and usually restricted to specialist centers. Pregnancy poses an additional problem, as autoantibodies may cross the placenta resulting in neonatal neutropenia after delivery. Currently, published evidence on management of these cases is lacking.

## Incidence and pathogeneisis

The true incidence of AIN is not known. Persistent neutropenia in adults is a common finding and is frequently not investigated if asymptomatic and mild (ANC  $1.0 \times 10^9$ – $2.0 \times 10^9$ /L). Cases are often labeled as chronic idiopathic neutropenia (CIN). It is probable that some cases with a presumptive diagnosis of CIN are immune mediated. The benign nature of asymptomatic CIN means that specialist investigation is often of little value and immunological studies are therefore not pursued. This may not be the case for women of childbearing age, as identification of immune-mediated cases may help with neonatal assessment.

The pathogenesis of AIN is similar to that of other immune cytopenias. It is an acquired disorder in which autoantibodies specific for neutrophil surface glycoproteins result in reduced neutrophil survival and neutropenia.

## Diagnosis

Patients with symptomatic neutropenia (recurrent infections, severe neutropenia) are likely to present outside of pregnancy and have an established diagnosis. Difficulty occurs in the asymptomatic patient if an incidental finding of neutropenia is made following FBC testing during routine ante-natal care. Assessment involves a careful history, examination of the other FBC indices and inspection of the blood film.

The differential diagnosis includes: drugs, viral infections, immune mediated disorders, large granular lymphocyte (LGL) disease (often associated with

ANC	Severity	Clinical effect
$>1.0 \times 10^{9}/L$	Mild	Usually asymptomatic
$0.5 \times 10^9 - 1.0 \times 10^9 / L$	Moderate	Usually asymptomatic
$0.2 \times 10^9 - 0.5 \times 10^9 / L$	Severe	Infections possible
$\leq 0.2 \times 10^{9}/l$	Very Severe	High risk of infection

Table 4.5 Severity of neutropenia according to the ANC

rheumatoid arthritis), benign ethnic neutropenia, and CIN. Important clinical and laboratory aids to diagnosis are listed below.

### History

- History of SLE, rheumatoid arthritis or other autoimmune disease suggests secondary immune neutropenia. (more common than primary AIN in adults.)
- Ethnic origin (ANC > 1.2 × 10<sup>9</sup>/L may be considered within normal limits for some African, Middle Eastern and Yemenite Jew populations).
- Ask about any recent viral illness.
- Assess risk factors for HIV.
- Assess for evidence of recurrent infections, particularly unusual infections or mouth ulcers (if there is a temporal pattern – consider cyclical neutropenia).
- Take a careful drug history (especially antithyroid drugs, phenothiazines, and NSAIDs), which are known to cause neutropenia.
- Is there a known family history of neutropenia?
- Is there a history of ITP or AIHA?

### Laboratory assessment

- A blood film should be examined to confirm neutropenia. Severity may be graded using the criteria in Table 4.5.
- Increase in LGLs on the blood film should be noted.
- The presence of abnormalities other than neutropenia suggests an alternative diagnosis to AIN.
- Asymptomatic cases with ANC  $>0.5 \times 10^9$ /L and where there is no apparent cause are best managed by repeating the test after 4 weeks. Further investigation during pregnancy is warranted if the neutropenia persists, or if the patient is symptomatic.
- Anti-neutrophil antibody results also produce frequent false negatives and positives, similar to

anti-platelet antibodies, making the test of little use. Repeat samples may help diagnosis in some cases.

• A bone marrow examination is of value in cases of severe neutropenia. The bone marrow appearances in AIN may show normal hematopoiesis or an apparent arrest at the metamyelocyte stage with a reduction in the number of mature neutrophils and band forms.

## Management

There are two main risks during pregnancy – the maternal risk of sepsis and the risk of neonatal neutropenia. Sepsis in pregnancy may provoke miscarriage or premature labor and is the main concern, for example, a normally benign urinary infection may progress to pyelonephritis and septicemia.

Information on neonatal outcomes in women with AIN is limited. Neutropenia from all causes in neonates is common. Information from neonates affected by neonatal alloimmune neutropenia (NAIN) suggests that infections are, in the main, mild and death or serious morbidity from sepsis is very rare.

As with ITP, steroids are the usual first line of treatment, if required. IVIG may be given if no response.

### Sepsis

Sepsis in individuals with severe neutropenia is an emergency. Untreated sepsis in the setting carries a significant mortality for both mother and baby. Blood cultures should be taken and broad-spectrum intravenous antibiotics commenced promptly according to local protocols. Fetuses tolerate pyrexia poorly, and neurological damage may occur if the baby suffers prolonged fever.

### Granulocyte colony stimulating factor (GCSF)

GCSF has significantly changed the management of severe chronic neutropenia. For many individuals the administration of low doses of GCSF 2–3 times per week substantially reduces the incidence of infection. GCSF has replaced traditional therapies such as IVIG, corticosteroids or splenectomy as first line therapy outside of pregnancy. Long-term follow-up to date has suggested that this is a safe treatment and therefore patients with symptomatic neutropenia are often on regular therapy.<sup>15</sup> It is not yet clear that GCSF is safe for use in pregnancy. Studies investigating prematurity have noted a potential association with spontaneous preterm birth and elevated cytokines including endogenous GCSF. In addition, GCSF carries a small risk of venous thrombo-embolism, which may constitute a significant risk factor for some pregnancies. It is known that GCSF crosses the placenta. Despite these reservations, it is likely that GCSF is relatively safe in pregnancy. Several cases of successful pregnancy with continuation of GCSF in pregnancy are documented in the published international severe chronic neutropenia registry and this is supported by individual case reports.

### Postpartum

Women with proven AIN or where AIN is strongly suspected are at risk of delivering a neutropenic baby. The neutrophil count at birth should be measured and subsequent measurements performed according to the degree of neutropenia and the infection risk. Immune neutropenia may take several weeks to resolve.

## Practical approach to pregnant patients with diagnosed AIN

- Individuals who are asymptomatic are unlikely to benefit from specific therapy.
- If the ANC is < 0.5 × 10<sup>9</sup>/L, advice on treating sepsis promptly with intravenous antibiotics is required.
- Individuals who are symptomatic and already on GCSF may benefit from continuing therapy but a careful discussion of the risks of therapy is necessary. Consideration can be given to stopping GCSF, particularly for the first trimester.
- Monitoring FBC to tailor GCSF dose may be required.
- The neonatal team should be alerted prior to delivery.
- A cord blood sample should be taken.
- A postpartum FBC should be sent.

# Management of a newly presenting case of neutropenia in pregnancy

- Exclude other causes of neutropenia.
- Check hematinics (ferritin, B12 and folate see Chapter 2).
- Assess for evidence of associated auto-immune conditions.
- If severe neutropenia, warn patient of risk of life-threatening infection ensure they

understand that prompt treatment is necessary, and have clear, efficient self-referral route.

• Treatment options should be discussed: steroids are first-line choice in pregnancy, with IVIG and GCSF as second- and third-line options if no response.

## Autoimmune hemolytic anemia (AIHA)

## Introduction

Hemolysis is defined as shortened red cell survival, the average lifespan of an erythrocyte being 120 days. Mild hemolysis is compensated for by an increase in bone marrow erythropoeisis and may not affect the hemoglobin concentration. Anemia occurs when red cell survival is sufficiently shortened to exceed this increase in erythropoetic activity. Causes of hemolysis are listed in Table 4.6. AIHA is a common cause of hemolysis but rarely complicates pregnancy. Nonimmune hemolysis occurs more frequently in pregnancy and is mostly associated with pre-eclampsia or other hypertension-related disorders. It is essential to distinguish between these types of hemolysis as the management is very different. AIHA may be further divided into "warm" and "cold" types. Warm AIHA is usually IgG mediated. Cold AIHA is mostly IgM and complement mediated. The blood film appearances and direct antiglobulin test (DAT) are characteristic. Treatment of AIHA in pregnancy is similar to outside pregnancy. Transplacental passage of IgG antibodies may occur, but neonatal hemolysis is rarely severe.

# Epidemiology and pathogenesis

AIHA in pregnancy is a rare disorder with an estimated incidence of 1:50 000 pregnancies.<sup>16</sup> Pregnancy appears to be a stimulus for AIHA with a  $4 \times$  higher incidence than outside pregnancy. Cases of AIHA may predate conception and relapse in pregnancy or occur as a new presentation. Secondary causes include lymphoproliferative disorders, infections (mycoplasma, Epstein-Barr virus) and connective tissue disorders. AIHA is caused by the production of autoantibodies directed against a red cell surface antigen, which on binding results in premature destruction of the erythrocyte. This is usually extravascular in the spleen or liver but occasionally may be intravascular. The antibodies are most frequently IgG followed by the IgM subtype. A spectrum of severity exists. In mild cases a positive direct antiglobulin test (DAT) is the only

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Immune	Autoimmune warm type	lgG mediated
	<ul><li>Autoimmune cold type</li><li>Autoimmune mixed type</li><li>Alloimmune</li></ul>	IgM mediated IgG and IgM mediated Reaction to blood transfusion,
Hereditary	<ul> <li>Disorder of hemoglobin synthesis</li> <li>Disorder of red cell enzymes</li> <li>Disorder of red cell membrane</li> </ul>	e.g. sickle cell anemia e.g. G6PD deficiency e.g. hereditary spherocytosis
Mechanical	• Red cell fragmentation	<ul> <li>Mechanical heart valve</li> <li>MAHA (TTP, HUS, HELLP syndrome, pre-eclampsia)</li> </ul>
Paroxysmal nocturnal Hemoglobinuria	Clonal stem cell disorder	Increased susceptibility to complement lysis
Drugs	Oxidative stress, immune	e.g. Dapsone
Infections	Bacterial enzymes	e.g. Clostridium perfringens

#### Table 4.6 Causes of hemolysis

abnormality found. More severe cases have evidence of compensated hemolysis with the most severe resulting in significant anemia.

## Diagnosis

Anemia during pregnancy is a common finding. For patients presenting during pregnancy, the diagnosis of AIHA requires careful exclusion of other causes of anemia, biochemical evidence of hemolysis and serological evidence that the hemolysis is immune mediated. Important clinical and laboratory features for diagnosis are summarized below.

### History

- Is the patient symptomatic of anemia?
- Is there a history of cardiovascular or pulmonary problems which may impair ability to cope with anemia?
- Is there evidence of a secondary cause, e.g. recent chest infection (mycoplasma) or autoimmune disorders?
- Is the patient on any drugs known to cause hemolysis (especially penicillins, methyldopa, NSAIDs)?
- Identify other potential causes of anemia (hematinic deficiency, hereditary disorders, etc).

### Examination

- Clinical examination may demonstrate evidence of a secondary disorder.
- Cases of chronic hemolysis (e.g. hereditary spherocytosis) can have mild splenomegaly present.

### Laboratory

Hemolysis is characterized by:

- ↑bilirubin, ↑LDH, ↑reticulocytes, ↓haptoglobins;
- blood film polychromasia, spherocytes, red cell agglutination (Cold AIHA);
- immune-mediated hemolysis characterized by positive DAT (Coombs test);
- Intravascular hemolysis characterized by urinary hemosiderin, hemoglobinuria.

## Management

The principal risk is of a sudden fall in hemoglobin resulting in symptomatic anemia and spontaneous abortion. Successful management requires maintaining an adequate hemoglobin level with red cell transfusion and giving specific therapy (usually prednisolone) to arrest the hemolysis. Although transplacental passage of antibodies occurs, the risk of developing anemia in *utero* or significant neonatal anemia with associated hyperbilirubinemia is small. Published experience of AIHA in pregnancy is limited, but the majority of reports are favorable using this approach.

### **Blood transfusion**

The presence of autoantibodies can cause difficulty in identifying suitable units for transfusion. Autoantibodies may mask alloantibodies present in the maternal serum, with the possibility of causing a hemolytic transfusion reaction. Specialist investigation is required to exclude an alloantibody or identify the specificity of an alloantibody if present. This may delay the provision of suitable units. Many hospital transfusion laboratories refer this work to specialist transfusion centers, and the following points should be considered.

- Ensure close liaison with the transfusion laboratory to ensure that adequate samples have been provided for testing.
- Ensure that the time within which blood is required is clearly agreed with the transfusion laboratory.
- In cases requiring emergency transfusion, the risks of issuing blood without compatibility being fully determined should be discussed between the hematologist and obstetrician.
- Patients with cold hemaglutinin disease (CHAD) may benefit from receiving transfusions via a blood warmer.

#### **Treatment of hemolysis**

Corticosteroids may be effective in reducing hemolysis. The risks of corticosteroid use are listed in Table 4.4a on ITP. Patients with warm AIHA are more likely to respond than those with cold AIHA. A similar treatment pattern to that for ITP may be used, and as with ITP the minimum dose possible to control hemolysis should be used.

Experience with other agents in pregnancy is limited. IVIG can be effective and its use may be justified in pregnancy if corticosteroids are ineffective or contraindicated. Rituximab is increasingly used outside of pregnancy but there are insufficient data currently available in pregnancy to advise its use.

#### **Additional measures**

• Folic acid 5 mg daily should be given. This prevents folate deficiency occurring as a result of

increased erythropoiesis. Increased dosage may occasionally be necessary.

 Thromboprophylaxis should be considered.
 Hemolysis is a prothrombotic condition and there is an increased risk of venous thromboembolism (VTE). Individual assessment of the degree of risk is necessary, and should include assessment of other risk factors for VTE. General measures should be emphasized, such as ensuring adequate hydration, and re-evaluation of degree of risk should continue through the pregnancy. The puerperium is a peak time for thrombotic events, and pharmacological thromboprophylaxis during the first 6 weeks postpartum is recommended.

#### Considerations for fetus and at birth

There is the potential for *in utero* hemolysis if transplacental passage of antibodies occurs. This applies only to cases of IgG mediated hemolysis. Unlike hemolytic disease of the newborn, the role of monitoring maternal antibody titers has not been established. Noninvasive monitoring for anemia using ultrasonography may be of value.

The neonatal team should be alerted prior to delivery and neonates should have a hemoglobin and bilirubin measured at birth. Neonates born to mothers with AIHA frequently have a positive DAT; however, hemolysis is usually mild if present. Significant anemia or elevated bilirubin levels requiring treatment is unusual. This is in contrast to hemolytic disease of the newborn (HDN), which may result in very severe hemolysis requiring in utero transfusion or neonatal exchange transfusion.

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# Section Feto-maternal alloimmune syndromes



Feto-maternal alloimmune syndromes

# Fetal/neonatal alloimmune thrombocytopenia

Michael F. Murphy

#### Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the commonest cause of severe neonatal thrombocytopenia, and is analogous to the fetal/neonatal anemia caused by hemolytic disease of the fetus and newborn (HDFN).<sup>1,2</sup> Fetal platelet antigens are expressed on platelets in normal amounts from as early as the 16th week of pregnancy. Feto-maternal incompatibility for human platelet alloantigens (HPAs) may cause maternal alloimmunization, and fetal and neonatal thrombocytopenia may result from placental transfer of IgG antibodies. Many HPA systems have been described<sup>3</sup>. The majority of HPA antigens such as HPA-1a are located on the  $\beta$ 3 subunit of the  $\alpha$ IIb $\beta$ 3 integrin (GPIIb/IIIa,CD41/CD61) which is present at high density on the platelet membrane. Others such as HPA-5b are on α2β1 (GPIa/IIa, CD49b). However, the antigen incompatibility HPA-1a is found in about 80% of cases of FNAIT in Caucasians and, in contrast to HDFN, FNAIT frequently occurs in first pregnancies.

Considerable progress has been made in the laboratory investigation of FNAIT since it was first recognized in the 1950s.<sup>1</sup> There have also been improvements in its management, particularly in the ante-natal management of women with a history of one or more pregnancies affected by FNAIT, resulting from a better understanding of the risk of severe hemorrhage and advances in fetal and transfusion medicine.

#### Epidemiology

The normal platelet count in the fetus and the neonate is the same as in adults. Neonatal thrombocytopenia has many causes, and is the commonest hematological problem in the newborn infant. A platelet count of  $< 150 \times 10^9$ /L occurs in about 1% of unselected neonates, and is  $< 50 \times 10^9$ /L in about 0.2%. FNAIT is the most important cause of severe fetal and neonatal thrombocytopenia, both because of its frequency and the severity of the bleeding associated with it. For example, FNAIT is associated with more severe fetal/neonatal bleeding than with maternal autoimmune thrombocytopenic purpura for reasons which are not entirely clear but could be due to associated platelet and/or endothelial dysfunction.

A fetal or neonatal platelet count of  $< 20 \times 10^9/L$  is usually caused by FNAIT due to anti-HPA-1a as are approximately half of the cases in which the neonatal platelet count is  $< 50 \times 10^9/L$ .

The most common entities in the differential diagnosis of severe fetal and neonatal thrombocytopenia are:

- congenital infections such as toxoplasmosis, rubella, and cytomegalovirus;
- maternal autoimmune thrombocytopenic purpura;
- chromosomal abnormalities;
- congenital heart disease;
- disseminated intravascular coagulation (DIC).

#### Incidence

Prospective studies in Caucasian populations for FNAIT due to anti-HPA-1a indicate that about 2% of women are HPA-1a negative, and that about 10% of HPA-1a negative women develop anti-HPA-1a.<sup>4</sup>

Alloimmunization to HPA-1a is HLA class II restricted. There is a strong association with HLADRB3\*0101 (HLADRw52a), which is present in 1 in 3 of Caucasian women, and HPA-1a alloimmunization is rare in HPA-1a negative women who lack this antigen.

Using data from prospective studies, the overall incidence of FNAIT due to anti-HPA-1a is estimated to be 1 in 1163 live births (86 per 100 000), and the incidence of severe thrombocytopenia (platelet count < 50  $\times$  10<sup>9</sup>/L) to be 1 in 1695 (or 59 per 100 000).<sup>4</sup>

FNAIT is under-diagnosed in routine clinical practice. The evidence for this is the mismatch in the incidence of FNAIT between prospective studies involving laboratory screening for HPA antibodies and the identification of clinically diagnosed cases. It is estimated that only 7%–23% of cases of FNAIT, and only 37% of severe cases, are detected clinically.

#### **Clinical diagnosis**

FNAIT is usually suspected in neonates with bleeding or severe, unexplained, and/or isolated postnatal thrombocytopenia. The clinical diagnosis is one of exclusion.

- The infant has no signs of DIC, infection or congenital anomalies known to be associated with thrombocytopenia.
- The mother has had a normal pregnancy with no history of autoimmune disease, thrombocytopenia, or drugs that may cause thrombocytopenia.

Specific criteria which distinguish cases of FNAIT from other causes of unexplained thrombocytopenia include:

- severe thrombocytopenia (platelet count < 50  $\times$  10<sup>9</sup>/L);
- no additional, non-hemorrhagic neonatal medical problems;
- intracranial hemorrhage (ICH) associated with one or more of:

Apgar score at 1 minute > 5; birthweight >2.2 kg; documented ante-natal or post-natal bleeding.

#### Laboratory diagnosis

Detailed laboratory investigations are required for confirmation of a provisional clinical diagnosis, and should be performed by an experienced reference laboratory. The diagnosis is based on:

- detection and identification of the maternal HPA antibody;
- determination of the HPA genotype of mother, father and, if needed, the child (or fetus).

In the past, it was difficult to differentiate between HLA and HPA antibodies in standard serological assays. The description of the monoclonal antibodyspecific immobilization of platelet antigens (MAIPA) assay overcame this problem. Rather than working with intact platelets, the assay involves capture of specific GPs using monoclonal antibodies enabling analysis of complex mixtures of platelet antibodies. However, it requires considerable operator expertise in order to ensure maximum sensivity and specificity, and the selection of appropriate screening cells is critical.

Immunization against HPA-1a and HPA-5b are responsible for up to 95% of cases of FNAIT. Antibodies against other HPAs are more frequently detected in recent large series of FNAIT. In some of these cases, testing against standard donor platelet panels may be negative. To pursue further investigation requires strong clinical suspicion of FNAIT. Possible approaches include:

- cross-match of maternal serum and paternal platelets using MAIPA;
- identification of a mismatch between maternal and paternal (or neonatal) genotypes for low frequency HPA antigens, and then screen maternal serum for the corresponding HPA antibodies.

#### **Clinical significance of FNAIT**

ICH is the major cause of mortality and long-term morbidity in FNAIT. The long-term outcome may be devastating with blindness and major physical and mental disability (Fig. 5.1). ICH was reported in a large review of the literature to occur in 74/281 (26%) of cases of FNAIT due to anti-HPA-1a with a mortality of 7%.<sup>5</sup>

Although there is a risk of hemorrhage due to severe thrombocytopenia at the time of delivery, 80% of ICH associated with FNAIT occur in utero, with 14% occurring before 20 weeks and a further 28% occurring before 30 weeks.<sup>5</sup> There may also be unusual presentations such as isolated fetal hydrocephalus, unexplained fetal anemia, or recurrent miscarriages.

Bleeding is more severe with FNAIT due to anti-HPA-1a than for example anti-HPA-5b, possibly due to the higher density of HPA-1a antigen sites on platelets.

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Fig. 5.1 Intracranial hemorrhage in FNAIT: MRI scan showing subacute hematoma (black arrow) and chronic hematoma (open arrow). Reproduced from De Vries *et al. Br J Obstet Gynaecol;* 95: 299–302.

## Prediction of the severity of FNAIT in subsequent pregnancies

#### Laboratory testing

Unfortunately, there is no reliable laboratory method to predict severe clinical disease, which might be used to identify pregnancies at risk of severe thrombocytopenia and ICH. Some studies have observed an association between high levels of maternal anti-HPA-1a and the severity of neonatal thrombocytopenia, but this is not a sufficiently reliable association to be clinically useful. Reliable methods for quantifying the other antibodies are not yet available. The lack of laboratory parameters predictive of severe disease remains one of the major barriers to optimizing ante-natal management for FNAIT, and is an important area for future research.

#### History of FNAIT in previous pregnancies

Subsequent pregnancies of HPA-1a alloimunized women with a history of a previously affected infant with FNAIT are well recognized to be associated with a high risk of recurrence of FNAIT and poor outcome. A detailed literature search found that the recurrence rate of ICH in the subsequent pregnancies of women with a history of FNAIT with ICH was 72% (confidence interval 46%–98%) without the inclusion of fetal deaths, and 79% (confidence interval 61%–97%) with their inclusion.<sup>6</sup> The risk of ICH following a previous history of FNAIT without ICH was estimated to be 7% (confidence interval 0.5%–13%).

These data provide the justification for ante-natal intervention in women with a past history of pregnancies affected with FNAIT, particularly where there has been fetal or neonatal ICH in a previous pregnancy, to reduce the risk of morbidity and mortality from severe hemorrhage.

If there is paternal heterozygosity for the relevant HPA, fetal platelet genotyping should be considered, for example, by obtaining a sample using amniocentesis.

## Consideration of ante-natal screening for FNAIT

Advances in the laboratory diagnosis and antenatal management of FNAIT have drawn attention to the fact that the first affected fetus/neonate is usually only recognized after bleeding has occurred or severe thrombocytopenia detected by chance. This raises the question of whether routine screening for FNAIT should be considered. It is recognized that there are significant shortcomings in the knowledge about FNAIT necessary for the introduction of an antenatal screening program.<sup>7</sup>

More research is required, for example, on the clinical outcome of first affected pregnancies, the identification of laboratory measures predictive of severe disease where ante-natal intervention might be justified, and the optimal approach for the ante-natal management of pregnant women with HPA antibodies, but with no previous history of affected pregnancies, as ante-natal treatment carries significant risks and costs.

#### **Management of FNAIT**

#### Post-natal

The thrombocytopenia in FNAIT usually resolves within 2 weeks, although it may last as long as 6 weeks. A cerebral ultrasound should be carried out to determine if ICH has occurred because of the changes in management that would occur if there had been a hemorrhage. The optimal post-natal management of FNAIT depends on its rapid recognition, and prompt correction by transfusion of platelet concentrates to neonates who are severely thrombocytopenic (platelet count  $<30 \times 10^9$ /L) or bleeding. It is not appropriate to wait for the laboratory confirmation of the diagnosis in suspected cases.

While there has been debate about the value of random donor platelets in the immediate post-natal management of FNAIT, two recent studies reported that random donor (i.e. not HPA-matched) platelets were often effective in increasing the platelet count in FNAIT. However, in some of the cases, spontaneous recovery of the neonatal platelet count may have been the reason for the apparent response to random donor platelet transfusions. Compatible platelet concentrates were shown in another study to produce a larger increase in platelet count and twice the length of survival of the transfused platelets compared to random donor platelets.<sup>8</sup>

Compatible platelet concentrates, for example, from HPA-1a and 5b negative donors, should be used initially, if they are available, on the basis of the certainty of their effectiveness in the more than 90% of cases of FNAIT which are due to anti-HPA-1a or anti-HPA-5b. Unfortunately, the routine availability of such HPA-1a and 5b-negative platelets for immediate use in suspected cases of FNAIT is limited to only a minority of countries, including England.

Although intravenous immunoglobulin (IVIG) is effective in at least 75% of cases, the platelet count does not increase in responders for 24–72 hours so it should not be used for the initial therapy of FNAIT. Its role in the management of post-natal FNAIT should be limited to those few cases with very prolonged and severe thrombocytopenia.

#### Provision of information to the mother

The parents should be provided with information about FNAIT once the platelet antigen typing and antibody results are complete, specifically to provide:

- 1. an explanation of the cause of FNAIT;
- 2. the risk of recurrence in subsequent pregnancies;
- 3. the options for ante-natal management as well as the fact that this is an evolving field;
- a request that the mother should notify the fetal medicine center as soon as she becomes pregnant;
- 5. her risk for the future of transfusion reactions, and potentially post-transfusion purpura (PTP),

although it appears that the risk of PTP is very low with leukocyte-reduced blood components which are now standard in the UK;

6. Testing of female relatives of the mother should be suggested.

#### Ante-natal

The traditional management of subsequent pregnancies in women with a previous history of FNAIT consisted of performing early elective Cesarean section, and then transfusing compatible platelets after birth. Major advances in the ante-natal management of FNAIT have been made in the last 25 years.<sup>1,2,9</sup>

#### Early ante-natal treatment strategies

In 1984, the use of ultrasound-guided fetal blood sampling (FBS) was described to obtain the fetal platelet count at 32 weeks' gestation in the second pregnancy of a woman whose first child had ICH due to FNAIT; the fetal platelet count was  $15 \times 10^9$ /L. There was no ultrasound evidence of ICH by 37 weeks, and an *in utero* transfusion of maternal platelets was given 6 hours prior to delivery by Cesarean section. As a result, the cord platelet count was  $95 \times 10^9$ /L and there were no signs of bleeding.

The use of *in utero* platelet transfusion (see Fig. 5.2) immediately before delivery was described in greater detail in a series of 9 cases, where FBS was carried out at 21 weeks' gestation to confirm the diagnosis of FNAIT.<sup>1</sup> FBS was repeated at 37 weeks with an in utero platelet transfusion if the fetal platelet count was  $< 50 \times 10^9$ /L followed by delivery 6–36 hours later. However, over the next 10 years, it became clearer that an affected fetus is at risk of ICH in utero, even before 20 weeks' gestation, indicating that earlier ante-natal intervention is required in cases likely to be severely affected. During this period, different groups began to explore alternative approaches to ante-natal management, one based around serial weekly fetal platelet transfusion, and the other around medical treatment of the mother with IVIG and/or steroids.

#### Serial fetal platelet transfusions

Early studies with fetal platelet transfusions highlighted the short survival of transfused platelets, and the difficulty of maintaining the fetal platelet count at a "safe" level. Further experience indicated that it was possible to maintain the count above  $30 \times 10^9$ /L using transfusions at weekly intervals (Fig. 5.3). This



**Fig. 5.2** Schematic diagram of ultrasound-guided fetal blood sampling and platelet transfusion.

was achieved by increasing the dose of platelets, whilst avoiding an unacceptable increase in the transfused volume, by concentrating the platelet collection by centrifugation and removal of plasma. Later improvements in apheresis technology allowed the preparation of leukocyte-depleted concentrated platelets suitable for fetal transfusion without the need for further processing.

Fig. 5.3 Pre- and post-transfusion platelet counts following serial FBS and platelet transfusions. The fetal platelet count was <10 x 10<sup>9</sup>/L at 26 weeks. The aim was to maintain the fetal platelet count above 30  $\times$  10<sup>9</sup>/L by raising the immediate post-transfusion platelet count to above 300  $\times$  10<sup>9</sup>/L after each transfusion. The fetal platelet count fell below 10  $\times$  10<sup>9</sup>/L on one occasion when there were problems in preparing the fetal platelet concentrate and the dose of platelets was inadequate. CS = Cesarean section. Reproduced from Practical Transfusion Medicine, 3rd edn. Murphy MF & Pamphilon D. Wiley-Blackwell Publishing, 2009.

#### Technical aspects and complications of FBS

The technique employed for trans-abdominal ultrasound-guided FBS and intravascular transfusion is the same as for red cell alloimmunization. Unlike HDFN, where the needle may be removed while the hematocrit is estimated before transfusion is commenced, removal of the needle from the umbilical cord in the presence of a very low platelet count can result in rapid exsanguination of the fetus. Very few operators check the platelet count during the procedure and it is standard practice to transfuse platelets to the fetus following FBS even if the procedure is undertaken for diagnosis or monitoring of FNAIT rather than part of serial fetal transfusions.

The main risks of FBS are severe cord bleeding, cardiac arrhythmias, and miscarriage. Pooling data from several studies indicates a fetal loss rate of 3/223 (1.3%)/procedure and 3/55 (5.5%)/pregnancy.

From 26 weeks' gestation, FBS and platelet transfusion should be performed in the operating theater where facilities are available to perform an emergency Cesarean section, should there be signs of fetal distress or bleeding from the sampling site. Unpublished data from the Oxford Rhesus Therapy Unit indicate that there is approximately a 4% chance of rapid delivery being required at the time of each transfusion.

The volume of platelet hyperconcentrate to be transfused is calculated from a formula:

Volume of concentrate = desired platelet increment  $\times$  feto-placental blood volume for gestational age  $\times R \div$  platelet count of the concentrate



**Table 5.1** Specification of the platelet product forintra-uterine transfusion

#### Donor

- HPA type compatible with maternal antibodies, usually HPA-1a negative
- Group O RhD negative for the first transfusion (for subsequent transfusions, the ABO and RhD group of the donor should be compatible with the fetal blood group which should be determined from a sample taken at the first FBS)
- No HPA or HLA antibodies
- No high titer ABO antibodies

#### **Platelet concentrates**

- High concentration of platelets (usually in the range  $2.5 \times 10^9 3.0 \times 10^{12}$ /L compared to  $1.4 \times 10^{12}$ /L for standard platelet concentrates for use in neonates or adults) to reduce the volume of the transfusion. The *hyperconcentrates* can be prepared using a modification of the procedure for collection of platelet concentrates by apheresis.
- Gamma-irradiated to prevent
  transfusion-associated graft-vs.-host disease
- CMV-seronegative
- Leukocyte-reduced
- Transfuse within 24 hours after collection

The feto-placental volume for gestational age is calculated from standard charts. In early fetal platelet transfusion studies, the immediate post-transfusion platelet increment was found to be 50% of that expected, i.e. 50% platelet recovery, probably because of pooling in the feto-placental circulation. The volume calculation takes account of this by introducing the factor R = 2, thus doubling the volume of platelets transfused.

The specification of the platelet product for intrauterine transfusion is provided in Table 5.1.

#### **Maternal treatment**

One of the main drivers for the development of maternally directed ante-natal treatment for FNAIT was concern about the risks of FBS and platelet transfusion.

#### Steroids

There is considerable experience from North America with the combined use of steroids and IVIG.<sup>10</sup> Although low dose steroids did not add significantly to the effect of IVIG, high dose steroids (prednisolone 60 mg and later 1 mg/kg) added substantially to the effect of IVIG. The use of 0.5 mg/kg prednisolone in the lowest risk cases (no previous sibling ICH, initial fetal count  $> 20 \times 10^9$ /L) demonstrated efficacy comparable to that of IVIG in this group of patients.

#### Intravenous immunogloblin (IVIG)

The first protocol involving maternal administration of IVIG was described in 1988. Initial FBS was carried out at 20-22 weeks' gestation to confirm the diagnosis of FNAIT and its severity. IVIG (dose 1 g/kg body weight/week) was administered to the mother, and FBS was repeated 4-6 weeks later to assess the effect of IVIG. None had ICH in contrast to three of their respective untreated siblings, two of whom had antenatal ICH, and there were no serious complications of treatment.Overall, there was an increase of  $36 \times 10^9$ /L between the first and second FBS, and an increase of  $69 \times 10^9$ /L between the first FBS and birth. Of fetuses 62%-85% responded to therapy depending on the definition of response used, and there were no cases with ICH. However, other reports described cases in which IVIG was ineffective in raising the fetal platelet count, and ante-natal ICH was reported during maternal treatment with IVIG.

#### **Complications of maternal teatment**

The use of IVIG is expensive, and both IVIG and prednisolone can cause adverse maternal effects. IVIG appears to be a safe blood product when administered to otherwise healthy young women. The risks of renal disease, hemolysis, fluid overload, and transmission of infection are extremely low, and none of these have been reported in a patient undergoing antenatal treatment for FNAIT. Headaches occur but usually lessen with time. Prednisolone has been widely used in pregnancy, and is known to cause fluid overload, high blood pressure, diabetes mellitus, irritability, and osteoporosis.

#### **Recent studies of maternal treatment**

A collaborative study in European centers reported in 2003 on the ante-natal management of FNAIT in 56 fetuses managed with either maternal treatment or platelet transfusions. Maternal therapy, predominantly IVIG, resulted in a platelet count exceeding 50  $\times$  10<sup>9</sup>/L in 67%. The most serious complications encountered were associated with FBS and platelet transfusion, and the results support the use of maternal therapy as first-line treatment for the ante-natal management of FNAIT. The association of lower pre-treatment platelet counts in cases with a sibling history of ante-natal ICH or severe thrombocytopenia favors stratification of ante-natal management on the basis of the history of FNAIT in previous pregnancies.

In 2006, the North American team reported two randomized controlled trials of maternal treatment stratified according to the previous history of FNAIT.<sup>11</sup>

- (1) "High risk" patients had either a sibling with peripartum ICH or one with an initial fetal platelet count  $< 20 \times 10^9$ /L. Patients underwent FBS at 20 weeks or later, and were randomized to receive IVIG alone (1 g/kg/week) or in combination with prednisolone 1 mg/kg/day. There was a satisfactory increase in the fetal platelet count in 89% of pregnancies receiving combination treatment compared to 35% receiving IVIG alone (P = < 0.05). In those with initial fetal platelet counts  $< 10 \times 10^9$ /L, 82% had a satisfactory response to IVIG and prednisolone compared to only 18% treated with IVIG alone (P = < 0.03). There was one ICH; this occurred in a pregnancy managed with IVIG alone.
- (2) "Standard" risk patients were those with a sibling who had not had an ICH and a fetal platelet count between 20 and  $100 \times 10^9$ /L. These patients underwent FBS near to 20 weeks, and were randomized to receive IVIG (1 g/kg/week) or prednisolone 0.5 mg/kg/day. Subsequent FBS was carried out in all patients at 3–8 weekly intervals. There were no significant differences in the responses to the two treatments. There were two ICHs; one in a fetus born at 38 weeks' gestation with a platelet count of  $172 \times 10^9$ /L, and one in an infant with a birth platelet count of  $68 \times 10^9$ /L delivered at 28 weeks because of bradycardia following FBS.

There were 11 serious complications out of a total of 175 (6%) FBS confirming the dangers of FBS and platelet transfusion in FNAIT. This study demonstrates that effective ante-natal treatment can be stratified according to the previous history of FNAIT.

#### The search for less invasive strategies for the ante-natal management of FNAIT

Concern regarding the safety of FBS and platelet transfusion has led to a search to develop less invasive treatment strategies involving maternal administration of IVIG while reducing or even avoiding FBS for monitoring the fetal platelet count and administering platelet transfusions.

Some studies suggested that the pre-treatment platelet count had predictive value for the response to maternal treatment. A review of patients treated in North America found that the response rate in fetuses with a pre-treatment platelet count of  $> 20 \times 10^9$ /L was 89%, but was only 51% in those with an initial fetal platelet count  $< 20 \times 10^9$ /L. The authors suggested that additional FBS might not be warranted in those cases with an initial fetal platelet count  $> 20 \times 10^9$ /L; any gain from identifying and intensifying treatment in "poor responders" would be offset by the complications of additional FBS.

The Leiden group have evaluated less intensive ante-natal treatment strategies over a number of years and found that that a non-invasive strategy based on treatment with IVIG without FBS appears to be effective when there is no history of ICH in a previous pregnancy.<sup>12</sup> The same group extended this approach to the management of seven high risk pregnancies where there had been a previous sibling history of ICH. IVIG was administered from 16-19 weeks' gestation in the six pregnancies where there had been previous antenatal ICH, and from 28-29 weeks in the case where ICH was post-natal. The total number of weekly IVIG infusions ranged from 8 to 21. The platelet count at birth ranged from  $10 \times 10^9 49 \times 10^9$ /L. No ICH was seen on ante-natal or post-natal ultrasound examinations, and all infants were doing well at follow-up at 3 months.

These recent studies indicating success with less invasive strategies suggest that further work is necessary to determine the optimal ante-natal management for FNAIT. An alternative to the "empirical" (no FBS) and "invasive" (FBS before and during treatment) approaches is to initiate maternal treatment (type and timing determined by consideration of the previous history of FNAIT) without performing FBS, and then to carry out FBS 4–8 weeks after the initiation of treatment to identify the non-responding cases which may benefit from a change in treatment. This is the approach being followed by some UK referral  $\label{eq:stability} \begin{array}{l} \textbf{Table 5.2} & \mbox{Suggested ante-natal management depending on } \\ \mbox{previous history of FNAIT}^* \end{array}$ 

#### (1) Ante-natal ICH in previous sibling:

#### ICH in second trimester

- At 12 weeks, IVIG 2 g/kg/week (given as 1 g/kg/twice a week)
- FBS at week 20-22

#### ICH in third trimester

- At 16 weeks, IVIG 1 g/kg of IVIG
- FBS at week 20-22

#### If fetal platelet count at first FBS > 30 $\times$ 10<sup>9</sup>/l:

- Continue current treatment
- Further FBS at 28 weeks at 34–36 weeks and/or pre-delivery

#### If fetal platelet count at first FBS < 30 $\times$ 10<sup>9</sup>/l:

- Add prednisolone 1 mg/kg/day
- Repeat FBS 2 weeks later. If no response, where relevant increase IVIG to 2 g/kg/week (given as 1 g/kg/twice a week) and repeat FBS at 2 weeks
- If no response to maximal combination therapy, proceed to weekly IUT and discontinue medical treatment
- If response to maximal combination therapy repeat FBS at 2–4 weekly intervals

### (2) Neonatal ICH or platelet count $\leq$ 50 $\times$ 10 $^{9}/l$ in previous sibling:

- IVIG 1 g/kg/week at 20 weeks
- FBS at 28–32 weeks

#### If fetal platelet count > 30 $\times$ 10<sup>9</sup>/l:

- Continue current treatment
- Further FBS at 34–36 weeks

#### If fetal platelet count at first FBS < 30 $\times$ 10<sup>9</sup>/l:

- Add prednisolone 1 mg/kg/day
- Repeat FBS 2 weeks later. If no response, where relevant increase IVIG to 2 g/kg/week (given as 1 g/kg/twice a week) and repeat FBS at 2 weeks
- If no response to maximal combination therapy, proceed to weekly IUT and discontinue medical treatment
- If response to maximal combination therapy, repeat FBS at 2–4 weekly intervals

#### Table 5.2 (cont.)

#### Mode of delivery:

Based on FBS at 30-32 weeks:

- If fetal platelet count ≥ 100 × 10<sup>9</sup>/L, proceed to spontaneous vaginal delivery with no further fetal blood sampling
- If fetal platelet count ≤ 100 × 10<sup>9</sup>/L, continue with treatment and perform repeat sampling at 35–37 weeks, with transfusion of platelets
- If fetal platelet count ≥ 50 at 35–37 weeks (prior to platelet transfusion), allow spontaneous vaginal delivery
- If platelet count < 50 × 10<sup>9</sup>/L at 35–37 weeks, discuss options:
- Induction of labor within 5 days of IUT
- Weekly IUT until either spontaneous labor, induction of labour or planned Cesarean section

There is no evidence to suggest that elective Cesarean section is safer than vaginal delivery, if the platelet count is above 50  $\times$  10  $^{9}/L$ 

\* developed by Rachel Rayment, Mike Murphy and Jim Bussel (unpublished data).

centers including our own (Table 5.2). Recommendations about the mode of delivery are also provided in Table 5.2.

## How to manage the 'non-responders' to initial maternal therapy

The options are to increase the dose of IVIG, add prednisolone, switch to serial platelet transfusions and/or consider early delivery. The North American group have developed this concept of "salvage" or "intensification" therapy. Only about 25% of "high risk" or "standard risk" patients required more intensive treatment because of a lack of response to their initial therapy. "Intensification" therapy comprised adding IVIG or prednisolone if not being used already, or increasing the dose of IVIG, and all but six had platelet counts at birth > 50 × 10<sup>9</sup>/L.

The ability to modify ante-natal treatment in an individual case does depend on the use of FBS to monitor the fetal platelet count. Although empirical treatment without knowledge of the fetal platelet count before or during treatment avoids the risks of FBS, it has the drawbacks of the administration of potentially unnecessary or inadequate treatment.

## Optimal approach for the modern ante-natal management of FNAIT

There has been huge progress in the ante-natal management of FNAIT over the last 20 years. However, the ideal effective treatment without significant side effects to the mother or fetus has yet to be determined.

There are some basic principles to consider in the management of an individual case.<sup>2</sup>

- 1. Obtain as much information as possible about the clinical history of previously affected pregnancies with FNAIT focusing on the neonatal thrombocytopenia to exclude other causes of thrombocytopenia. It is important to determine as conclusively as possible if an ICH has occurred and if so, when.
- 2. Ensure that comprehensive laboratory investigations have been carried out in a reference laboratory, including testing for HPA antibodies and the identification of their specificity, and HPA genotyping of the mother and her partner. If the partner is heterozygous for the relevant HPA, the fetal HPA genotype should be established.
- 3. Affected fetuses should be managed in referral centers with experience in the ante-natal management of FNAIT. Close collaboration is required between specialists in fetal medicine, obstetrics, hematology/transfusion medicine, and pediatrics.
- 4. The mother and her partner should be provided with detailed information about FNAIT and its potential clinical consequences, and the benefits and risks of different approaches to ante-natal management.
- 5. Maternally administered therapy should be the first-line approach in all cases. This is based on data describing the effectiveness and safety of maternal treatment in contrast to the toxicity of serial FBS to deliver weekly fetal platelet transfusions.
- 6. An important goal is to minimize the number of FBS. However, the debate between empirical treatment and treatment guided by measurement of the fetal platelet count using FBS is not yet resolved. Either approach is acceptable until the

issue is resolved by further clinical trials. It is to be hoped that there will be developments in laboratory testing allowing non-invasive assessment of the likely severity of FNAIT in individual cases.

- 7. Different centers currently have different strategies based on their own experience and those of published studies. Stratification of ante-natal treatment based on the history of FNAIT in previous pregnancies is common (and appropriate) to both empirical and "invasive" approaches to treatment.
- 8. Further progress is only likely to be achieved by conducting randomized controlled trials to resolve outstanding management issues. Patients should be entered into trials, wherever possible. Even referral centers see relatively small numbers of patients, and to obtain sufficient patient numbers for adequately powered trials, collaboration will be required between referral centers.

#### Summary

There have been considerable advances in the clinical and laboratory diagnosis of FNAIT, and its postnatal and ante-natal management. The ante-natal management of FNAIT has been particularly problematic, because severe hemorrhage occurs as early as 16 weeks' gestation and there is no non-invasive investigation which reliably predicts the severity of FNAIT in utero. The strategies for ante-natal treatment have included the use of serial platelet transfusions, which while effective are invasive and associated with significant morbidity and mortality. Maternal therapy involving the administration of intravenous immunoglobulin and/or steroids is also effective and associated with fewer risks to the fetus. Significant recent progress has involved refinement of maternal treatment, stratifying it according to the likely severity of FNAIT based on the history in previous pregnancies. However, the ideal ante-natal treatment, which is effective without causing significant side-effects to the mother or fetus, has yet to be determined, and further clinical trials are needed.

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## Feto-maternal alloimmune syndromes **Red cell alloimmunization**

Alec McEwan

#### Introduction

Hemolytic disease of the newborn (HDN) describes a process of rapid red blood cell breakdown, which puts the baby at risk of anemia and kernicterus (bilirubin induced cerebral damage) within the first few days of life. A variety of etiologies are recognized; however, this chapter focuses on red cell alloimmunization, i.e. the immune-mediated destruction of erythrocytes initiated by maternal red cell antibodies which reach the fetal circulation by transportation across the placenta, onwards from approximately 12 weeks' gestation.

#### Pathogenesis

Antibodies recognizing red cell surface antigens usually arise secondary to a blood transfusion, or following the birth of a baby with a different blood group to the mother. Fetal red blood cells "traffick" into the maternal circulation throughout pregnancy, but "isoimmunization" against foreign antigens occurs most frequently around the time of delivery when the size of feto-maternal hemorrhage (FMH) tends to be greatest. Other events associated with FMH are listed in Table 6.1. These red cell antibodies can, in a subsequent pregnancy, reach the fetal circulation and cause immune mediated destruction of fetal red blood cells. This transplacental transportation of maternal immunoglobulin G begins in the early second trimester and red cell antibodies recognizing certain erythrocyte antigens may bind and bring about premature destruction of the fetal red cells by the reticuloendothelial system. One of the breakdown products of heme is bilirubin, and levels rise within the fetus and amniotic fluid, although placental transfer limits this accumulation. Progressive anemia initially stimulates the bone marrow first but, as its capacity to maintain the hemoglobin levels is exceeded, extramedullary hematopoiesis becomes increasingly important. This hyperactivity of the reticuloendothelial system results in fetal hepatosplenomegaly. A degree of portal hypertension and hypoalbuminaemia secondary to liver dysfunction may contribute to extracellular fluid accumulation within the fetus (hydrops fetalis); however, cardiac dysfunction is more likely to be the main explanation for hydropic change. Fetal anemia induces a high-output cardiac state and a degree of hypoxia may directly impair myocardial contractility. Hydrops is characterized by skin edema, pleural and pericardial effusions, cardiomegaly, atrioventicular valve dysfunction, ascites, polyhydramnios, and placentomegaly, all of which can be detected by ultrasound scanning (Fig. 6.1-6.3). These changes are seen only when fetal hemoglobin levels decline well below the normal range and are a late feature of erythroblastosis fetalis. Intrauterine death will ensue in severe cases if the problem is not treated, or the baby delivered.

HDN describes the consequences of this antenatal pathogenic process which continues on into the newborn period. Maternal immunoglobulin G (IgG) remains with the baby for 4-6 months after birth and top-up blood transfusions may be needed by the infant whilst hemolysis continues. Far more concerning than this semi-chronic post-natal anemia, however, is the risk of kernicterus which occurs within the first few days of life. The immature fetal liver is unable to conjugate the excessive circulating bilirubin and, as serum levels rise, it permeates the bloodbrain barrier. The globus pallidus of the basal ganglia and the brain stem nuclei are the structures most at risk of damage from the unconjugated bilirubin, which is thought to uncouple phosphorylation from oxidation, resulting in reduced ATP synthesis and impairment of energy-dependent metabolism. Athetoid cerebral palsy, other movement disorders, deafness and

*The Obstetric Hematology Manual*, ed. Sue Pavord and Beverley Hunt. Published by Cambridge University Press. © Cambridge University Press 2010.

 Table 6.1
 Clinical scenarios associated with FMH and risk of isoimmunization (adapted from RCOG Green top guideline (No. 22))

Any birth (including by cesarean section)

Manual removal of retained placenta

Stillbirths and intrauterine deaths

Abdominal trauma in the third trimester

Delivery of twins

Unexplained hydrops fetalis

Invasive pre-natal diagnostic procedures such as amniocentesis or CVS

Antepartum hemorrhage

External cephalic version

Hydatidiform mole

Termination of pregnancy (prophylaxis is recommended at all gestations and with all methods)

Ectopic pregnancy (regardless of mode of treatment)

Spontaneous miscarriage  $\geq 12$  weeks (see below)



**Fig. 6.2** Ante-natal ultrasound showing a transverse section through the fetal cranium. The calipers are measuring 9 mm of scalp edema. Edema can collect throughout the skin of the fetus in severe anemia. This results from a combination of high output cardiac failure and also possible hepatic dysfunction and hypoproteinemia.



**Fig. 6.1** Ante-natal ultrasound showing a transverse section through the upper fetal abdomen at the level of the stomach and liver. The calipers are measuring a 10 mm rim of ascites. There are numerous etiologies for fetal ascites, but fetal anemia (from any cause) is one of the more common explanations.

impaired eye movements may all be long-term sequelae of kernicterus.

Repeated exposure of an isoimmunized woman to the same red cell antigen, as occurs in successive pregnancies, will further stimulate antibody production. Subsequent pregnancies, which express the blood group in question, have a tendency to show more severe hemolysis, and at earlier gestations.



**Fig. 6.3** Ante-natal ultrasound showing a transverse section through the fetal chest. A slender fetal pericardial effusion and a small left sided pleural effusion behind the heart can be seen. The heart is also subjectively enlarged. These features are all consistent with, but are non-specific signs of, fetal anemia.

#### Genotype and phenotype

There are almost 30 different blood grouping systems, but the ABO and Rhesus groups are arguably the most important clinically. The Rhesus D (RhD) antigen was discovered in 1939, but the full complexity of this blood group system has only become evident much more recently with the advent of molecular biology.

Of white Europeans, 16% are RhD negative, 5% of West Africans, and virtually no Chinese. Of all deliveries in the UK, 10% are of RhD positive babies born to RhD negative women. In the absence of preventive measures, 1 in 6 RhD negative women will isoimmunize if they deliver a term RhD positive baby, and in the 1950s 1 in 2000 babies died of HDN, principally due to RhD isoimmunization.

The Rhesus proteins are coded for by two genes, which share a major degree of homology. *RHD* and *RHCE* lie very close to one another on chromosome 1, back-to-back, and are thought to have arisen from a duplication event involving the original ancestral Rhesus gene, which can still be found in rodents and most other mammals. The Rhesus proteins are characterized by 12 intramembranous segments and 6 extra cellular "surface" loops. Their function remains unclear, although ammonium ion transportation and gas exchange across the erythrocyte cell membrane have been postulated.

The RhD negative phenotype is recognized in the laboratory by failure of red cells to agglutinate with standard anti-D reagents (antibodies). The underlying genetic explanation for this phenotype is more complex. In Europeans, 90% of RhD negative individuals have a complete deletion of *RHD*, with the remaining cases being explained by nonsense and frameshift mutations which truncate the protein. However, in the majority of African individuals typed as RhD negative the genotype is very different. The two common *RHD* variants resulting in the D negative phenotype are the RHD pseudogene, *RHD* $\psi$ , which codes for a non-functional protein, and the *Cde<sup>s</sup>* allele which contains segments from both the *RHD* and the *RHCE* genes.

The situation is confused even further by alleles of *RHD*, which cause subtle *qualitative* changes in the extracellular surface loops of the RhD protein, meaning that serological tests are only weakly positive with standard anti-D reagents. Furthermore, missense mutations causing single amino acid substitutions in the intramembranous or cytoplasmic portions of the RhD protein may impair integration of the protein into the membrane, so bringing about a *quantitative* reduction in the number of cell surface antigen sites per red blood cell. This too may reduce the agglutination response of these cells to standard laboratory anti-D antibodies. These "partial D" and "weak D" pheno**Table 6.2** Key events in the history of prevention of RhDisoimmunization

- **1938** Darrow concludes that "erythroblastosis fetalis" results from the formation of a maternal antibody against some component of fetal blood
- **1939** Levine and Stetson postulate that maternal immunization is caused by a fetal antigen inherited from the father which is lacking in the mother
- 1940 Landsteiner and Wiener discover the Rhesus antigen
- **1948** Wiener suggests that the initiating process is occult placental hemorrhage
- **1957** Kleihauer devises a test able to detect fetal cells in the maternal circulation
- **1961** Stern gives RhD positive red blood cells to RhD negative volunteers, both with and without anti-D, and shows that alloimmunization can be prevented
- **1966** Freda demonstrates that isoimmunization can be prevented by giving anti-D to recently delivered RhD negative women
- **1969** Widespread introduction of routine post-natal prophylaxis with anti-D following multicenter trials

types, as they are respectively known, can be important from a clinical perspective and will be discussed in greater detail later.

The DNA sequence of the *RHCE* gene shows far less variation, and differences at just five amino acid positions result in the four different antigens C, c, E, and e. Each allele expresses only C or c, in combination with E or e, and, amongst Europeans, the Ce haplotype is most common.

#### Prevention of RhD isoimmunization

Antibodies against all the Rhesus proteins, and other red cell antigens, can cause erythroblastosis and HDN; however, anti-D has historically been of greatest significance. Prevention of RhD isoimmunization, and improvements in the ante-natal and neonatal care of isoimmunized women and their babies, has all but eradicated serious morbidity and mortality associated with this condition. Some of the key landmarks in the evolution of this success story are listed in Table 6.2. By the early 1960s Stern had demonstrated that exogenous anti-D given to RhD negative individuals could prevent immunization occurring when RhD positive blood was transfused into them.

Exogenous anti-D is produced by exposing RhD negative volunteers to the RhD antigen. These individuals are either male, or are women who have completed their families. They regularly donate their blood, and cold-ethanol precipitation is used to separate the Table 6.3 Tests used to quantify the size of a FMH

*Kleihauer* : Fetal hemoglobin (HbF) is more resistant to acid or alkaline elution than adult hemoglobin. After treatment, any erythrocytes containing HbF retain their hemoglobin and can be stained and recognized. Unfortunately, some adults have persistent HbF production, and this can confuse matters. Furthermore, quantification is less precise with bigger bleeds.

**Flow cytometry**: This uses immunofluorescently stained antibodies to recognize fetal erythrocytes, which can then be flow-sorted and quantified. This method is often preferred for larger bleeds.

immunoglobulins from their hyperimmune plasma. Following the emergence of variant Creutzfeldt–Jakob disease in the UK, only plasma from US volunteers has been used more recently, although it is not known for certain if prions can be transmitted via transfused immunoglobulins. A solvent/detergent treatment inactivates HIV, hepatitis B and hepatitis C. BPL, one of the major manufacturers of anti-D, estimates a risk of viral infection of 1 in 10 000 billion doses of their product and, to date, there have been no recorded cases.

There were theoretical concerns that passive anti-D might itself cause haemolysis within the fetus. There is certainly no doubt that it can cross the placenta. Although a small number of babies were born in the anti-D trials with a weakly positive direct antiglobulin test (DAT), the reaction was insufficiently strong to cause significant hemolysis or anemia.

Delivery was recognized to be the time of greatest risk for FMH and by the end of the 1960s widespread post-natal prophylaxis had been introduced. A Cochrane review of six eligible trials of routine postpartum anti-D prophylaxis gives a relative risk of 0.12 for RhD alloimmunization in the subsequent pregnancy, i.e. a tenfold reduction in the incidence of isoimmunization.<sup>1</sup> Various doses of anti-D have been tried, and indeed protocols still vary around the world today. Doses of less than 500 iu are associated with a greater risk of isoimmunization; however, higher doses do not seem to confer any obvious benefit. 125 iu anti-D, is able to neutralize 1 ml of fetal red blood cells. Feto-maternal hemorrhage (FMH) of  $\geq$  30 ml occurs in only 0.6% of all deliveries. A dose of 1500 iu has been adopted in the USA to cover the possibility of larger hemorrhages. In the UK and France, a smaller dose of 500 iu is routinely used; however, a test is also performed to quantify the size of the FMH (Table 6.3). Occasional bleeds exceeding 4 ml are recognized and a higher dose of anti-D is administered.

The anti-D is usually given by intramuscular injection (although intravenous preparations are available) and ideally should be given within 72 hours of delivery (or any other possible sensitizing event). There may, however, be benefit in giving anti-D as much as 9–10 days following potential isoimmunizing events.

Later came the recognition that a variety of events during pregnancy might cause or be associated with FMH, other than delivery, and that these might subsequently also lead to isoimmunization (Table 6.1). The RCOG Green-Top Guideline (No. 22) lists these situations and recommends the use of anti-D prophylaxis in these scenarios also.<sup>2</sup> The RhD antigen is thought to be expressed as early as 7-8 weeks gestation and there is no doubt that FMH can be demonstrated during the first trimester. As little as 0.25 ml of fetal RhD positive blood may be sufficient to cause isoimmunization and older studies have shown that this value is often exceeded with FMH occurring after 8 weeks. The studies examining the risk of first trimester isoimmunization are old, and few in number.<sup>3</sup> The risk probably lies between 0 and 3%, but does seem to be higher when the uterus is instrumented.

The RCOG have recommended anti-D only for miscarriages prior to 12 weeks if the uterus is instrumented. After 12 weeks, and before 20 weeks, 250 iu of anti-D should be given for all threatened and actual miscarriages. Miscarriages and other potential sensitizing events after 20 weeks should be covered by 500 iu of anti-D and a Kleihauer should be taken to identify those cases where the size of the FMH exceeds 4 ml.<sup>2</sup>

#### Routine antenatal prophylaxis

Even in the absence of defined events known to be associated with FMH, leakage of fetal red blood cells into the maternal circulation is known to occur throughout pregnancy. Beyond 28 weeks' gestation the quantity of trafficked cells can be great enough to bring about alloimmunization. Indeed, "silent" FMH will cause RhD isoimmunization in 1%–2% of all RhD negative women with RhD positive pregnancies.

There is good-quality evidence supporting the use of routine ante-natal anti-D prophylaxis (RAADP) to prevent these isoimmunizations. A consensus conference hosted by the RCOG and RCP in 1997 came out strongly in favor of routine ante-natal prophylaxis. Crowther subsequently published a systematic review in the Cochrane database, although only two trials were deemed of high enough quality to be included. This review reported a relative risk of isoimmunization of 0.4 in the women receiving RAADP. More recently, a Technology Appraisal Guidance (No. 41), produced by NICE,<sup>4</sup> has reviewed the wider evidence from nine trials. Although the trials varied in design and methodology, they gave remarkably consistent results. Without RAADP the isoimmunization rate ranged from 0.9%–1.6%. This fell to approximately 0.3% in the groups receiving RAADP.

A number of attempts at estimating the cost effectiveness of this intervention have been made. The number of HDN related deaths would be reduced from approximately 30 to 10 per year in the UK if all women received RAADP. The cost-benefit seems clear for women in their first pregnancy, but less so for parous women. Ultimately, however, both the RCOG and NICE have recommended RAADP for all RhD negative women, irrespective of parity.

The following dosage schedules are currently in use in the UK:

- A 500 iu at 28 weeks and 34 weeks' gestation
- B A single dose of 1500 iu at 28 weeks' gestation

Schedule A was used in the only randomized controlled trial of RAADP (Hutchet) and was most widely adopted in the UK.<sup>4</sup> The half-life of anti-D is 24 days and theoretically there is less circulating anti-D left at 40 weeks' gestation with schedule B than with A. The trials using this regime however did not show significantly poorer results. Commercially available preparations of 1500 iu anti-D have recently become available in the UK and there is a move toward schedule B, mostly for reasons of convenience and patient preference (one injection rather than two).

#### Refusal of anti-D prophylaxis

A small minority of women will refuse anti-D, either as part of RAADP or following potentially sensitizing events (including delivery), perhaps due to safety fears or "needle phobia." The woman should be provided with good-quality information to ensure that this choice is truly informed; however, the final decision of course must lie with her. Declining anti-D prophylaxis carries no risk when;

- 1. the woman is confident she is not going to have further children (e.g. requesting sterilization); *or*
- 2. when the father of the baby, or the fetus itself, is known with certainty to be RhD negative.

Widespread non-invasive pre-natal fetal RhD testing is possible (see later) and, if adopted, will mean that RAADP and the use of anti-D following sensitizing events will be reserved for women carrying a fetus which is RhD positive, or of unknown status.<sup>5</sup>

## Traditional management of isoimmunization

Despite effective prophylaxis programs, new cases of RhD isoimmunization do arise, either because guidelines are not followed appropriately, women fail to seek medical advice around the time of potentially sensitizing events, or because of "silent" isoimmunizations, perhaps occurring prior to 28 weeks' gestation. Management of these pregnancies has become limited to a relatively small number of centers. Preventing morbidity and mortality in these cases necessitates the identification of pregnancies at risk, subsequent monitoring of disease severity, and timely intervention in the form of intrauterine transfusion and/or delivery of the baby. Modern management is quite different to that of even just 10 years ago and, to best appreciate the recent advances made, a rapid review of traditional methods is included here.

#### **Historical perspectives**

Routine maternal blood typing and serological testing was introduced in the 1950s. RhD negative women with anti-D antibodies were recognized as being at risk of having their pregnancies complicated by hydrops, stillbirth, and hemolytic disease of the newborn. Approximately 85% of the white European and North American population is RhD positive, and just over half are heterozygous. The offspring of RhD heterozygous males and RhD negative women are at 50% risk of being RhD positive themselves, and 50% will be RhD negative. The RhD negative fetus is at no risk of hemolysis, whatever the levels of maternal anti-D. Although RhD negativity in male partners could be determined with certainty, predicting whether a RhD positive man was homo- or heterozygous was imprecise prior to the advent of molecular biology and relied on the results of serological testing with anti-sera to the D, C, c, E and e antigens and racially specific incidence charts. However, this prediction was inexact and, when a male partner was thought to be heterozygous, the status of the fetus remained unclear. A RhD negative pregnancy could be exposed to serial invasive testing when there was no actual risk.

With the development of molecular genetic techniques, and improved understanding of the Rhesus gene cluster, it became possible to determine RhD status precisely using DNA amplification techniques.<sup>6</sup> These are able to sensitively distinguish between homozygotes and heterozygotes and can be applied to DNA from amniocytes to precisely assign RhD positive or negative status to the fetus of a couple where the male partner is heterozygous. A single amniocentesis meant that further testing could be avoided in 50% of cases (those found to be RhD negative). Surveillance and invasive testing could then be appropriately focused on the RhD positive pregnancies.

A number of different factors have been used to time interventions in Rhesus disease. The simplest and least sensitive of these is previous obstetric history. Walker showed how, in a RhD isoimmunized pregnancy, the risk of stillbirth was 8% if there was no previous history of HDN. This rose to 18% if a previous child had been moderately affected and to 58% if there was a previous history of stillbirth caused by hemolytic disease. The tendency for the disease to become more severe, and at progressively earlier gestations, was well recognized. Recent retrospective reviews of isoimmunized pregnancies have confirmed these historical conclusions. However, relying on previous history to guide intervention was imprecise and hazardous.

Coombs demonstrated that the strength of anti-D isoimmunization could be measured by serially diluting maternal serum until agglutination of RhD positive red blood cells no longer occurred. The more doubling dilutions were required to lose this reaction, the more anti-D must have been there to begin with. Serial dilutions of 1/2, 1/4, 1/8, 1/16, 1/32, 1/64, 1/128 indicated progressively higher starting levels of anti-D. More recently, levels of anti-D have been quantified more precisely in "international units per ml" (IU/ml) using different techniques. Significant hemolysis is unlikely at levels below 4 IU/ml and is unlikely to be severe at levels below 10-15 IU/ml. However, this threshold too is insensitive and the relationship between absolute anti-D levels and disease severity weakens in pregnancies beyond the first where antibodies are detected.

Nevertheless, these factors have been used (and still are to some degree) to decide when to investigate

further with amniocentesis, perform fetal blood sampling, or indeed deliver.

#### Amniocentesis

Immune-mediated hemolysis within the fetus generates bilirubin, which is excreted by the fetal kidneys into the amniotic fluid. Ballantyne, at the end of the nineteenth century, recognized that yellow staining of amniotic fluid was associated with the subsequent development of severe jaundice in the newborn. Bevis recognized that the degree of yellow pigmentation of amniotic fluid samples taken during pregnancy offered a guide to the final outcome; however, reliable measurement of bilirubin concentrations proved difficult and the alternative technique of measuring the optical density shift caused by the bilirubin was adopted. Using a spectrophotometer, the optical density of amniotic fluid is assessed across a wide spectrum of wavelengths. Bilirubin causes a shift in absorption at the 450 nm wavelength and the degree of this shift ( $\Delta$  OD450) is proportional to the concentration of bilirubin. In the early 1960s, Liley published a chart which could be used to estimate the risk of severe anemia in an isoimmunized pregnancy based on the  $\Delta$  OD450 of amniotic fluid collected by amniocentesis after 27 weeks' gestation; the higher the  $\Delta$  OD450, the greater the chance of severe fetal anemia. Results falling above a certain threshold ("Zone 3") would prompt intrauterine blood sampling and a subsequent transfusion if the fetus was found to be significantly anemic. When managing a RhD isoimmunized pregnancy, the timing of the first amniocentesis was decided by a number of factors, including previous history and anti-D titer (or concentration). If the  $\Delta$  OD450 fell below these thresholds, repeated amniocenteses were subsequently required at intervals of 1 to 4 weeks, depending on the initial result, the rate of rise between successive samplings, the Rhesus history and the anti-D level. In a group of pregnancies with a high incidence of fetal anemia, the sensitivity for detection of severe anemia (Hb of less than 5 SD below the mean) was found to be approximately 80%,<sup>7</sup> meaning that 1 in 5 severely anemic fetuses would be missed by the screening test. Reducing the  $\Delta$  OD450 threshold above which fetal blood sampling would be performed did improve the sensitivity to nearly 100% but went hand-in-hand with a drop in the specificity (below 50%) and positive predictive value, meaning that a significant number of fetal blood samplings were being

Table 6.4 The disadvantages of amniocentesis and  $\Delta\,\text{OD450}$  measurements in the assessment of immune-mediated fetal anemia

- 0.5–1.0% risk of miscarriage/preterm delivery/chorioamnionitis/peri-natal loss with each procedure
- Limited performance as a screening test, particularly at gestations <28 weeks
- Cause of fetomaternal hemorrhage and subsequent rise in antibody levels in 50% of cases (Bowell *et al.*)
- A surrogate marker for fetal anemia. Particularly problematic in Kell isoimmunized pregnancies (see later)
- Unpleasant for the woman

prompted by the  $\Delta$  OD450 when, in fact, the fetus was not severely affected (false positives). Other studies quote somewhat different sensitivities and specificities but the overall message remains the same. Later, the Liley charts were extrapolated backwards to 20 weeks' gestation but this too was associated with a reduction in the sensitivity, as demonstrated by Nicolaides. These were not the only weaknesses of amniocentesis used in this way (Table 6.4).

Nevertheless, when the procedure-related risks associated with amniocentesis (0.5%-1.0%) were compared with those of fetal blood sampling (1%-4%) the benefit in "screening" by  $\Delta$  OD450 prior to fetal blood sampling seemed clear. The optimum timing of first, and repeated, amniocenteses required significant experience but it soon became adopted as standard practice in most centers. Some questioned whether, with improvements in fetal blood transfusion techniques, it should be abandoned; however, the practice continued until newer non-invasive methods became more widespread at the beginning of the new millennium. It is rare now for amniocentesis to be performed in the management of RhD isoimmunization.

#### Fetal blood transfusion

Pre-natal treatment options for RhD hemolytic disease, other than preterm delivery, really began in the 1960s when Liley showed that the fetus could be transfused in utero by injection of blood into the fetal peritoneal cavity under X-ray guidance. A radio-opaque dye was injected into the amniotic cavity and taken up by the fetus. On reaching the bowel, it outlined the peritoneal cavity, into which the blood was injected. Erythrocytes were then absorbed directly across the bowel wall into the fetal intravascular compartment. This hazardous procedure was later superseded by ultrasound guided transfusions into the peritoneal **Table 6.5** Historical landmarks in the development of fetal blood transfusion

1963	(Liley)	X-ray guided intraperitoneal IUT
1964	(Freda and Adamsons)	Direct IUT through hysterotomy incision
1981	(Rodeck)	Fetoscopically guided intravascular IUT
1981	(Berkowitz and Hobbins)	Ultrasound guided intraperitoneal IUT
1986	(Nicolaides and Rodeck)	Ultrasound guided intravascular IUT

cavity and then directly into the fetal circulation. The timeline of the evolution of this remarkable fetal therapy is detailed in Table 6.5.

Intraperitoneal transfusion (IPT) had a number of drawbacks. No pre- or post-transfusion fetal hemoglobin level or hematocrit was available, so the volume to be transfused was, at best, an educated guess. Absorption of the donated red cells across the bowel wall was slow and this was of particular concern for the very anemic fetus where immediate and rapid correction was needed. The presence of edema in the bowel wall of a hydropic fetus could interfere with absorption completely. Furthermore, overdistension of the fetal abdomen by the donated blood possibly endangered the fetus by interfering with venous return and cardiac output. As intravascular transfusion (IVT) became more popular, comparative studies suggested a sixfold greater risk of fetal death following IPT.

Ultrasound guided direct intravascular transfusions are performed via a number of different routes. Direct intracardiac transfusion is possible but, for understandable reasons, is not ideal. The majority of fetal IVT are performed into the umbilical vein at the insertion of the umbilical cord into the placenta or percutaneously into the intrahepatic portion of the umbilical vein.<sup>8</sup> A free loop of cord can be used if the placental insertion cannot be accessed. There is little evidence to suggest any one method is superior to the others. Whichever route is favored, the uterine wall, amniotic membrane, and sometimes the placenta, must be breached by the needle. The risk of fetal loss, membrane rupture, bradycardia, or fetal bleeding requiring delivery is quoted between 2% and 4% per procedure, but this depends on gestation, operator experience, and fetal condition prior to the transfusion. Transfusions below 20 weeks gestation are a particular challenge and fetal loss rate is at least 10% if there is hydrops.

The blood used for a fetal transfusion is crossmatched against the maternal blood and should be fresh, CMV negative, and irradiated. The crossmatched unit ideally has a hematocrit of 75%-80%, so as to minimize the volume load of the transfusion on the fetus. A degree of "over transfusion" to a hematocrit of 40%-50% will prolong the interval between subsequent transfusions. However, the transfused blood is acidotic and this and the volume load can be hazardous to the very compromised hydropic fetus. In these cases, a hematocrit of 25% should be aimed for with the first transfusion which can be followed 2 or 3 days later with a second "top-up." The total volume (in ml) to be transfused  $(V_{\rm T})$  is determined by the fetoplacental blood volume ( $V_{\text{Fet}}$ ), which increases with gestation, the hematocrit of the fetal and donated blood (Hct<sub>Fet</sub> and Hct<sub>Don</sub>), and the target "desired" hematocrit (Hct<sub>Des</sub>) according to the equation:

$$V_{\rm T}({\rm ml}) = V_{\rm Fet}({\rm ml}) imes rac{{
m Hct}_{
m Des} - {
m Hct}_{
m Fet}}{{
m Hct}_{
m Don} - {
m Hct}_{
m Des}}$$

There is a steady increase in the total blood volume of the fetoplacental circuit ( $V_{\text{Fet}}$ ) with advancing gestation, from approximately 25 ml at 20 weeks' gestation to 100 ml at 28 weeks', and 210 ml at 34 weeks' gestation.

Maternal sedation is usually employed because the procedure can be uncomfortable and may last more than 30 minutes. These sedative drugs may also help to reduce fetal movement. Antibiotics and oral tocolytics are used by some operators, but there is no evidence to support or refute this practice. The maternal abdomen is sterilized and draped and strict aseptic technique is followed. Local anesthetic is injected into the maternal abdominal wall. Under ultrasound guidance, a 20 Gauge needle is inserted through the uterine wall into the umbilical cord, or the vessels within the fetal liver. A small sample of blood is taken to confirm correct positioning and the hematocrit measured immediately, so that the total volume required can be calculated rapidly. Transfusion of blood at 5 ml per minute is usually tolerated well by the fetus. A post-transfusion hematocrit is taken to help guide the interval between transfusions. The hematocrit drops by approximately 1% per day, but this rate may decline as subsequent transfusions replace the fetal RhD positive blood with donated RhD negative blood, which survives longer. The interval is usually 2-3 weeks and newer scanning techniques may help to fine-tune this (see later). Serial transfusions are usually performed until 34–36 weeks' gestation, after which delivery is organized. Severe, early onset hemolytic disease may necessitate more than five transfusions in a single pregnancy. A vaginal birth is aimed for unless there are other obstetric factors, or the fetus is sick.

#### **Recent advances in management**

Despite the declining incidence of RhD isoimmunization, the management of affected pregnancies has not stood still. The need for invasive assessment of the pregnancy at risk can be directed now with greater precision, and newer treatment options have shown promise in helping to avoid the need for transfusions at very early gestations.

#### Non-invasive testing for fetal RhD status

The plasma of pregnant women contains free (i.e. noncell associated) fetal DNA (ffDNA) in significant quantities, from the early first trimester. The main source of this DNA is debated, but it probably originates from trophoblastic cells at the maternal-fetal interface. This DNA is fragmented and is degraded rapidly. Maternal free DNA is present in much larger quantities. Lo, in 1997, demonstrated how ffDNA could be used for the non-invasive pre-natal diagnosis of fetal RhD status<sup>9</sup> and, since then, the same principles have been applied to non-invasive fetal sexing and the inheritance of paternally derived disease causing mutations. This technology is strongly promoted by "SAFE" (The Special Non-invasive Advances in Fetal and Neonatal Evaluation Network), a multinational European group established in 2004 and funded by monies from the European Union.<sup>10</sup>

A RhD negative woman should have no RhD DNA sequences in her plasma because her negative status is usually caused by a deletion of the RhD gene (but see later). If DNA probes designed to recognize RhD gene exons are added to her plasma, along with DNA polymerase, then no product should form if the fetus is also RhD negative, because there are no binding sites for the probes. If the fetus is RhD positive, then the probes will bind to the ffDNA and a PCR product will be produced, which can be detected easily using standard molecular techniques. Three separate exons from RHD are amplified, and if only one or two of the PCR products is generated then the result is considered equivocal and further investigation is required before a result can be given.

Use of this technology has become almost routine practice in the UK, and in parts of Europe, where the father of the baby is a RhD positive heterozygote, where his status is unknown, or if paternity is uncertain. The team performing this work in the UK is based at the International Blood Group Reference Laboratory in Bristol, and their results are impressive.<sup>11</sup> Over a thousand samples have so far been tested and there have only been two false positive and two false negative results. The accuracy of the test is independent of gestation, however the rate of inconclusive results is higher at gestations below 16 weeks and the test must be repeated in a fifth of cases (personal communication March 2008). A simple maternal blood test effectively avoids the need for amniocentesis to determine fetal RhD status when the father is heterozygous, or his blood group is unknown. This, in turn, bypasses the 1% risk of miscarriage associated with the amniocentesis, and the likely fetomaternal transfusion of red cells which may cause a subsequent rise in anti-D levels in already isoimmunized women. A RhD negative result provides welcome relief and reassurance without having put the pregnancy under any risk at all.

#### Middle cerebral artery blood flow

Since the late 1980s the relationship between fetal anemia and the velocity of blood flow in the middle cerebral artery (MCA) has been clearly documented. This can be measured using ultrasound, and a collaborative group, led by Mari,<sup>12</sup> are usually credited with enhancing the profile of this technique so that today it has effectively replaced amniocentesis in the monitoring of pregnancies complicated by red cell antibodies.

A decrease in total red cell mass results in a reduction in blood viscosity and an increase in cardiac output. The effect on viscosity is thought to be the principal mechanism causing an increase in fetal peak systolic blood flow velocities (PSV). The vessel where this can be measured most easily and reliably is the middle cerebral artery.

The technique is not difficult; however, a number of factors influence the MCA PSV (see Table 6.6) and guidelines must be adhered to strictly. The angle of insonation of the pulse wave Doppler must be as close to 0 degrees as possible, or angle correction must be used. The vessel must be insonated within the first 2 mm of the proximal portion of the vessel as it arises

#### Table 6.6 Factors influencing the MCA PSV value

#### Fetal

Gestational age Fetal activity Cardiac status Gender Uterine contractions

#### Technical

Angle of insonation of Doppler wave Positioning of the Doppler gate along the MCA



Fig. 6.4 Power Doppler study showing the fetal Circle-of-Willis and the near-field middle cerebral artery (MCA)

from the Circle of Willis (see Figs. 6.4 and 6.5). Measurements taken at a distal point in the vessel may be  $6-10 \text{ cm s}^{-1}$  less than values taken proximally. Usually the MCA closest to the transducer is chosen, for ease, but the far-field vessel gives similar results. The fetus must be quiescent as fetal movement and breathing can have a significant impact on the values obtained.

Normal ranges and charts (Fig. 6.6) are available to plot the values onto and these show a normal gradual increase in the MCA PSV as gestation advances. Although the trend in values is important in any particular case, the most valuable indicator of significant fetal anemia has proven to be a threshold of 1.5 MoM (multiples of the median). Below this level, it is highly unlikely that the fetus will be more than just mildly anemic. The higher the value lies above this line, the more likely moderate or severe anemia becomes. If the MCA PSV in an "at-risk" pregnancy is found to fall above this threshold, the study will usually be repeated within 24 hours. If the finding is persistent, then fetal blood sampling (with or without transfusion) will usually be performed soon after. MCA PSV studies are usually performed at intervals varying from 3 days to





4 weeks, depending on the perceived degree of risk, and previous values.

The collaborative group found a 100% sensitivity for the prediction of moderate to severe anemia, with a false positive rate of 28%.<sup>13</sup> This compares very favorably with amniocentesis. Other studies have failed to achieve quite such impressive results, although those of Zimmermann are typical and are at least as good as amniocentesis. They found a sensitivity of 88% and a positive predictive value of 53%, i.e. approximately 1 in 10 cases of moderate-severe anemia were missed and half of all cases with a PSV greater than 1.5 MoM required transfusion. They recommended that **Fig. 6.5** Color Doppler measurement of middle cerebral artery peak systolic velocity (MCA PSV). This study was performed at 22 weeks' gestation. A PSV of almost 50 cm s<sup>-1</sup> in the MCA at this gestation is well above 1.5 multiples of the median and did indeed indicate fetal anemia in this case. Although the circulation is hyperdynamic in fetal anemia, the actual cause of the rise in blood velocity is thought to be a reduction in blood viscosity secondary to a falling fetal hematocrit. The fetal hemoglobin was found to be 4 g/dl on subsequent testing.

Fig. 6.6 A chart showing median fetal middle cerebral artery peak systolic velocities (MCA PSV) throughout the second and third trimesters. An imaginary line has been drawn at 1.5 multiples of this median value and acts as an action line to prompt fetal blood sampling +/transfusion. Superimposed is a fictitious case of severe RhD isoimmunization with a RhD positive fetus. The blue arrows show where maternal IVIG was given, and the red arrows represent fetal blood transfusions. The MCA PSV can be seen to fall immediately following a fetal blood transfusion, but gradually increases again as hemolysis continues. As the fetal RhD positive blood becomes replaced by successive donations of RhD negative blood, the interval between transfusions increases. However, this donated blood also has a limited lifespan, even though it is not subject to the antibody mediated hemolysis.

this technique should not be used after 35 weeks' gestation, when the false positive rate is higher. Other studies have suggested that the MCA PSV operates well in the second trimester, in contrast to  $\Delta$  OD450.<sup>13</sup> Even if MCA PSV only matches the predictive abilities of liquor  $\Delta$  OD450 measurements, the advantage remains clear; the technique is non-invasive. Indeed, by adopting MCA PSV measurements as the method of determining when fetal blood sampling is required, the number of invasive procedures can be reduced by two-thirds. Furthermore, reducing the time interval between MCA studies should improve the sensitivity of the test. Recent studies show that it remains a **Table 6.7** Possible mechanism of action of IVIG in Rhesus D isoimmunization

Increased catabolism of maternal IgG

Competitive blockade of placental IgG transport mechanisms

Fc receptor blockade within the fetal reticuloendothelial system

Precipitation of immune complexes by excess antibody

Antigen neutralization

Binding of exogenous anti-idiotypic Ab to endogenous Ab

useful tool for timing second, third, and subsequent fetal blood transfusions.

#### Adjunctive ante-natal treatments

Targeting the maternal immune response is a tempting strategy for tackling severe cases of isoimmunization. The knowledge that disease severity is, at least in part, related to absolute anti-D levels led to the proposal that plasmapheresis might help ameliorate the disease. Anti-D levels can be kept under control with this technique, but it is not without maternal risk, causes a rebound of antibody levels when treatment comes to an end, and was never convincingly shown to make a difference in erythroblastosis fetalis. For these reasons, its use as an adjunct to well-established management techniques had fallen out of favor until more recently when it has been used in combination with a second form of immunomodulation which itself has shown greater promise. The use of intravenous immunoglobulin (IVIG) to prevent/treat fetal and neonatal alloimmune thrombocytopenia is described in Chapter 5 and there is more evidence of its value in this condition than there is for Rhesus isoimmunization. Nevertheless, non-randomized studies provide support for its use in cases of severe RhD isoimmunization. 1 g/kg is administered on a weekly or fortnightly basis from 13 to 20 weeks' gestation, the aim being to delay the onset of moderate-severe hemolysis to a point in the pregnancy where IVT can be more readily and reliably performed. The number of cases of hydrops can be reduced, as can the number of fetal blood transfusions needing to be performed. Table 6.7 lists some of the possible mechanisms by which IVIG might work. A more recent study has reported on a combination of IVIG with serial plasmapheresis from 12 weeks' gestation for women with the most severe histories, with impressive outcomes.<sup>14</sup> The contribution of the two different methods of immunomodulation is not possible to 
 Table 6.8
 Management strategies where moderate to severe HDN is expected

Close communication with neonatal team			
Planned delivery (induction or Cesarean section)			
Cord blood analysis for bilirubin, Hb, group and DCT			
Drainage of effusions and ascites in the hydropic infant			
Phototherapy			
Intravenous immunoglobulin			
Exchange transfusion			
Recombinant erythropoietin			
Top-up blood transfusions			

assess. IVIG is expensive, and prepared from multiple donors. Rarely, it may cause unpleasant and potentially serious side effects, including;

- pyrexia and rigors;
- headache, backache, and myalgia;
- hypotension and tachycardia;
- tachypnea and chest tightness;
- alopecia;
- hemolytic anemia;
- renal impairment.

Figure 6.6 illustrates how serial MCA PSV monitoring, early IVIG administration and multiple fetal blood transfusions can support a pregnancy at risk of early and severe erythroblastosis fetalis through to a gestation where induction can be expected to bring about the normal birth of a non-hydropic baby with adequate hemoglobin levels.

#### **Pediatric management**

It is rare now for a baby to be born at risk of HDN without the prior knowledge of maternity and pediatric staff. A multidisciplinary approach is vital for optimizing outcomes. Infants born with only a low risk of significant hemolysis should, at the very least, have cord blood sent for Coombs test (DCT), blood group, hemoglobin and bilirubin levels. Close observation over the next 2–3 days is necessary and repeat bilirubin estimations may be required, as may phototherapy.

Management strategies for more significant cases of HDN are listed in Table 6.8.

It is far preferable to treat a hydropic fetus *in utero* than it is to deliver the baby in such poor condition. However, complications from an intrauterine transfusion may precipitate the unplanned delivery of such a baby in which case intubation, ventilation,

and drainage of pleural effusions and ascites will be required. These babies are volume overloaded, making transfusion hazardous (although still necessary). They are at risk of hypoglycemia, hypocalcemia, hyponatremia, hyperkalemia, hyperbilirubinemia, acidosis, and renal failure. Mortality rates are high.

With modern ante-natal and fetal management, this situation is fortunately rare. Nevertheless, planning delivery is important for the cases of moderate or severe erythroblastosis fetalis, even if intrauterine transfusions have minimized the risk. Bilirubin levels will rise sharply after birth and phototherapy must begin immediately.

Light from the blue-green region of the spectrum (425–490 nm) is most effective at converting non-polar bilirubin to water-soluble photoisomers and fluorescent tubes producing irradiance of >30  $\mu$ W/cm<sup>2</sup>/nm are optimal. The surface area of the baby exposed to the light is crucial, and fiber-optic pads placed under the neonate, or the use of specifically designed "bili-beds," ensure that this is maximized. Bilirubin levels must be measured regularly and phototherapy may need to continue for a number of days. Gestation specific charts are available for bilirubin levels and thresholds for exchange transfusion are recognised. A rise in serum bilirubin beyond these levels puts the newborn at increasing risk of kernicterus.

Severe anemia, high absolute bilirubin levels, excessive rise in bilirubin concentration, and unsafe bilirubin-to-albumin ratios are all indicators for exchange transfusion. An intravenous catheter is placed into the inferior vena cava via the umbilical vein through the cord stump and the entire blood volume of the neonate is usually replaced twice ("double-volume" exchange) by removing neonatal blood and replacing it with RhD negative blood in 5-10 ml aliquots. This process removes bilirubin and antibody-coated red blood cells, and at the same time provides new albumin with unoccupied bilirubin binding sites and RhD negative erythrocytes. Between 70% and 90% of all fetal red blood cells are removed, but because most of the bilirubin is in the extravascular compartment, 75% of total body bilirubin remains and can cause a rebound rise in serum levels soon after the exchange, necessitating a repeat procedure. The inherent risks of exchange transfusion are substantial, however (Table 6.9),<sup>15</sup> and experience with the technique is declining. As many as 1-in-20 infants undergoing exchange transfusion may die and 1-in-4 suffer non-fatal complications. Much of this morbidity and mortality is found in preterm

Table 6.9 Potential complications of exchange transfusion

Haematological : Over-anticoagulation with hemorrhage, anemia, neutropenia, thrombocytopenia

**Cardiac** : Volume overload, congestive heart failure, hypertension, arrhythmia, arrest

**Metabolic** : Acidosis, hypocalcemia, hypoglycemia, hyperkalemia, hypernatremia,

Vascular : Thromboembolic events, necrotizing enterocolitis, vessel perforation

Infectious : Bacterial, viral, malarial

Other : Hypothermia, apnea, bowel perforation

babies, emphasizing again the massive impact that ante-natal management has had on this condition by delaying the gestation at which the baby needs to be born. Furthermore, intra-uterine transfusions provide the fetus with red blood cells not at risk of immunemediated hemolysis. By the third IUT, the fetal blood will be almost entirely RhD negative. At birth therefore, these babies paradoxically are less likely to need exchange transfusion.

Avoiding exchange transfusion is clearly beneficial. The use of intravenous immunoglobulin is well established now in the treatment of neonatal alloimmune thrombocytopenia and HDN. Although a number of mechanisms are possible, the main action is thought to be a blockade of Fc receptors in the reticuloendothelial system. IVIG reduces carboxyhemoglobin levels, a sensitive indicator of hemolysis. Although IVIG is prepared from multiple donors, and is extremely expensive, its use as an adjunct in moderate-to-severe HDN seems justified. A Cochrane systematic review in 2002 concluded that IVIG significantly reduces the need for exchange transfusion (RR = 0.28), and reduces the number of exchanges needed when they cannot be avoided.<sup>16</sup> However, better quality studies are few in number and there has been a call for larger randomized trials. It should be used only as an adjunct to phototherapy and 0.5-1.0 g/kg is usually given as a single dose soon after delivery.

The baby remains at risk of developing anemia for some months, for two reasons. Firstly, maternal antibodies circulate for 4–6 months and continue to cause low-grade hemolysis. Secondly, intrauterine and newborn transfusions may suppress normal erythropoiesis and it may be a number of months before reticulocytes appear. During this time, "top-up" blood transfusions may be required, although these carry minimal risk in comparison with exchange transfusion. Regular recombinant erythropoietin (EPO) injections can be used during this time to limit the number of top-up transfusions required.

#### **Rhesus D variants**

RHD is a complex gene and much variation exists within it, particularly between racial groups. Understanding this is crucially important for a number of reasons. Phenotypic tests of RhD status examine how blood from an individual behaves when it is added to serum containing anti-D antibodies. Agglutination indicates that the individual is RhD positive. Genotypic tests of RhD status look for key DNA sequences from *RHD*. The entire gene cannot be examined, so sections from a variety of coding exons are chosen for multiplication, using the polymerase chain reaction. If a PCR product is produced, then the assumption is made that the individual is phenotypically RhD positive.

RhD variants can confuse this. The common cause for RhD negativity in Africans is an allele called the RHD pseudogene (RHD $\psi$ ) which contains a 37 base pair insert in exon 4 and a nonsense mutation in exon 6, which effectively make the protein non-functional. Phenotypically, these individuals are RhD negative, but genetic tests might, for example, amplify exon 7 successfully and give a false positive result for RhD status. Amplifying more exons, such as exon 5, would allow clarification because this exon is amplified from the normal RHD but not  $RHD\psi$ . This has particular relevance to non-invasive pre-natal RhD testing. Knowledge of the racial origin of the woman's partner is clearly important. A second common African variant is the RHD/CE hybrid allele, of which there are more than 20. In these alleles, entire segments of the RHCE gene have been substituted into RHD. These red blood cells will agglutinate with polyclonal serum, but fail to react with monoclonal antibodies raised specifically against the extracellular loops coded by the missing exons. Although certain RHD exons will amplify with standard RHD probes, not all will (because they are missing), and this allows them to be distinguished from true RhD positive individuals using genetic rather than serological tests.

These RHD/CE hybrids are usually known as "partial D" alleles. The changes usually affect a long string of amino acids which is always located on the erythrocyte surface. The protein is altered so dramatically in these external "antigenic" portions that it is not recognized by anti-D and these individuals are prone to true RhD isoimmunization if exposed to normal RhD positive red cells. In the majority of cases, women with these alleles should be treated like RhD negative women and offered RhD negative blood if it is required and anti-D if the fetus is possibly or definitely RhD positive. It is very important that genetic tests in this group do not falsely classify them as RhD positive and a variety of strategies are in place in most laboratories to prevent this happening. The most common European partial D variant is DNB, caused by a missense mutation, which alters one amino acid in the sixth extracellular loop of the protein.

The second group of RHD variants is known as "weak D." The changes within these alleles substitute amino acids in the transmembranous portions of the protein. The surface antigenic sites are unaltered; however, integration of the weak D protein into the cell membrane is hindered or rendered unstable, effectively reducing the number of RHD antigenic sites expressed per red cell. The effect is quantitative rather than qualitative. Blood from these individuals will eventually show agglutination with anti-D if given more time and assisted by the addition of anti-human globulin reagent. Weak D type 1 is the most common European weak D variant and is caused by a single missense mutation at amino acid 270. Most women with weak D variants (type 1-3) can be given RhD positive blood and do not need prophylactic anti-D, although there are a few exceptions.

The term "Du" was previously applied to variants of *RHD*. In view of the complexity of the situation, and the consequences of treating women as RhD positive when in fact they carry a variant which puts them at risk of isoimmunization against RhD, it is recommended that advice is taken from the laboratory performing the serological and molecular tests in each case where a variant is identified.

#### Other red cell antibodies

Table 6.10 lists some of the other red cell antigens, which have been documented to be the target of maternal antibodies, resulting in hemolytic disease. Those highlighted are the most significant from a clinical perspective. Certain red cell antibodies never cause hemolysis. Regional blood transfusion services will advise where rare antibodies are discovered on antenatal screening. 
 Table 6.10
 Other red cell antigens implicated in fetal/neonatal hemolytic disease

Kell Rhesus c, C and E A and B Fy<sup>a</sup> (Duffy) and Fy<sup>b</sup> Jk<sup>a</sup> (Kidd) and Jk<sup>b</sup> S, M and U Lu<sup>a</sup>

Isoimmunization against the Kell antigen deserves special mention. Although there are four separate Kell antigens, Kell 1 causes most concern. Anti-Kell1 antibodies are the second most common cause of fetal immune mediated hemolysis and early onset anemia and hydrops have been well documented. Nine out of 10 of the general population are Kell<sub>1</sub> negative and only 1 in 20 babies of Kell<sub>1</sub> negative women are Kell<sub>1</sub> positive. The Kell antigen is expressed on red cell progenitors in the bone marrow and it is via these cells that anti-Kell<sub>1</sub> antibodies are able to suppress hematopoiesis, as well as causing hemolysis. This made ante-natal surveillance with amniocentesis unreliable because  $\Delta$  OD450 of amniotic fluid acts only as a surrogate for hemolysis and cannot estimate the impact that the antibodies have on erythropoeisis. Fortunately, this problem is not shared by MCA PSV, which is used in exactly the same way as in RhD isoimmunization. In approximately half of all cases of Kell isoimmunization the cause is a previous blood transfusion where cross-matching did not take account of Kell status of the woman, or donor. The remainder result from FMH occurring at the delivery of a previous Kell positive baby. Absolute levels of anti-Kell antibodies are less useful in the prediction of disease severity. Noninvasive pre-natal diagnosis (NIPD) for fetal Kell status is available through the BTS laboratory in Bristol and is particularly helpful because most Kell positive individuals are heterozygous. NIPD is also possible for the Rhesus c and E antigens, although currently relatively few tests have been performed, when compared with RhD, meaning that the degree of diagnostic certainty is less. Anything more than mild disease is very unlikely with RhE antibodies.

Women who have the blood group O quite commonly have antibodies to the A- and B-antigens, although these are more likely to be of the IgM class which does not cross the placenta. Anti-A and anti-B IgGs can reach the fetal circulation, but only mild hemolysis is the general rule for two reasons. Firstly, these antigens are expressed on a wide variety of cell types, effectively diluting their effect on red blood cells. Secondly, cell-surface expression is incomplete during gestation and develops gradually, thus limiting the risk before birth. Jaundice caused by ABO incompatibility is usually mild and readily treated with phototherapy.

#### The future

The successes of recent years have not brought research and progress in the prevention and management of RhD hemolytic disease to a close. Although polyclonal anti-D is a safe product, it is pooled from various donors and anxieties about viral and prion disease transfection continue. The infection of hundreds of Irish women with hepatitis C in 1977–78 following the administration of contaminated anti-D illustrates this point all too well and currently 4 out of 10 women in the UK receiving anti-D will in fact be carrying a RhD negative fetus. The anti-D for these women is unnecessary, unpleasant, expensive, and not without a degree of risk.

Limiting the administration of anti-D to only those RhD negative women carrying a RhD positive fetus is a worthy goal. The techniques used for non-invasive pre-natal fetus RhD testing (see above) are time consuming and expensive, although very accurate. Application of this technology to all pregnant RhD negative women is impractical. Mass screening requires an automated test, and robotic systems have been developed and tested recently with very promising results. Results from a Bristol study have given a detection rate for fetal RhD positive status of 99.7% for a false positive rate of 2%.5 These false positives represent a group of RhD negative women who would continue to receive anti-D unnecessarily, but 2% nevertheless is a significant improvement on 38%. Of greater concern are the false negative results (i.e. failure to detect fetal RhD positivity) of which there were only 3 cases from nearly 1200 RhD positive pregnancies. Although these women would be at a three fold greater risk of isoimmunization because they would not receive ante-natal prophylactic anti-D (they would still receive post-natal anti-D), mathematical modeling shows that this actually equates to only one extra case of hemolytic disease in 86 000 future pregnancies.

An alternative approach to improve on the safety of anti-D prophylaxis is to use recombinant monoclonal antibodies (mAb) produced from hybridoma or human B-cell lines, instead of polyclonal antibodies collected from human serum. A number of these cell lines exist and progress to date has recently been summarized by Kumpel.<sup>17</sup> Results with some of the mAb are encouraging and D-immunization can be prevented in RhD negative volunteers transfused with RhD positive cells. A "clean" and effective recombinant anti-D mAb may be on the horizon, but hurdles still exist, not least obtaining ethical approval for large-scale trials.

More distant are further exciting possibilities.<sup>18</sup> Mutated recombinant anti-D monoclonal antibodies have been designed and produced, which are able to bind to the RhD antigen but have a much lower affinity for the Fc $\gamma$  receptor on macrophages than normal anti-D.<sup>19</sup> These mutated antibodies would displace endogenous anti-D from its binding sites on the RhD antigen. Complement mediated lysis, hemolysis and phagocytosis could all be reduced. There are many difficulties to overcome. The lifespan of these antibodies is limited and very high and frequent maternal administrations might be needed for transplacental transfer to maintain sufficient levels in the fetus.

A welcome move in neonatal care would be the avoidance altogether of exchange transfusion. The use of IVIG seems to have made some headway with this however a further option is close at hand. Competitive heme oxygenase inhibitors, such as tinmesoporphyrin, have recently undergone phase III trials and are already available for certain conditions. This structural analog of heme competitively blocks heme-oxygenase, a rate limiting enzyme in bilirubin production. Heme is left unaltered to be excreted in bile. It does not pass through the blood-brain barrier and does not accumulate in tissues. Several randomized trials have confirmed that these substances can prevent and block jaundice progression in the newborn. In the future these drugs may result in a reduction in the need for phototherapy, and exchange transfusion for HDN may become a procedure confined to the history books.

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Section 3 Chapter

# Acute management of suspected thromboembolic disease in pregnancy

Andrew J. Thomson and Ian A. Greer

#### Introduction

Antenatal and postnatal venous thromboembolism (VTE) is around 10 and 25 times more common respectively, than in non-pregnant women of the same age and is the major cause of direct maternal mortality in the developed world. European studies have consistently found the pregnancy-related VTE mortality to be 8.5 - 14 per million live births.<sup>1,2</sup> In the United Kingdom, sequential reports from Confidential Enquiries into Maternal Deaths have demonstrated that VTE remains the main direct cause of maternal death and have highlighted failures in obtaining objective diagnoses and employing adequate treatment.<sup>3</sup> Fatal pulmonary embolism (PE) arises from deep venous thrombosis (DVT), many cases of which are not recognized clinically and are only identified at post-mortem following a maternal death.<sup>3</sup> The subjective, clinical assessment of DVT and PE is particularly unreliable in pregnancy and a minority of women with clinically suspected VTE has the diagnosis confirmed when objective testing is employed.<sup>4</sup> Acute VTE should be suspected during pregnancy in women with symptoms and signs consistent with possible VTE,<sup>4-6</sup> particularly if there are other risk factors for VTE (see Tables 8.1 and 8.2).7-11 The symptoms and signs of VTE include leg pain and swelling (usually unilateral), lower abdominal pain, low grade pyrexia, dyspnoea, chest pain, haemoptysis and collapse.

#### **Epidemiology of VTE during pregnancy**

Virchow's triad for VTE consists of alterations in normal blood flow (stasis), trauma or damage to the vascular endothelium and alterations in the constitution of blood (hypercoagulability), and describes the three broad categories of factors that contribute to thrombosis. During normal pregnancy, hypercoagulability results from increases in the levels of factor VIII and fibrinogen, reduction in protein S levels, a resistance to activated protein C and impaired fibrinolysis. Studies assessing blood flow velocity in the lower limbs in pregnancy have shown an extensive reduction in flow of up to 50% by 29 weeks' gestation, reaching its nadir at 36 weeks. The changes in both blood flow velocity and coagulation factors may persist for up to 6 weeks after delivery. The third component of Virchow's triad, damage to the vascular endothelium, arises during the course of vaginal or abdominal delivery – whilst VTE can occur at any stage of pregnancy, the puerperium is the time of greatest risk.

Almost 90% of cases of DVT occur in the left leg in pregnancy, in contrast to the non-pregnant situation, where only 55% occur on the left.<sup>4</sup> This may reflect compression of the left iliac vein by the right iliac artery and the ovarian artery, which cross the vein only on the left side. Over 70% of DVTs in pregnancy arise in the iliac and femoral veins rather than the calf veins, whereas in non-pregnant patients only about 9% arise in the ilio-femoral area. This is of importance since ileo-femoral DVTs are more likely to result in PE than are calf vein thromboses.

#### Assessment and diagnosis of acute VTE in pregnancy

Clinical diagnosis of both DVT and PE is unreliable. In non-pregnant patients where DVT is suspected, the diagnosis is confirmed in about 20–30% of cases when objective testing is performed. During pregnancy, clinical assessment is even more unreliable since many of the symptoms and signs of VTE, such as leg swelling,

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Table 7.1 – Symptoms and signs of VTE in pregnancy

#### Deep venous thrombosis

- leg pain or discomfort
- tenderness
- swelling
- lower abdominal pain
- increased temperature and oedema
- elevated white cell count

#### Pulmonary thromboembolism

- chest pain
- dyspnoea
- haemoptysis
- tachycardia
- focal signs in the chest
- raised jugular venous pressure
- collapse
- abnormalities on the chest X-ray
- symptoms and signs associated with DVT

chest pain and dyspnea, are commonly found in normal pregnancy (Table 7.1). As a consequence, the accuracy of clinical diagnosis falls to about 8% for DVT and to less than 5% for suspected PE.<sup>4–6</sup>

It is therefore essential that objective testing is performed in women with suspected VTE. Failure to identify VTE will place the mother's life at risk, whilst unnecessary treatment is associated with risks, inconvenience and costs during the pregnancy and may also have implications for her future health care (including future use of oral contraception and hormone replacement therapy, and thromboprophylaxis in future pregnancies). There are no well-designed large clinical trials to support the management of suspected VTE in pregnancy and guidelines are therefore empirical and based on extrapolation from studies performed in non-pregnant patients.<sup>1,2,4</sup>

If there is a delay in obtaining objective tests, the woman should be commenced on anticoagulant therapy, unless contraindicated, until testing can be performed.

#### **Diagnosis of DVT**

Compression Duplex ultrasound of the entire proximal venous system is the optimal initial diagnostic test for DVT in pregnancy. If the initial ultrasound shows an abnormality in the popliteal or femoral veins, the diagnosis of proximal DVT is confirmed and anticoagulant treatment should be commenced and continued. A normal ultrasound does not exclude a calf DVT and therefore, if ultrasound is negative and a high level of clinical suspicion exists, the patient should remain anticoagulated and the ultrasound repeated in one week or an alternative diagnostic test employed. If repeat testing is negative, anticoagulant treatment can be discontinued.<sup>4</sup>

For the diagnosis of iliac vein thrombosis, which may present with back pain and/or swelling of the entire limb, pulsed Doppler, magnetic resonance venography or conventional contrast venography should be considered.

#### **Diagnosis of PE**

When a woman with suspected PE is haemodynamically stable, a chest X-ray (CXR) should be performed. CXR may identify other pulmonary disease such as pneumonia, pneumothorax or lobar collapse. Whilst the CXR is normal in over half of pregnant patients with objectively proven PE, abnormal features caused by PE include atelectasis, effusion, focal opacities, regional oligaemia or pulmonary edema. The radiation dose to the fetus from a CXR performed at any stage of pregnancy is negligible. If the CXR is abnormal, ventilation perfusion (V/Q) scanning is unreliable and CT pulmonary angiography (CTPA) should be performed.<sup>4–6</sup>

If the CXR is normal, the authors recommend that bilateral Doppler ultrasound leg studies should be performed. A diagnosis of DVT may indirectly confirm a diagnosis of PE and since anticoagulant therapy is the same for both conditions, further investigation is not usually necessary. This would limit the radiation doses, particularly associated with CTPA, given to the mother and her fetus.<sup>4</sup>

The choice of technique for definitive diagnosis (V/Q scan or CTPA) may depend on factors such as local availability and guidelines, and should usually be made after discussion with a radiologist. During pregnancy the ventilation component of the V/Q scan can often be omitted, thereby minimizing the radiation dose for the fetus. In the United Kingdom, the British Thoracic Society<sup>5</sup> recommends CTPA as firstline investigation for non-massive PE in non-pregnant patients. This technique has potential advantages over radionuclide (V/Q) imaging including better sensitivity and specificity, (at least in non-pregnant patients) and a lower radiation dose to the fetus (see section below). In addition it can identify other pathology such as aortic dissection. The main disadvantage of CTPA is the high radiation dose to the maternal breasts associated with an increased lifetime risk of developing breast cancer. This is particularly relevant when it is

known that only around 5% of such investigations will have a positive result. In addition, conventional CTPA may not identify small peripheral PEs, although this is overcome by the latest multidetector row spiral CT techniques. In contrast to CTPA, V/Q scanning may be delayed because of availability of isotope. Despite these potential advantages of CTPA, many authorities, including the authors, continue to recommend V/Q scanning, where possible, as first-line investigation in pregnancy because of its high negative predictive value in this situation, its substantially lower radiation dose to pregnant breast tissue, and because most pregnant women in the UK will not have co-morbid pulmonary pathology.<sup>4,12</sup>

## Radiation exposure associated with diagnostic tests

CTPA delivers less radiation to the fetus than V/Q scanning during all trimesters of pregnancy. It has been estimated that the risk of fatal cancer to the age of 15 years is <1/1,000,000 after in utero exposure to CTPA and 1/280 000 following a perfusion scan. While CTPA is associated with a lower risk of radiation for the fetus, this must be offset by the relatively high radiation dose (20 mGy) to the mother's thorax and in particular breast tissue. The delivery of 10 mGy of radiation to a woman's breast increases her lifetime risk of developing breast cancer. It has been estimated that the increased risk is 13.6% (background risk 1/200), a figure that has been cited widely (4, 12). More recently, authorities have suggested that this risk is an overestimate. Nevertheless, breast tissue is especially sensitive to radiation exposure during pregnancy, and it therefore seems sensible to recommend that lung perfusion scans should be considered the investigation of first choice for young women, especially if there is a family history of breast cancer or the patient has had a previous chest CT scan. Radiation exposure from pulmonary angiography is approximately 0.5 mSv to fetus, and 5 to 30 mSv to mother.

#### D-dimer testing in pregnancy

Outwith pregnancy, a normal plasma D-dimer level has been shown to have excellent negative predictive value in patients with a low clinical probability score for VTE. However levels increase physiologically throughout pregnancy, becoming elevated at term and in the post-natal period in most healthy pregnant women. Furthermore, D-dimer levels are increased if there is a concomitant problem such as pre-eclampsia, preterm labour, and placental abruption. Thus the probability of a negative result is lower and objective testing is more often required. For this reason guidelines produced by the Royal College of Obstetricians and Gynaecologists in the United Kingdom,<sup>4</sup> do not recommend that D-dimer levels are evaluated in pregnant women with suspected VTE. In contrast, the European Society of Cardiology<sup>13</sup> recommend that D-dimer levels should be measured, as a proportion of patients will have a normal result and be able to avoid unnecessary imaging. It should be noted, however, that although the SimpliRED test has been reported to have a negative predictive value of 100% in pregnancy, false negative results have been reported.

## Thrombophilia testing in acute VTE pregnancy

Almost half of all women who have an episode of VTE in pregnancy, will have an underlying heritable or acquired thrombophilia.<sup>14</sup> The prevalence rates for thrombophilias in European populations is shown in Table 12.2 and the relative risk of each condition, shown by metaanalysis, is shown in Table 7.2. Performing a thrombophilia screen in the acute stages of thrombosis may give misleading results and is not routinely recommended. Levels of antithrombin, protein C and protein S may fall, particularly if thrombus is extensive. In addition, protein S levels fall in normal pregnancy and an acquired activated protein C resistance is found with the APC sensitivity ratio test in around 40% of pregnancies, due to the physiological changes in the coagulation system. Clearly, genotyping for factor V Leiden and prothrombin G20210A will not be affected by pregnancy or thrombus. Whilst the results of a thrombophilia screen will not influence the immediate management of acute VTE, they might provide information that can influence the duration and intensity of anticoagulation, such as when antithrombin deficiency or antiphospholipid syndrome is identified.

#### Initial treatment of VTE in pregnancy

Before anticoagulant therapy is initiated, blood should be taken for a full blood count and coagulation screen. Urea, electrolytes and liver function tests should also **Table 7.2.** Risk of pregnancy associated VTE in women withunderlying thrombophilia (14)

	Relative Risk of
Thrombophilic defect	thrombosis
Factor V Leiden <b>(heterozygote</b> )	8.32
Factor V Leiden (homozygote)	34.4
Prothrombin 20210A <b>(heterozygote)</b>	6.8
Prothrombin 20210A <b>(homozygote)</b>	26.4
Protein C deficiency	4.76
Protein S deficiency	3.19
Antithrombin deficiency	4.69

be checked to exclude renal or hepatic dysfunction, which are cautions for anticoagulant therapy.

The treatment of VTE in pregnancy is heparin. Vitamin K antagonists are rarely employed in this setting as they cross the placenta and are associated with increased pregnancy loss, a specific embryopathy and other abnormalities in the first trimester, as well as fetal haemorrhagic complications and central nervous system anomalies at any stage of pregnancy. Although for many years, unfractionated heparin (UFH) was the standard anticoagulant used during and outwith pregnancy, it has now largely been replaced by low molecular weight heparin (LMWH). Meta-analyses of randomised controlled trials (RCTs) in non-pregnant patients indicate that LMWHs are more effective and are associated with a lower risk of haemorrhagic complications and lower mortality than unfractionated heparin in the initial treatment of DVT. A meta-analysis of RCTs has shown equivalent efficacy of LMWH to unfractionated heparin in the initial treatment of PE. A systematic review of LMWH in pregnancy has confirmed its efficacy and safety in the management of acute thrombosis and in the provision of thromboprophylaxis. Furthermore, compared with UFH, LMWH is associated with a substantially lower risk of heparin-induced thrombocytopenia, haemorrhage and osteoporosis.<sup>1,2,4,15-17</sup> Neither UFH nor LMWH cross the placenta and both are safe for breast feeding.

Whilst several LMWH preparations are available, most experience currently exists with enoxaparin, dalteparin and tinzaparin. In non-pregnant patients with acute VTE, LMWH is usually administered in a once daily dose. In view of recognised alterations in the pharmacokinetics of dalteparin and enoxaparin during pregnancy, a twice daily dosage regimen is recommended for these LMWHs in the treatment of VTE in pregnancy, (enoxaparin 1mg/kg twice daily; dal-teparin 100 units/kg twice daily). Preliminary biochemical data suggest that once daily administration of tinzaparin (175 units/kg) may be appropriate in the treatment of VTE in pregnancy. Whichever, preparation of LMWH is employed, the woman should be taught to self-administer the drug by subcutaneous injection, allowing further management on an outpatient basis until delivery.<sup>4</sup>

In the very early management of DVT, the leg should be elevated and a graduated elastic compression stocking applied to reduce oedema. Once full anticoagulation has been commenced, the woman should be encouraged to mobilize whilst wearing compression hosiery as this has been shown to reduce pain and swelling in the affected leg. Studies in non-pregnant patients have shown that early mobilization, with compression therapy, does not increase the likelihood of developing PE and helps prevent the development of post-thrombotic syndrome. For patients with persisting leg oedema after DVT, class II compression hosiery is more effective than class I stockings. Where DVT threatens leg viability through venous gangrene, the leg should be elevated, anticoagulation given and consideration given to surgical embolectomy or thrombolytic therapy.<sup>4</sup>

#### Monitoring of LMWH therapy

Experience indicates that satisfactory anti-Xa levels (peak anti-Xa activity, 3 hours post-injection, of 0.5–1.2 u/ml) are obtained using a weight-based regimen and monitoring of anti-Xa is not routinely required in patients with VTE on therapeutic doses of LMWH, particularly as there are concerns over the standardization and accuracy of anti-Xa monitoring. There may be a case for monitoring levels at extremes of body weight (<50 kg and  $\geq$ 90 kg), and women with other complicating factors including renal disease and recurrent VTE.<sup>4,16</sup>

Guideline documents from North America<sup>2</sup> recommend that routine platelet count monitoring is not required in obstetric patients who have received only LMWH as heparin induced thrombocytopenic thrombosis is not a feature in pregnancies managed exclusively with LMWH. If unfractionated heparin is employed, or if the obstetric patient is receiving LMWH after first receiving unfractionated heparin, or if she has received unfractionated heparin in the past, the platelet count should ideally be monitored every 2– 3 days from day 4 to day 14, or until heparin is stopped, whichever occurs first.

#### **Maintenance treatment of VTE**

Women with ante-natal VTE can be managed with subcutaneous LMWH for the remainder of the pregnancy using LMWH administered subcutaneously. It is our practice to continue with the initial dose regimen throughout pregnancy despite the pregnancy-associated weight gain, (since LMWH does not cross the placenta and therefore the weight of the feto-placental unit is not relevant). If LMWH therapy requires monitoring, for example in extremes of body weight or renal impairment, the aim is to achieve a peak anti-Xa activity, three hours post-injection of 0.5 - 1.2 u/ml.

It is not yet established whether the initial dose of LMWH can be reduced to an intermediate dose after an initial period of several weeks of therapeutic anticoagulation, although this practice has been successfully employed in some centres. Outwith pregnancy in patients with underlying malignancy, a reduction in dose has been shown to be safe after 4 weeks of therapeutic anticoagulation. Although there have been no studies directly comparing these two types of dosing strategies in pregnant women, this type of modified dosing regimen may be useful in pregnant women at increased risk of bleeding or osteoporosis.<sup>18</sup>

#### Management at the time of delivery

For women on therapeutic anticoagulation, a planned delivery, either through induction of labour or elective caesarean section, allows accurate timing of events and minimizes the risk of the woman having to deliver on full anticoagulation. The dose of LMWH should be reduced to a once daily thromboprophylactic dose on the day before induction of labour or caesarean section. When a woman presents whilst on a therapeutic, twice daily regimen of LMWH, regional techniques should not usually be employed for at least 24 hours after the last dose of LMWH. LMWH should not be given for at least four hours after the epidural catheter has been removed and the cannula should not be removed within 12 hours of the most recent injection.<sup>4</sup>

For delivery by elective caesarean section, the treatment doses of LMWH should be omitted for 24 hours prior to surgery. A thromboprophylactic dose of LMWH (enoxaparin 40mg; dalteparin 5000iu; tinzaparin 75 iu/kg) should be given by three hours postoperatively (>4 hours after removal of the epidural catheter, if appropriate), and the treatment dose recommenced that evening. There is an increased risk of wound haematoma following caesarean section with both unfractionated heparin and LMWH of around 2%. For this reason, wound drains should be considered at caesarean section, and the skin incision should ideally be closed with staples or interrupted sutures to allow easy drainage of any haematoma.

If the thrombosis occurred in the last week of pregnancy, consideration should be given to the use of unfractionated heparin (since it can be relatively easily reversed using protamine sulfate and has a short duration of action). If spontaneous labour occurs in women receiving therapeutic doses of subcutaneous unfractionated heparin, careful monitoring of the anticoagulant effect by measuring the activated partial thromboplastin time (APTT) is required. Subcutaneous unfractionated heparin should be discontinued 12 hours before and intravenous unfractionated heparin stopped 6 hours before induction of labour or regional anaesthesia. It should be noted however that the aPTT is less reliable in pregnancy due to increased levels of FVIII and heparin binding proteins, which can lead to an apparent heparin resistance.<sup>4,18</sup>

## Postpartum anticoagulation and duration of anticoagulation therapy

In the United Kingdom, it is recommended that in non-pregnant patients, anticoagulant therapy should be continued for 6 weeks for calf vein thrombosis and 3 months for proximal DVT or PE when VTE has occurred in relation to a temporary risk factor, and 6 months for a first episode of idiopathic VTE.<sup>4</sup> The presence of ongoing risk factors and the safety of LWMH have led authorities to propose that anticoagulant therapy should be continued for the duration of the pregnancy and until at least six weeks postpartum and to allow a total duration of treatment of at least 3 months. Both heparin and warfarin are satisfactory for use postpartum - in our experience most women prefer to use LMWH (which can be used with once daily dosing postpartum) because they have become accustomed to its administration, and they appreciate the convenience of not having to attend clinics to have their INR checked. Before discontinuing treatment the ongoing risk of thrombosis should be assessed



Figure 7.1. Management of women with clinically suspected massive PTE

including a review of personal and family history of VTE and any thrombophilia screen results. Thrombophilia screening should be discussed and arranged if required.

Neither heparin (unfractionated or LMWH) nor warfarin is contraindicated in breastfeeding. There are little published data on whether LMWHs are secreted in breast milk, although extensive experience of enoxaparin in the puerperium reports no problems during breastfeeding and other heparins are known not to cross the breast. Furthermore, neither unfractionated heparin nor LMWH are orally active and no effect would therefore be anticipated in the fetus.

The post-thrombotic syndrome is a common complication following DVT.<sup>18</sup> It is found in over 60% of cases followed up over a median of 4.5 years. It is characterized by chronic persistent leg swelling, pain, a feeling of heaviness, dependant cyanosis, telangiectasis, chronic pigmentation, eczema, associated varicose veins and in some cases lipodermatosclerosis, and chronic ulceration. Symptoms are made worse by standing or walking and improve with rest and recumbancy. The syndrome is more common where there is a recurrent DVT, with obesity and where there has been inadequate anticoagulation. It is recommended that graduated elastic compression stockings (class II) should be worn on the affected leg for two years after the acute event to reduce the risk of post-thrombotic syndrome. This recommendation is based upon studies in non-pregnant patients where such therapy reduces the incidence of post thrombotic syndrome from 23% to 11% over 2 years. Graduated elastic compression stockings will improve the microcirculation by assisting the calf muscle pump, reducing swelling and reflux, and reducing venous hypertension.<sup>4</sup>
### Management of massive, life-threatening PE

Massive, life-threatening PE may be defined as embolus associated with haemodynamic compromise (a systolic blood pressure <90 mmHg or a drop in systolic blood pressure of  $\geq$  40mmHg from baseline for a period >15 minutes), not otherwise explained by hypovolaemia, sepsis or new arrhythmia. This is an obstetric and medical emergency and hospitals should have in place guidelines for the management of non-haemorrhagic obstetric shock (see figure 7.1). The collapsed, shocked pregnant woman needs to be assessed by a multi-disciplinary resuscitation team of experienced clinicians including senior obstetricians, physicians and radiologists, who should decide on an individual basis whether a woman receives intravenous unfractionated heparin, thrombolytic therapy or thoracotomy and surgical embolectomy.

Oxygen should be administered and the circulation supported using intravenous fluids and inotropic agents if required. Intravenous unfractionated heparin is the traditional method of heparin administration in acute VTE and remains the preferred treatment in massive PE because of its rapid effect and extensive experience of its use in this situation. The diagnosis should be established using either portable echocardiogram or CTPA performed within 1 hour of presentation.

In massive life-threatening PE with haemodynamic compromise there is a case for considering thrombolytic therapy as anticoagulant therapy will not reduce the obstruction of the pulmonary circulation. After thrombolytic therapy has been given an infusion of unfractionated heparin can be given. There are now a large number of published case reports on the use of thrombolytic therapy in pregnancy, streptokinase being the agent most frequently employed. Streptokinase, and probably other thrombolytic agents, do not cross the placenta. No maternal deaths associated with thrombolytic therapy have been reported, and the maternal bleeding complication rate is approximately 6%, which is consistent with that in non-pregnant patients, receiving thrombolytic therapy. Most bleeding events occur around catheter and puncture sites, and, in pregnant women, from the genital tract. If the patient is not suitable for thrombolysis or moribund, a discussion with the cardiothoracic surgeons with a view to urgent thoracotomy should be had.4

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# Thromboembolism and anticoagulation

# Thromboprophylaxis

Sarah Germain and Catherine Nelson-Piercy

## Introduction and epidemiology

Venous thromboembolism (VTE) remains the leading direct cause of maternal death in the UK. In the latest CEMACH report "Saving Mothers Lives: Reviewing maternal deaths to make motherhood safer, 2003-5"1 there were 33 deaths from VTE and eight from cerebral vein thrombosis. Although the absolute numbers of both fatal and non-fatal VTE in pregnancy and the puerperium are small, with an overall incidence of approximately 2 per 1000 births,<sup>2,3</sup> many are preventable. Successive enquiry reports have highlighted the need to identify risk factors for VTE early in pregnancy and ensure adequate thromboprophylaxis is employed. The Royal College of Obstetricians and Gynaecologists have published guidelines regarding thromboprophylaxis covering both the ante-natal and post-natal periods<sup>4,5</sup> and these have recently been updated.<sup>6</sup> Despite this, a recent case control study of 143 cases of ante-natal pulmonary embolism (PE) in the UK, by the UK Obstetric Surveillance System (UKOSS), demonstrated that, although nine of the women should have received ante-natal thromboprophylaxis according to national guidelines, only 33% had actually done so, and 50% of the six women who had a PE while on prophylactic low molecular weight heparin (LMWH) were receiving lower than recommended doses.<sup>7</sup>

Traditionally, VTE has been considered a complication of late pregnancy and Post-Cesarean section. The Confidential Enquiries into Maternal Deaths have shown that this is by no means the case, with twothirds of ante-natal fatal pulmonary VTE in 2003– 2005 occurring in the first trimester, and just over half of the post-natal deaths from pulmonary VTE after vaginal delivery.<sup>1</sup> A study from the USA found that 44% of deep vein thromboses DVTs in pregnancy occurred in the first trimester,<sup>8</sup> and a more recent Spanish study similarly found that 40% of ante-natal VTE were in the first trimester.<sup>9</sup> These all emphasize the need for risk assessment pre-pregnancy and institution of prophylaxis if appropriate in early pregnancy. Although numerically most VTE occurs ante-natally, the highest risk per day is during the immediate post-partum period, and this is demonstrated by a cohort study from the USA, which showed that the annual incidence of VTE was five times higher among post-partum compared to pregnant women.<sup>3</sup>

As clinicians we therefore ideally need to identify women at risk prior to conception, or at least early in pregnancy, then establish their level of risk, and finally initiate an appropriate thromboprophylaxis regimen, which extends into the puerperium. We also need to be aware that a woman who starts pregnancy as "low risk" of VTE may develop or acquire risk factors as pregnancy progresses, and thromboprophylaxis may need to be introduced at that point or after delivery.

# Pathogenesis and risk factor assessment

Pregnancy itself puts all women at higher risk of VTE, with a four to ten-fold increase compared to an age-matched non-pregnant female population.<sup>3,5</sup> This is primarily related to the pro-coagulant changes that occur during pregnancy to promote hemostasis post-delivery,<sup>2</sup> and are evident from early in the first trimester. Other components of Virchow's triad are also present, namely increased venous stasis and vascular trauma, the latter particularly around the time of delivery. Superimposed on this background risk, are a range of additional risk factors which may either predate the pregnancy or develop during the pregnancy or puerperium, and can be persistent or transient.

*The Obstetric Hematology Manual*, ed. Sue Pavord and Beverley Hunt. Published by Cambridge University Press. © Cambridge University Press 2010.

 
 Table 8.1
 Additional risk factors for VTE in pregnancy and the puerperium\*

Pre-exi	isting
1	F

Age >35 years Obesity (BMI > 30 kg/m<sup>2</sup>, either pre-pregnancy or in early pregnancy) Parity  $\geq 3$ Gross varicose veins Paraplegia Sickle cell disease Smoking ART Inflammatory disorders (e.g. inflammatory bowel disease) Some medical disorders (e.g. nephrotic syndrome, certain cardiac diseases) Myeloproliferative disorders (e.g. essential thrombocythemia, polycythemia vera) New onset or transient Ovarian hyperstimulation syndrome **Hyperemesis** Dehvdration Severe infection (e.g. pyelonephritis) Long-distance travel Immobility (> 4 days bed rest)

Pre-eclampsia Excessive blood loss/blood transfusion Surgical procedure in pregnancy or puerperium (e.g. ERPC, postpartum sterilization)

#### Specific to postpartum VTE only

Cesarean section (especially in labor) Prolonged labor Midcavity instrumental delivery Immobility after delivery

\* Adapted from ref. 6

VTE = venous thromboembolism; BMI = body mass index; ERPC = evacuation of retained products of conception; ART = Assisted Reproductive therapy.<sup>6</sup>

The major additional risk factors are a previous VTE and/or a documented thrombophilia.<sup>2</sup> A history of thrombosis increases the risk of pregnancy-related VTE to 2%–12%.<sup>2</sup> De Stefano *et al.* found recurrence rates following a single previous DVT or PE of 5.8% for ante-natal and 8.3% for post-natal VTE.<sup>10</sup>

Thrombophilias may either be heritable (antithrombin deficiency, Protein C deficiency, Protein S deficiency, Factor V Leiden, or Prothrombin gene variant) or acquired (antiphospholipid syndrome, including lupus anticoagulant and anticardiolipin antibodies). Up to 50% of women who develop VTE during pregnancy or the postpartum period have an underlying thrombophilia.<sup>11</sup> The relative risk of VTE in pregnancy varies depending on the thrombophilia, but can be as high as ten fold with antithrombin deficiency. The most important determinant of 
 Table 8.2
 Quoted adjusted odds ratios for individual risk factors

Risk factor for VTE	aOR	95% CI
Previous VTE 11	24.8	17.1-36
<b>Age</b> > <b>35</b> <sup>14</sup>	1.3	1.0-1.7
<b>BMI &gt; 30</b> <sup>12</sup>	5.3 4.4	2.1–13.5 3.4–5.7
Smoking <sup>13</sup>	2.7	1.5-4.9
Parity $\geq$ 3 <sup>14</sup>	2.4	1.8-3.1
Medical conditions <sup>11</sup>	2.0-8.7	
Sickle cell disease, SLE, heart disease, anemia, infection,		2.0-3.2
Hyperemesis	2.51	
Immobility <sup>13</sup>	7.7 (an) 10.8 (pn)	3.2–19 4–28.8
Immobility <sup>13</sup> Pre-eclampsia <sup>13</sup>	7.7 (an) 10.8 (pn) 3.1	3.2–19 4–28.8 1.8–5.3
Immobility <sup>13</sup> Pre-eclampsia <sup>13</sup> +Fetal growth restriction	7.7 (an) 10.8 (pn) 3.1 5.8	3.2–19 4–28.8 1.8–5.3 2.1–16
Immobility <sup>13</sup> Pre-eclampsia <sup>13</sup> +Fetal growth restriction ART <sup>13</sup>	7.7 (an) 10.8 (pn) 3.1 5.8 4.3	3.2-19 4-28.8 1.8-5.3 2.1-16 2.0-9.4
Immobility <sup>13</sup> Pre-eclampsia <sup>13</sup> +Fetal growth restriction ART <sup>13</sup> Twins <sup>13</sup>	7.7 (an) 10.8 (pn) 3.1 5.8 4.3 2.6	3.2-19 4-28.8 1.8-5.3 2.1-16 2.0-9.4 1.1-6.2
Immobility <sup>13</sup> Pre-eclampsia <sup>13</sup> +Fetal growth restriction ART <sup>13</sup> Twins <sup>13</sup> APH <sup>13</sup>	7.7 (an) 10.8 (pn) 3.1 5.8 4.3 2.6 2.3	3.2-19 4-28.8 1.8-5.3 2.1-16 2.0-9.4 1.1-6.2 1.8-2.8
Immobility <sup>13</sup> Pre-eclampsia <sup>13</sup> +Fetal growth restriction ART <sup>13</sup> Twins <sup>13</sup> APH <sup>13</sup> PPH <sup>13</sup>	7.7 (an) 10.8 (pn) 3.1 5.8 4.3 2.6 2.3 4.1	3.2-19 4-28.8 1.8-5.3 2.1-16 2.0-9.4 1.1-6.2 1.8-2.8 2.3-7.3
Immobility <sup>13</sup> Pre-eclampsia <sup>13</sup> +Fetal growth restriction ART <sup>13</sup> Twins <sup>13</sup> APH <sup>13</sup> PPH <sup>13</sup> Cesarean section <sup>14</sup>	7.7 (an) 10.8 (pn) 3.1 5.8 4.3 2.6 2.3 4.1 3.6	3.2-19         4-28.8         1.8-5.3         2.1-16         2.0-9.4         1.1-6.2         1.8-2.8         2.3-7.3         3.0-4.3
Immobility <sup>13</sup> Pre-eclampsia <sup>13</sup> +Fetal growth restriction ART <sup>13</sup> Twins <sup>13</sup> APH <sup>13</sup> PPH <sup>13</sup> Cesarean section <sup>14</sup> Varicose veins	7.7 (an) 10.8 (pn) 3.1 5.8 4.3 2.6 2.6 2.3 4.1 3.6 2.4	3.2-19 4-28.8 1.8-5.3 2.1-16 2.0-9.4 1.1-6.2 1.8-2.8 2.3-7.3 3.0-4.3 1.04-5.4

VTE risk in a pregnant woman with a thrombophilia is a personal or family history of VTE.

Additional risk factors are detailed in Table 8.1, adapted from the Royal College of Obstetricians Green Top Guideline on Reducing the risk of Thrombosis and Embolism during pregnancy and the puerperium.<sup>6</sup> All are accepted VTE risk factors, but the degree of increased VTE risk associated with them varies, as indicated in Table 8.2. Of particular importance are obesity and increasing maternal age.

The growing problem of maternal obesity in association with VTE is highlighted in the findings from both the most recent Confidential Enquiry into Maternal Deaths (2003–5)<sup>1</sup> and the UKOSS study of antenatal PE,<sup>7</sup> that have already been discussed. The latter demonstrated that one of the main risk factors was a BMI >30 with an adjusted odds ratio (OR) of 2.65 (95% confidence interval (CI) 1.09–6.45). Similarly, a recent case control study from Denmark of 129 cases of VTE in pregnancy or the puerperium demonstrated an adjusted OR of 5.3 (95% CI 2.1–13.5) for obesity (BMI >30), with a higher risk of PE (adjusted OR 14.9, 95% CI 3.0–74.8) than of DVT (adjusted OR 4.4, 95% CI 1.6–11.9)<sup>12</sup> The only other risk factors that reached statistical significance in these two studies were multiparity (adjusted OR 4.03, 95% CI 1.60–9.84)<sup>7</sup> and current smoking (adjusted OR 2.7, 95% CI 1.5–4.9),<sup>12</sup> although Knight *et al.* highlight the difficulty of obtaining sufficient power to show other associations, even in a large national study such as theirs, as ante-natal PE is still a relatively rare condition.<sup>7</sup>

### Management

### Management strategy

The management strategy for thromboprophylaxis during pregnancy and the postpartum period is detailed in Table 8.3. All women should have an assessment of risk factors for VTE, in early pregnancy, or ideally pre-pregnancy. It is particularly important to identify those with a previous VTE and/or known thrombophilia. If there is a past history of VTE, then the details of presentation, means of diagnosis, and drug treatment and length of course should be determined. If deemed appropriate, women with a previous VTE should be screened for both heritable and acquired thrombophilia prior to pregnancy, as interpretation of some of the tests (especially protein S) is unreliable in pregnancy. The other risk factors detailed in Table 8.1 should also be considered, as well as any family history of VTE in a first-degree relative.

Following discussion with the woman, a written plan can then be made for ante-natal thromboprophylaxis, if required, and prescribed if the woman is already pregnant. Women should be taught how to self-administer subcutaneous LMWH. If the woman is not yet pregnant, the prescription can still be given, so LMWH can be started as soon as a pregnancy test is positive. This is particularly for women in the very high and high risk groups, as the pregnancy-related increase in VTE risk starts from the beginning of the first trimester.<sup>8,9</sup> The recommendations should be detailed in a letter copied to both the GP and patient, so prophylaxis can be started without the woman needing to come back to the hospital clinic first.

It is important to remember that the VTE risk may change for a particular woman as pregnancy progresses, for example, if she develops pre-eclampsia, and the risk factor assessment should be repeated if there is any change in circumstances, and LMWH initiated as appropriate. It may be that the additional risk factor is only temporary, for example hyperemesis gravidarum, and the original regimen can be returned to once the condition or situation has resolved.

Issues regarding anticoagulant use peri-delivery should be discussed, including epidural timing, and again documented in the ante-natal notes (discussed further in Chapter 10). Assessment by an obstetric anesthetist in the ante-natal period if the woman is using ante-natal LMWH, especially if at high prophylactic or therapeutic dose, should be part of this process.

A clear plan for postpartum prophylaxis should also be documented in the obstetric notes. The level of risk will need to be reassessed post-natally, as it may be increased depending on the mode of delivery and any associated complications. Women on longterm warfarin are usually managed with high-dose prophylactic LMWH for the first week post-natally and then converted back to warfarin. Follow-up should be arranged for those women with a previous VTE who have not had a thrombophilia screen, once they have completed the 6-week post-natal anticoagulant course, so they can be investigated for an underlying thrombophilia.

# Non-pharmacological and pharmacological measures used

Thromboprophylaxis involves both nonpharmacological and pharmacological measures, and the various modalities and drugs that can be used are discussed below.

## Non-pharmacological

Non-pharmacological measures include appropriate hydration, early mobilization after surgery or delivery, graduated compression stockings (TEDS), and pneumatic compression boots. The aim is to improve blood flow and decrease stasis in the femoral and popliteal vessels.

No randomized controlled trials have been carried out in pregnancy to study the efficacy of TEDS or pneumatic compression for thromboprophylaxis, but the latter have been shown to be cost-effective when used at Cesarean section,<sup>16</sup> and trials outside of pregnancy have demonstrated significant reduction in incidence of VTE when used peri-operatively. These measures are also not associated with the potential hemorrhagic side effects of the pharmacological

Pre-pregnancy	Assess women with prior history of VTE and/or known thrombophilia Consider VTE risk factors when giving pre-pregnancy counseling to women with other medical problems Make plan for future pregnancy regarding thromboprophylaxis and document in letter to GP and patient Consider giving high risk women prescription for LMWH to start with positive pregnancy test
Ante-natal	Assess all women for VTE risk factors at booking Determine need for ante-natal thromboprophylaxis and prescribe if required Liaise with obstetric hematologist and/or obstetric physician Discuss implications of anticoagulants peri-delivery Arrange assessment by obstetric anesthetist if using ante-natal LMWH Document plan for peri-delivery and postpartum periods in obstetric notes Reassess woman's risk status, need for LMWH, and LMWH dose if events change in pregnancy (e.g. acquire additional risk factors detailed in Table 8.1)
Peri-delivery	Liaise with obstetric anesthetist regarding timing of regional analgesia and anesthesia.
Postpartum	Reassess woman's risk status depending on mode of delivery and any obstetric complications Prescribe postpartum prophylaxis if required Arrange follow-up for thrombophilia testing once off anticoagulants if previous VTE and not already tested
VTE = venous thror	nboembolism; LMWH = low molecular weight heparin.

Table 8.3 Management strategy for thromboprophylaxis in pregnancy and the postpartum period

agents discussed below. They can be of particular use in patients requiring Cesarean section or having prolonged bedrest.

### Pharmacological

Aspirin, heparin, and warfarin are the main pharmacological agents to be used in thromboprophylaxis, and each will be discussed in turn. Although they differ in their ability to cross the placenta, all are safe to use in breast-feeding mothers.<sup>17</sup>

### Aspirin

Aspirin inhibits the enzyme cyclo-oxygenase in platelets, thus reducing thromboxane production and platelet aggregation. Aspirin is known to be effective in reducing the risk of VTE in both surgical and medical patients but no randomized controlled trials have been carried out looking at the use of aspirin as thromboprophylaxis in pregnancy. However studies of its use for a range of other indications in pregnancy have shown it to be safe at low dose (75 mg).<sup>17</sup> It may therefore be reasonable to consider low dose aspirin for women who have an increased risk of VTE, but not high enough to warrant LMWH, although its use for this indication is controversial, and recent guidelines do not recommend it.<sup>6,17</sup>

### Heparin

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Neither unfractionated (UH) nor low molecular weight (LMWH) heparin cross the placenta, so there are no adverse effects on the fetus.

LMWHs are now the anticoagulants of choice in the UK for prophylaxis and treatment of VTE in pregnancy, for the vast majority of cases. LMWH have a longer half-life and increased bioavailability, which allows once daily dosing for prophylaxis. UH is usually only used for thromboprophylaxis if there is an allergy to LMWH or in renal failure.

Hospitals differ in the LMWH used, and Table 8.4 details the recommended, prophylactic and therapeutic doses for the different LMWHs available. Doses need to be adjusted according to maternal weight in early pregnancy.<sup>18</sup>

UH is a heterogenous mixture of high molecular weight molecules (3 000–30 000 daltons), whereas LMWHs are a derivative of UH with molecular weights of 4 000–5 000 daltons. This affords LMWH a number of advantages over UH, including predictable and reliable pharmacokinetics, a higher ratio of anti-Xa to anti-IIa activity, providing good antithrombotic effect with possibly a lower risk of bleeding. They also have less of an effect on platelet aggregation, function and activation, and bind platelet factor 4 less well, hence reducing the risk of both early and late heparininduced thrombocytopenia (HIT).<sup>19</sup>

Heparin-induced osteoporosis is an important risk, especially if heparin is required throughout the ante-natal period, but the risk is much lower with LMWH (0.04%) than UH (2%).<sup>19</sup> Also, even if there is loss in bone density during pregnancy (up to 5%), this usually improves on stopping breast feeding postpartum. LMWHs in prophylactic doses have not been associated with a reduction in bone density

Dose (based on early pregnancy maternal weight)	Enoxaparin**	Dalteparin	Tinzaparin
Standard prophylactic <50 kg 50–90 kg 91–130 kg 131–170 kg	20mg od 40mg od 60mg od or 40mg bd 80mg od or 40mg bd	2500 units od 5000 units od 7500 units od or 5000 bd 10,000 units od or 5000 units bd	3500 units od 4500 units od 7000 units od
High prophylactic	40 mg bd	5000 units bd	4500 units bd
Treatment/therapeutic <50 kg 50–90 kg >90 kg	1 mg/kg bd 40 mg bd 60–80 mg bd 100 mg bd	100 units/kg bd 5000 units bd 6000–8000 units bd 10 000 units bd	175 units/kg od
* Adapted from <sup>4,14</sup> ; ** 100 units/mg od = once daily; bd = twice daily.			

 Table 8.4
 Ante-natal prophylactic and therapeutic doses of different low molecular weight heparins\*

over and above what would be expected in normal pregnancy.<sup>20</sup>

Of women, 1%–2% may develop a local allergic skin rash with LMWH. The first-line pragmatic approach is to substitute with an alternative LMWH, but there may be cross-reactivity, as also occurs with UH.<sup>19</sup> If this is the case, or if other complications such as HIT develop, then consideration of alternative heparinoids such as danaparoid or the synthetic pentasaccharide fondaparinux is appropriate. However, HIT has never been described with LMWH in a pregnant woman.<sup>2,17</sup>

### Warfarin

Warfarin crosses the placenta and is teratogenic.<sup>17</sup> The characteristic "warfarin embryopathy" includes chrondrodysplasia punctata, nasal hypoplasia, and short proximal limbs. The period of greatest risk is between 6 and 12 weeks. Warfarin is also associated with an increased rate of miscarriage and stillbirth, and in the third trimester a significant risk of fetal intracerebral hemorrhage and maternal retroplacental bleeding, especially after 36 weeks' gestation. Use in the second trimester has been linked to microcephaly and neurological abnormalities, which may be due to over-anticoagulation of the fetus.

Because of these effects, warfarin is not used routinely during pregnancy, and most women requiring thromboprophylaxis or treatment can be managed with LMWH or unfractionated heparin. There are some women though, who that require continued full anticoagulation with warfarin throughout pregnancy until planned delivery. The only non-controversial indication for use of warfarin in pregnancy is for women with a metal prosthetic heart valves (particularly of the older type and those in the mitral position), whose thrombotic risk is extremely high, and in whom valve thrombosis carries a high mortality rate (see Chapter 9).

In other high-risk women the decision is more difficult, and the risk/benefit balance for the particular individual has to be considered. This would include those with a known thrombophilia and VTE or cerebral arterial thrombosis despite full dose LMWH. A compromise option here is to use LMWH for the highest risk periods for warfarin side effects, namely, the first trimester and after 36 weeks' gestation, and convert back to warfarin for the second and early third trimesters. This obviously requires very close supervision and thorough discussion with the woman.

### Recommendations

Although VTE in pregnancy and postpartum is a major cause of maternal morbidity and mortality, the absolute risk for most women is low and there are few randomized controlled trials of thromboprophylaxis in the pregnancy-related setting on which to base recommendations. A Cochrane review published in 2002, looking at trials of thromboprophylaxis during pregnancy and the early puerperium, concluded there was insufficient evidence on which to base recommendations, as the number of trials and sample sizes were too small.<sup>21</sup> A number of professional bodies have drawn

Risk level	Risk factors	Recommended thromboprophylaxis
Very high	Previous VTE on long-term warfarin +/– thrombophilia antithrombin deficiency or APS	High prophylactic or therapeutic dose LMWH Requires specialist management by experts in hemostasis and pregnancy
High	Previous recurrent VTE Previous VTE: • plus thrombophilia • plus family history of VTE • plus other risk factor(s)* • on COCP or during pregnancy • at unusual site Asymptomatic thrombophilia: • Antithrombin deficiency • Combined defects • Homozygous factor V Leiden • Homozygous factor V Leiden • Homozygous prothrombin gene defect • Compound heterozygote Three or more other risk factors* Three or more risk factors plus admission to hospital	Prophylactic dose LMWH
Intermediate	Previous single VTE without family history, thrombophilia or other risk factor(s)* Other asymptomatic thrombophilias including APS (not covered above)	Close surveillance Advise to keep mobile and avoid dehydration consider TEDS
Lower	less than 3 other risk factors*	Advise to keep mobile and avoid dehydration Consider TEDS
*See Table 8.1		

Table 8.5 Ante-natal VTE risk factor assessment and thromboprophylaxis management

VTE = venous thromboembolism; COCP = combined oral contraceptive pill; LMWH = low molecular weight heparin;

APS = anti-phospholipid syndrome; TEDS = graduated compression stockings.

up guidelines,<sup>4–6,17</sup> many recommendations are based on low grade evidence. However, recent data show that risk assessment and allocation of thromboprophylaxis according to such guidelines is efficacious and cost effective, with few clinically significant adverse events.<sup>22,23</sup>

### Ante-natal

Recommendations for ante-natal assessment and management of VTE risk are given in Table 8.5. It is important to remember that there are probably many heritable thrombophilias as yet undiscovered and therefore unable to be confirmed with in vitro testing. So, if the history is suspicious, for example, previous VTE in an unusual site or previous recurrent VTE especially associated with as family history of VTE, it is sensible to treat these women as high risk, even without an identifiable thrombophilia, and give both ante-natal and post-natal LMWH prophylaxis. In comparison, women with a single previous VTE related to a temporary but non-estrogen related (pregnancy or the combined oral contraceptive pill) risk factor, who have no identifiable thrombophilia or additional current risk factor, do not require antenatal LMWH.<sup>24</sup> A recent study from Italy of 88 women who became pregnant after a single previous episode of VTE, with no ante-natal thromboprophylaxis, demonstrated no recurrence of VTE in pregnancy if the initial VTE was related to transient risk factors other than pregnancy or oral contraceptive use.<sup>10</sup> This contrasted with a 7.5% recurrence rate if the first VTE was unprovoked, or estrogen related.

Women who are on long-term warfarin outside pregnancy because of previous VTE or stroke associated with APS are at very high risk of recurrence, and should be managed with high prophylactic or sometimes full therapeutic LMWH ante-natally, depending on the clinical history, under the care of an expert in hemostasis and pregnancy.

Even women without a previous VTE or identified thrombophilia may require ante-natal thromboprophylaxis due to other risk factors. Those with at least three of the risk factors detailed in Table 8.1 should be considered for LMWH ante-natally and those with two risk factors require LMWH during hospital

Risk level	Risk factors	Recommended prophylaxis		
Very high	Previous VTE on long-term warfarin +/– thrombophilia antithrombin deficiency or APS	LMWH until re-established on warfarin		
High	<ul> <li>Any other previous VTE</li> <li>Asymptomatic thrombophilia:</li> <li>Antithrombin deficiency</li> <li>Combined defects</li> <li>Homozygous factor V Leiden</li> <li>Homozygous prothrombin gene defect</li> <li>Compound heterozygote</li> <li>Extended major pelvic or abdominal surgery (e.g. CS hysterectomy)</li> <li>Paralysis of lower limbs</li> </ul>	6 weeks prophylactic dose LMWH		
Intermediate	Emergency CS in labor Any CS plus any other risk factor Three or more other risk factors* Asymptomatic thrombophilia: • Heterozygous factor V Leiden • Heterozygous prothrombin gene defect	7 days prophylactic dose LMWH** Consider extending if other risk factors or positive family history		
Lower	CS not in labor no other risk factors Less than 3 other risk factors*	Early mobilization and avoidance of dehydration Consider TEDS		
* See Table 8.1: ** See text – there is minimal evidence to determine optimum duration of postpartum thromboprophylaxis.				

Table 8.6 Post-natal VTE risk factor assessment and thromboprophylaxis management

\* See Table 8.1; \*\* See text – there is minimal evidence to determine optimum duration of postpartum thromboprophylaxis. VTE = venous thromboembolism; LMWH = low molecular weight heparin; CS = Cesarean section; TEDS = graduated compression stockings.

admissions. This stresses the importance of repeated risk assessment as pregnancy progresses. It also highlights the need to assess all pregnant women for their thromboembolic risk, not just women under the care of hematologists with previous VTE and/or thrombophilia.

Interestingly, the UKOSS<sup>7</sup> study demonstrated that approximately one-third of women with an ante-natal PE had no classical risk factors for VTE disease (apart from pregnancy), and only 9 of the 99 who did would have been eligible for thromboprophylaxis under the 2004 RCOG guidelines.<sup>5</sup> Knight *et al.* discuss inclusion of women with at least two risk factors being eligible, but also acknowledge that this requires an estimated 9% of maternities to receive LMWH, or 5.5% if just multiparity was added as a risk factor. They suggest further studies are required to assess the cost benefit of this inclusion.<sup>7</sup>

### Post-natal

Table 8.6 details recommendations for post-natal assessment and management of VTE risk. The most recent RCOG guidelines supersede an order guideline regarding women who have had a Cesarean section.<sup>4,6</sup> There is significant variation between units as to how aggressively these are applied, with some prescribing

LMWH to all who have undergone Cesarean section, while others just for emergency Cesarean section in labor.

It is important to remember that thromboprophylaxis should not be limited to those who have delivered by Cesarean section, as women die from VTE even after a normal vaginal delivery. Women with at least two persisting risk factors from Table 8.1 should be considered for postpartum LMWH.

The immediate postpartum period is the time of highest risk for VTE, and post-natal LMWH should be continued for at least 7 days. Recently published data, assessing changes in thromboelastography parameters in the postpartum period suggest the risk is high for 7 days.<sup>25</sup> There is also emerging evidence that it may take several weeks for the hypercoagulable state of pregnancy to return to non-pregnant levels,<sup>24</sup> therefore for high risk patients, for example, those with a previous VTE or thrombophilia, it is standard practice to continue LMWH for six weeks.

# Dilemmas – current research and future direction

- Identification of other thrombophilias
- Cost-benefit analysis of extending ante-natal thromboprophylaxis

• Investigation of the optimal duration of postpartum thromboprophylaxis in women with risk factors other than previous VTE or thrombophilia.

## Summary

- Venous thromboembolism (VTE) is the leading direct cause of maternal mortality in the UK, but many cases are potentially preventable.
- Risk factors for VTE should be identified pre-pregnancy, or at least early in pregnancy, and reassessed throughout pregnancy and the puerperium, as level of risk may change.

- Pregnancy itself is a risk factor for VTE, and additional risk factors include previous VTE, thrombophilia, and obesity.
- Thromboprophylaxis should be introduced depending on the level of risk. Guidelines are given for both ante-natal and post-natal management, and in particular for the highest risk period immediately postpartum.
- Thromboprophylaxis includes both non-pharmacological and pharmacological measures, mainly low molecular weight heparin.
- Further research is required to identify additional thrombophilias, assess whether thromboprophylaxis should be extended, and determine optimal duration for postpartum thromboprophylaxis.

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# Thromboembolism and anticoagulation

# **Prosthetic heart valves**

Claire McLintock

## Introduction

Patients with mechanical heart valves require longterm anticoagulation, but the choice of anticoagulant for these women during pregnancy presents a major challenge. Oral anticoagulants such as warfarin and coumadin are the most effective agents for prevention of maternal thromboembolism, but freely cross the placenta and are teratogenic. They also cause late fetal loss in as many as one in ten pregnancies. Anticoagulation with unfractionated heparin (UFH) and low molecular weight heparin (LMWH), which do not cross the placenta will reduce the risk of these adverse fetal outcomes. However, there is concern that these drugs are less effective at preventing maternal valve thrombosis and systemic thromboembolism. Therein lies the challenge: the anticoagulant that is safest for the mother's physical health carries the greatest potential risk for her infant. Many women will choose a treatment that is safest for her baby, even if her own health may be compromised. Despite being advised that thrombotic complications may necessitate urgent valve-replacement surgery or lead to major neurological sequelae, many women are reluctant to take oral anticoagulants during pregnancy when informed about fetal risks. At worst, some women are noncompliant with all therapy, causing even greater maternal risk. This chapter addresses the management of pregnancy in women with mechanical heart valves and discusses the maternal and fetal risks associated with the different anticoagulant options, to enable clinicians and women to make the most informed choice in this challenging clinical situation.

## Indication for valve replacement

The most common indications for replacement of a native heart valve are congenital valvular disease and

rheumatic heart disease. While the incidence of congenital valvular disease is relatively stable at around 0.25% of births, there is marked variation in the rates of rheumatic fever and rheumatic heart disease (RHD) across different countries. Rheumatic fever is certainly more common in resource-poor countries and communities, but it is also prevalent in countries such as New Zealand and Australia with high rates in the indigenous Aboriginal and Maori people in these countries and in Pacific Island people in New Zealand and the Pacific region (Table 9.1).<sup>1–3</sup>

 Table 9.1
 Rates of acute rheumatic fever in different regions of the world

Country	Ethnicity	Rate of acute rheumatic fever in children aged 5–14 y (rate per 100 000)
Sub-Saharan Africa <sup>1</sup>		13.4
South-central Asia <sup>1</sup>		54.0
New Zealand <sup>2</sup>	Maori Pacific Island peoples European	30.4 77.7 1.7
Australia <sup>3</sup>	Aboriginal and Torres Strait Islander peoples Other Australian people	162–375 1.0
China <sup>1</sup>		21.2

# Consideration of valve type in women of child bearing age

For patients who require heart valve replacement, the alternatives include bioprosthetic valves – either homograft (human tissue) or heterograft (porcine or

Table 9.2 Mechanical valve typ	es
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Valve type	
Ball and cage	Starr-Edwards®
Tilting disc	Bjork-Shiley <sup>®</sup> Medtronic-Hall <sup>®</sup>
Bileaflet	St Judes <sup>®</sup> CarboMedics <sup>®</sup> On-X <sup>®</sup> ATS valve <sup>®</sup>

bovine tissue) - or mechanical valves (Table 9.2). The major advantage of bioprosthetic valves for women of child-bearing age is that, in the absence of other thromboembolic risk factors, oral anticoagulant therapy is not required. The disadvantage is the high rate of structural valve deterioration, the commonest reason for replacement of bioprosthetic valves. Structural deterioration of bioprosthetic valves in the mitral position occurs more commonly than of those in the aortic or tricuspid position and was reported in 84% of bioprosthetic mitral valves by 10 years. Although valve deterioration occurred more rapidly in younger patients, it was not further accelerated by pregnancy.<sup>4</sup> In contrast, structural valve failure is extremely uncommon with mechanical heart valves, but the risks of valve thrombosis and systemic thromboembolism mean that patients must take long-term oral anticoagulant therapy. When considering which type of valve to use in young women, clinicians should take into account the impact of the decision on management and outcome of future pregnancies.<sup>5</sup>

### Prevention of thromboembolism

An overall approach to management of women with prosthetic heart valves is summarized in Figure 9.1. Thromboembolic complications of mechanical valves include valve thrombosis, causing valve obstruction or systemic embolization, mainly cerebrovascular accidents (CVA) but also myocardial infarction or embolization into peripheral arteries. Systemic thromboembolism can develop from either obstructed or non-obstructed valves. Prevention of these complications is the main indication for long-term anticoagulation. Outside of pregnancy, the rate of major systemic embolization in patients with mechanical valves is around 1% per year in patients taking warfarin, 2% per year in patients taking aspirin, and 4% per year in patients on no anticoagulation.<sup>6</sup> Additional risk factors for thromboembolism are shown in Table 9.3. The 
 Table 9.3
 Risk factors for thromboembolism in patients with prosthetic valves

Valve related factors	Older type ball-cage valves, i.e. Starr-Edwards valve Valve in mitral position ≥2 prosthetic valves
Clinical risk factors	Previous thromboembolism Atrial fibrillation Dilated left atrium Heart failure

prothrombotic changes of pregnancy further increase the risk of thromboembolism with events reported in 4% of women taking warfarin during pregnancy.<sup>7</sup>

# Anticoagulant management during pregnancy

Available guidelines accurately state that continuation of oral anticoagulants (OAC) is the safest option for the mother for prevention of valve thrombosis and recommend that they should be used during pregnancy in spite of the known fetal risks (Table 9.4). Most suggest continuation of OAC throughout pregnancy, perhaps substituting adjusted-dose UFH or LMWH during the first trimester, the teratogenic risk-period.<sup>8-10</sup> However, ongoing use of OAC is associated with a significant risk of late fetal loss, as high as 10%, mainly as a result of complications from fetal anticoagulation. Maternal concern relating to these fetal risks and the desire for a healthy baby often means that women opt for the most dangerous option of all, taking no anticoagulation during pregnancy. The recent American College of Chest Physicians Guidelines on Anticoagulant Therapy<sup>8</sup> is the first published guideline to recommend either adjusted dose LMWH or unfractionated heparin (UFH) throughout pregnancy or until the beginning of the 13th week of pregnancy, switching to warfarin until close to delivery.

Unfractionated heparin and LMWH are recommended for prevention and treatment of thrombosis during pregnancy in women who are at risk of thromboembolism from other causes.<sup>8</sup> These agents do not cross the placenta, are not teratogenic and have no fetal anticoagulant effect. LMWH with its more predictable anticoagulant effect and better side effect profile has supplanted UFH for treatment and prevention of venous thromboembolism during pregnancy. Data relating to the safety and efficacy of LMWH in prevention of thromboembolic complications in pregnant women with mechanical heart valves are limited,

	Warfarin	LMWH	UFH	Aspirin
American College of Chest Physicians 2008 <sup>8</sup>	Only for women at very high risk thromboembolism, i.e. history thromboembolism, older type valve in mitral position	Can be used throughout pregnancy. Twice daily dose-adjusted, manufacturers peak anti-Xa level (1.0 U/ml) 4h post-dose	Can be used throughout pregnancy. Initial dose 17 500–20 000 U every 12 h. 6 hour post-injection aPTT 2x baseline or anti-Xa levels 0.35–0.70 U/mL	75–100 mg throughout pregnancy for high risk women
American Heart Association 2008 <sup>9</sup>	Reasonable to avoid 6–12 weeks' gestation. Embryopathy risk 4–10%. INR target 3.0 (range 2.5–3.5). Discontinue 2–3 weeks before planned delivery	Can be used 6–12 weeks' gestation. Twice daily, dose-adjusted with 4 h post-dose target anti-Xa levels 0.7–1.2 U/ml	Can be used 6–12 weeks' gestation. Continuous iv UFH or dose-adjusted s/c UFH bid. Starting dose s/c 17 500–20 000 U every 12h. Target aPTT 2x baseline	75–100 mg during second and third trimesters
European Society of Cardiology 2007 <sup>10</sup>	Favored in first trimester if dose ≤5 mg. Favored anticoagulant during the second and third trimester until week 36.	Currently not recommended – insufficient safety and efficacy data	Close monitoring is required when used	Not discussed
All auidelines recomme	end full discussion of the risks and	benefits of anticoagulant regir	nens.	

 Table 9.4
 Summary of published guidelines of management of anticoagulation in pregnant women with mechanical heart valves



Fig. 9.1 Approach to management of women with mechanical heart valves in pregnancy.

but some studies suggest that it is less effective than warfarin at preventing maternal thromboembolism. A major systematic review by Chan and co-workers<sup>7</sup> compared the maternal and fetal outcome of different anticoagulant regimens in 1234 pregnancies in 976 women in women with mechanical heart valves from 28 studies of women conducted between 1966 and 1997. Comparisons were made across four broad categories of anticoagulant regimens:

oral anticoagulants throughout pregnancy (792 pregnancies);

- unfractionated heparin in the first trimester followed by oral anticoagulants (230 pregnancies);
- unfractionated heparin throughout pregnancy (21 pregnancies);
- antiplatelet agents or no anticoagulant therapy (102 pregnancies).

Since that time, a number of further studies have been published,<sup>11-13</sup> including reviews of pregnancy outcomes in women taking LMWH at some stage during pregnancy.<sup>14,15</sup> A summary of published data of maternal and fetal outcomes in pregnancies where women

 Table 9.5
 Maternal and fetal outcomes in pregnancies in women with mechanical heart valves related to anticoagulant

 management approach
 Image: Comparison of the second second

Anticoagulant regimen	Pregnancies	Miscarriage N (%)	Stillbirth* ( <sup>Σ</sup> )	Warfarin embryopathy	Maternal thromboembolic complications
Warfarin throughout pregnancy <sup>7,12,13,27</sup>	983	253 (25.7%)	13/127 <sup>§</sup> (10.2%)	39/740 (5.3%)	36 (3.7%)
Warfarin-UFH-warfarin <sup>7,11,13</sup>	285	66 (23.4%)	3/43 <sup>§</sup> (7.0%)	6/229 (2.6%)	28 (9.9%)
Warfarin-LMWH-warfarin <sup>15</sup>	56	4 (7.1%)	1/51 (1.9%)	0	5 (8.9%)
LMWH throughout <sup>11,13,15</sup>	29	2 (8.3%)	0	0	1 (4.2%)

\* pregnancies included in Chan review excluded as stillbirths not reported as a separate group.

<sup>§</sup> excluding spontaneous miscarriages and terminations of pregnancy.

have received different anticoagulant regimens is presented in Table 9.5.

# Anticoagulation with warfarin during pregnancy

Oral anticoagulants, such as warfarin and acenocoumarol, are the most effective agents for prevention of valve thrombosis and systemic thromboembolism during pregnancy in women with mechanical heart valves. Disadvantages of oral anticoagulants include teratogenicity, high rates of spontaneous abortion and late fetal loss as well as neurological abnormalities in surviving infants.

## Fetal effects of warfarin

Exposure to warfarin in the first trimester causes warfarin embryopathy in as many as 6% of infants. Hall and co-workers<sup>16</sup> recommended that nasal hypoplasia and stippled epiphyses should be the minimal features required to classify a case as warfarin embryopathy. These features are not described in women who substitute heparin for warfarin between 6-12 weeks of pregnancy or who are exposed to warfarin from the second trimester onwards. A recent review of 63 published cases of warfarin-related abnormalities<sup>17</sup> described skeletal anomalies in 81% of cases (n=51)with mid facial hypoplasia described in 47 infants and epiphyseal calcific stippling of long bones, vertebrae, calcanei, or phalanges in 32 infants. Breathing and feeding problems were present in 24 of 47 infants who had severe midfacial hypoplasia. The period of exposure to warfarin, common to infants who developed embryopathy, was between 6 and 9 weeks' gestation. Long-term follow-up information was available on 20 of 46 children in this cohort who survived the neonatal period with abnormalities persisting in about half of the children with midline hypoplasia and spinal deformities. These teratogenic effects are unlikely to be caused by inhibition of Vitamin K-dependent clotting proteins by warfarin, as these are not produced by the fetal liver until after 12–14 weeks' gestation. Vitamin K-dependent proteins are also important in development of bone and cartilage and inhibition of these proteins may account for this teratogenic effect of warfarin.

Microcephaly, cerebral atrophy, hydrocephalus, optic atrophy, and intracranial hemorrhage are among the central nervous system abnormalities described in 1% of liveborn infants exposed to warfarin during pregnancy. The prevalence of long-term neurological problems, such as developmental delay and low IQ, in infants who appear normal after in-utero exposure to warfarin is still debated.

## Warfarin and pregnancy outcome

Warfarin exposure during pregnancy is associated with increased rates of spontaneous miscarriage and a 10% rate of late fetal loss, Table 9.5. The majority of late losses are thought to be due to fetal intracranial hemorrhage (ICH) as a result of anticoagulation of the fetus. Warfarin freely crosses the placenta so it will inhibit fetal vitamin K-dependent clotting proteins that are produced from 12–14 weeks' gestation. As vitamin K levels in the fetus are one-tenth of the levels in the mother, the dose of warfarin taken by the mother to achieve a therapeutic INR will cause severe over-anticoagulation in the fetus, possibly with INR levels as high as those that develop in elderly patients on warfarin who become vitamin K deficient when they are unwell, stop eating, and take antibiotics.

# Effect of warfarin dose on pregnancy outcome

Vitale and co-workers<sup>18</sup> described increased fetal complication rates in women with mechanical heart valves taking sodium warfarin doses of >5 mg during pregnancy compared to women on lower doses. This dosedependent relationship was further examined in an updated publication of their pregnancy cohort including 71 pregnancies in 52 consecutive patients.<sup>19</sup> Fetal losses were reported in 78.8% of 33 pregnancies in women taking >5 mg warfarin, including 21 spontaneous abortions between 12 and 20 weeks' gestation and five stillbirths after 20 weeks' gestation. Of 38 pregnancies in women taking <5 mg of warfarin daily only two spontaneous abortions (5.3%) were reported. The cause of spontaneous abortion or stillbirth was not reported. Rates of classical embryopathy did not differ between groups with skeletal anomalies reported in three infants; two with nasal hypoplasia (one in a term infant in the  $\leq$ 5 mg warfarin group and one in a spontaneously aborted fetus in the >5 mg group) and cervical spine abnormalities reported in a spontaneously aborted fetus from the higher dose group. This dosedependent relationship with adverse fetal outcome is not described in all studies<sup>4</sup> and the clinical impact of such an association is uncertain as OAC dosage is determined by maternal INR.

# Anticoagulation with heparin during pregnancy

# Unfractionated heparin and antiplatelet agents

Unfractionated heparin and antiplatelet agents such as aspirin were used as alternatives to warfarin for anticoagulation of pregnant women with mechanical heart valves prior to the development of LMWH. Although use of antiplatelet agents avoided the risk of congenital anomalies the thromboembolic complications were reported in 29% of pregnancies where women took antiplatelet agents alone.<sup>7</sup> Similarly, no fetal anomalies were reported in pregnancies where UFH was substituted for warfarin prior to six weeks gestation and continued until completed 12 weeks' gestation. Variation in rates of thromboembolic complications with UFH are likely to be confounded by differences in heparin dosing, anticoagulant monitoring, and duration of treatment. Thromboembolic complications occurred in 9.9% of these pregnancies where women received UFH (Table 9.5) including events in the two recent studies<sup>11,13</sup> where the dose of UFH was adjusted to keep the activated partial thromboplastin time (aPTT) at two to three times baseline levels. In 21 pregnancies where UFH was used throughout, thromboembolic complications were reported in 33%.7 Concerns with maternal safety with UFH provided the impetus to explore the efficacy of LMWH with its more predictable anticoagulant effect as an alternative anticoagulant for women with mechanical heart valves who do not wish to take warfarin during pregnancy. Long-term use of therapeutic dose UFH also increases the risk of osteoporosis and heparininduced thrombocytopenia.

# Maternal and fetal outcomes in women receiving LMWH during pregnancy

Limited data are available of pregnancy outcome in women with mechanical heart valves treated with LMWH during pregnancy; outcomes in women taking either LMWH during the first trimester only or throughout pregnancy account for only 4.1% and 2.1% of published reports, respectively (Table 9.5). In their review of published studies of pregnancy outcome in women with mechanical heart valves who received LMWH during pregnancy, Oran and coworkers reported seven episodes of valve thrombosis and two CVAs in 81 pregnancies, a complication rate of 11.1%.<sup>15</sup> Single case reports and small case series accounted for six of the thromboembolic events in this review. Limiting analysis to studies including  $\geq$ 5 pregnancies the rate of valve thrombosis was 4.8%. Dose adjustment of LMWH in response to anti-Xa levels appears to be a key factor in management of anticoagulation with LMWH in pregnant women with mechanical heart valves: six of the seven valve thromboses in Oran's review occurred in women who did not have anti-Xa levels measured.

Another consideration with heparin use is the risk of heparin-induced thrombocytopenia and bone

Table 9.6 Quick-reference guide: estimates of maternal and fetal risks with different anticoagulant regimens for pregnant women with mechanical heart valves

Anticoagulant regimen	Maternal valve thrombosis and systemic thromboembolism	Spontaneous abortion	Late fetal loss	Warfarin embryopathy
Warfarin continued throughout pregnancy	Low	High	Moderate	Moderate
Dose-adjusted UFH weeks 6–12, then warfarin	Moderate	High	Moderate	No risk
Therapeutic-dose LMWH weeks' 6–12 with anti-Xa monitoring, then warfarin	? Low	Moderate	Low	No risk
Therapeutic-dose LMWH throughout pregnancy started <6 weeks' gestation with anti-Xa monitoring	? Low	Moderate	Low	No risk
Low risk <5% Moderate risk = 5%–10% High risk >10%				

mineral density loss. This is less common with LMWH than with UFH.

### **Role of aspirin**

Outside of pregnancy, low dose aspirin (100–150 mg) is recommended in addition to warfarin for patients with mechanical heart valves with other thromboembolic risk factors (Table 9.3). Low dose aspirin has been shown to reduce the risk of major thromboembolic events such as valve thrombosis and CVA in patients at the expense of an increase in minor, but not major bleeding.<sup>20</sup> The prothrombotic changes of pregnancy could also be considered as an additional risk factor for thromboembolism supporting the use of low dose aspirin during pregnancy in addition to warfarin or heparin.

A simplified summary of risks and benefits associated with UFH, LMWH and warfarin is provided in Table 9.6.

Although there are limited published data relating to use of LMWH for anticoagulation during pregnancy in women with mechanical heart valves, it is possible that thromboembolic complications may in part relate to suboptimal LMWH doses. Regular monitoring of anti-Xa levels with dose-adjustment of LMWH may provide more effective thromboprophylaxis. The high risk ante-natal medical clinic at National Women's Health, Auckland City Hospital has published one of the largest single case series of women with mechanical heart valves treated with enoxaparin and aspirin during pregnancy.<sup>21</sup> Women attending this clinic are informed that the safest option for them is not to become pregnant but those who choose to proceed with pregnancy have in-depth counseling of the  
 Table 9.7
 Anticoagulant options offered to women with mechanical heart valves attending high-risk medical ante-natal clinic, National Women's Health, Auckland City Hospital, New Zealand

- **Option 1.** Substitution of warfarin with therapeutic dose enoxaparin (1 mg/kg bd) and aspirin 150 mg before 6 weeks' gestation, continued until planned delivery
- **Option 2.** Substitution of warfarin with therapeutic dose enoxaparin before 6 weeks until 12 completed weeks, reverting to warfarin until 34–36 weeks, then therapeutic dose enoxaparin until planned delivery. Aspirin 150 mg throughout pregnancy.
- **Option 3.** Warfarin and aspirin 150 mg throughout pregnancy, switching to therapeutic enoxaparin and aspirin at 34–36 weeks' gestation until planned delivery.

Low-dose aspirin (100–150 mg) recommended for all women

maternal and fetal risks and benefits of different anticoagulant agents and provide written consent for their choice of one of three anticoagulant regimens (Table 9.7). Regular anticoagulant monitoring is carried out with target therapeutic ranges of INR and anti-Xa levels as listed in Table 9.8. Low-dose aspirin is recommended for all women.

The thromboembolic complications reported with dose-adjusted UFH and the variable dose-response rates with this agent suggest that it may be a less reliable alternative to LMWH. Given the significant advantages in terms of fetal outcome, perhaps monitored therapeutic-dose LMWH for prevention of maternal valve thrombosis and systemic thromboembolism could be an attractive alternative to warfarin for use in this clinical setting.<sup>22</sup> Certainly, it would seem premature to contraindicate use of therapeutic dose LMWH during pregnancy for these women<sup>23</sup> given the lack of an acceptable alternative anticoagulant and also the

Drug	Laboratory test	Valve type	Anticoagulant target range
Enoxaparin (1 mg/kg bd)	Anti-Xa levels – 3–5 days after first dose then monthly	All valves	Trough (pre-dose) 0.4–0.7 IU Peak (4 h post-dose) 0.7–1.2 IU
Warfarin	Monthly INR	Starr–Edwards valves Bileaflet and tilting disc valves	3.0–4.5 2.5–3.5

Table 9.8Anticoagulant monitoring for women with mechanical heart valves attending high-risk medical ante-natal clinic, NationalWomen's Health, Auckland City Hospital, New Zealand

continued emergence of safety and efficacy data of its use in this clinical setting. In the absence of a randomized clinical trial, clinicians must rely on bestpractice guidelines based on existing evidence and experience.

Other critical issues to consider when deciding on anticoagulant management in pregnant women with mechanical heart valves include the cost of LMWH and access to laboratory testing for anti-Xa levels. In countries with limited resources it may be more appropriate to treat women with warfarin but these decisions will rest with individual clinicians.

### Other management issues

Regular follow-up during pregnancy is essential to make sure frequent monitoring of anticoagulation is done, and careful clinical assessment to detect any cardiac complications. Table 9.9 lists important aspects of care. The infants of mothers with congenital heart disease have a five- to tenfold increased risk of congenital heart defects themselves and careful anatomy scan or fetal echocardiogram is required at 20–24 weeks' gestation.

 Table 9.9
 Summary of ante-natal care required for women with mechanical heart valves: other maternal and fetal issues

Management of pregnancies in women with mechanical heart valves: other issues

- Regular patient review: every 4 weeks until 28 weeks' gestation, every two weeks until 34 weeks' gestation then weekly until delivery
- Urgent assessment if patient concerns about possible thromboembolism, change in cardiac symptoms, bleeding, preterm labor
- (3) Clinical assessment to include enquiry about symptoms of systemic thromboembolism, heart failure, cardiac rhythm, maternal hypertension.
- (4) Careful auscultation of maternal heart at each visit: new murmurs.
- (5) Maternal echocardiogram every trimester or more frequently if clinical concern
- (6) Fetal surveillance: regular scans for fetal growth, evidence of intracranial hemorrhage

## Management of labor and delivery

Management of women in the peri-delivery period requires close clinical monitoring, given the bleeding risks associated with therapeutic anticoagulation. The mode of delivery should be determined by obstetric indications but vaginal delivery is preferable to Cesarean section as it minimizes time off therapeuticdose anticoagulation – the increased risk of bleeding from the operative site necessitates a delay in restarting anticoagulation postpartum. A planned delivery allows for better control and adjustment of anticoagulation.

### Women on oral anticoagulants

Women should stop warfarin by 34–36 weeks' gestation to allow normalization of the infant's INR and minimize the risk of fetal intracranial hemorrhage at delivery. Although cessation of OAC leads to normalization of the woman's INR within 3–4 days, the process often takes much longer in the infant as it is likely to be over-anticoagulated given the immaturity of its coagulation system. Anticoagulant options for women who have taken warfarin until the peri-delivery period include:

- continuous intravenous unfractionated heparin aiming for aPTT 2–3x baseline;
- dose-adjusted subcutaneous UFH bid aiming for aPTT 2–3x baseline;
- therapeutic dose LMWH with monitoring of anti-Xa levels (see Table 9.8).

Tables 9.10 and 9.11 summarize peri-delivery management of anticoagulation for planned vaginal delivery or cesarean section, respectively. Gradual reintroduction of intravenous UFH, as outlined in Tables 9.10 and 9.11, is the preferred option for anticoagulation in the immediate postpartum period. Intravenous UFH has the advantage over LMWH of allowing more flexible dose adjustment including more **Table 9.10**Management of anticoagulation prior to inductionof labor for planned vaginal delivery in women onsubcutaneous LMWH (National Women's Health, Auckland CityHospital, New Zealand)

- (1) 36 hours prior to planned CS last dose s/c LMWH
- (2) 24 hours prior to induction start IV UFH infusion 5000 U bolus dose then 1200 U/h
- (3) Check aPTT 6-hourly target aPTT 2–3 × baseline\*
- (4) Discontinue iv UFH when woman in established labor
- (5) If regional analgesia required stop iv UFH 4 hr prior to epidural catheter placement, check aPTT back to baseline prior to placement, restart iv UFH 3 hours after catheter placement
- (6) 4–6 h postpartum, restart iv UFH at 500 U/h (no bolus dose) if no bleeding concerns then increase dose by 250 U every 4–6 hours until aPTT 2–3 x baseline\*
- (7) Start oral anticoagulant on first postpartum day if uncomplicated vaginal delivery or day 2–3 if Cesarean section or other bleeding complications
- \* therapeutic range may vary between centers, being dependent on the sensitivity of the aPTT reagent used. It should also be noted that the aPTT can be less reliable in pregnancy due to increased levels of factor VIII and heparin binding proteins.

 Table 9.11
 Management of anticoagulation prior to elective

 Cesarean section in women on subcutaneous LMWH (National
 Women's Health, Auckland City Hospital, New Zealand)

- (1) 36 hours prior to planned CS last dose s/c LMWH
- (2) 24 hours prior to planned CS start iv UFH infusion 5000 U bolus dose then 1200 U/h
- (3) Check aPTT 6-hourly target aPTT 2-3 × baseline\*
- (4) Stop iv UFH 4 hr prior to epidural catheter placement for regional anesthesia, check aPTT back to baseline prior to placement.
- (5) 6–12 h post-delivery, restart iv UFH at 500 U/h (no bolus dose) if no bleeding concerns, then increase dose by 250 U every 4–6 hours until aPTT 2–3 x baseline\*
- (6) Delay starting oral anticoagulant until epidural catheter removed if remains in situ for post-operative pain management
- \* therapeutic range may vary between centers, being dependent on the sensitivity of the aPTT reagent used. It should also be noted that the aPTT can be less reliable in pregnancy due to increased levels of factor VIII and heparin binding proteins.

rapid and complete reversal of its anticoagulant effect in the event of clinically significant bleeding in the postpartum period, especially as oral anticoagulants are restarted. Some centers may lack the experience of managing intravenous UFH infusions so an alternative may be to use intermediate doses of LMWH i.e. enoxaparin 40mg daily then twice daily until the first few days postpartum until the INR is therapeutic. However, not only is there the concern of a higher risk of valve thrombosis with low doses of LMWH, if bleeding does occur, the anticoagulant effect cannot be completely reversed. In the case of an obstetric emergency such as preterm labor or placental abruption, rapid reversal of anticoagulation is required. Management of heparin reversal with protamine is outlined in Chapter 10. Effective reversal of oral anticoagulation requires administration of 5.0–10.0 mg vitamin K1 intravenously, as well as prothrombin concentrate or fresh frozen plasma.

### Prevention of infective endocarditis

Antibiotic prophylaxis against infective endocarditis is recommended for women with prosthetic heart valves following vaginal delivery or Cesarean section, given the high risk of adverse outcome should this complication occur.<sup>24</sup> Women who have prosthetic heart valves as a result of rheumatic heart disease require secondary prevention of acute rheumatic fever and rheumatic heart disease for a minimum of 10 years after the most recent episode or until 30–40 years of age (whichever is longer). Benzathine penicillin-G, benzylpenicillin, or erthyromycin are considered safe in pregnancy.

### Management of valve thrombosis

Development of neurological symptoms, chest pain or symptoms of heart failure, or detection of a new cardiac murmur warrants exclusion of valve thrombosis using transthoracic or transesophageal echocardiography. Minor valve thromboses can often be managed by increasing the intensity of anticoagulation, but for more severe thromboses valve replacement surgery is usually required, although some centers have reported success with thrombolysis using rtPA or streptokinase.<sup>25</sup> Women with valve thrombosis should be managed jointly by the obstetric and cardiothoracic surgical team. Readers are referred to recent review articles discussing management issues in pregnancy.<sup>26–28</sup>

### Summary

The clinical challenge of managing anticoagulation in pregnancy in women with mechanical heart valves is set to continue. These women and the clinicians caring for them are faced with a true dichotomy: the choice of warfarin or heparin. Taking warfarin in pregnancy minimizes the risk of thrombotic complications but carries a high-risk of adverse fetal outcome; LMWH has an uncertain maternal risk but the fetal complications are very low. Experience suggests that, given the choice, many women will opt for what is safer for the baby – especially if it is their first pregnancy or they have had a bad fetal outcome with warfarin previously. However, women who develop complications with valve thrombosis or stroke due to suboptimal anticoagulation also place their babies at risk. Data relating to the safety and efficacy of LMWH continues to emerge and in the absence of a randomized trial, data from registries such as the International Registry of Pregnancies in Women with Mechanical Heart Valves developed by the ISTH Subcommittee on Women's Health Issues in Thrombosis and Haemostasis may help provide clearer guidance for management in the future.

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## Thromboembolism and anticoagulation

# Section 3 Chapter

# Management of anticoagulants at delivery

Christina Oppenheimer and Paul Sharpe

## Introduction

This chapter will address the practical obstetric and anesthetic management of women on prophylactic heparin and therapeutic anticoagulation in the peripartum period, and the dilemmas for obstetricians, anesthetists, and hematologists. Also considered will be issues surrounding use of thrombolytic agents in pregnancy and unusual but complex situations such as cardiopulmonary bypass in pregnancy.

Increasing use of prophylactic anticoagulants in pregnancy, both for venous thromboprophylaxis and to modify fetal risk, as in antiphospholipid syndrome, means that more women are now reaching the peri-partum period on anticoagulants, usually a low molecular weight heparin. Therapeutic doses are used for treatment of acute venous thromboembolic events, prevention of thromboembolism in women with cardiac disease including mechanical heart valves, acute cardiac events and cardiomyopathy, and those on longterm anticoagulation outside of pregnancy for a variety of other indications. This situation necessitates careful assessment of risks, close multidisciplinary discussion and planning, and expert management by the medical and midwifery teams during labor or Cesarean section. Careful discussion of risks and therapeutic decisions with the patient and her partner are also essential.

# Thromboprophylaxis

The use of a variety of anticoagulants in obstetric practice has been increasing steadily over the last 15 years, bringing with it increasing awareness of the need for attention to thromboprophylaxis, but also the need to adapt and plan for the risks associated with this. Thromboprophylaxis guidance from the Royal College of Obstetricians and Gynaecologists (RCOG)<sup>1</sup> and the recent report from the Confidential Enquiry into Maternal Health (CEMACH)<sup>2</sup> have both significantly raised awareness of the importance of risk assessment for venous thromboembolism, and hence increased use of low molecular weight heparins in particular (Chapter 8). The recent and rapid rise in prevalence of obesity in women of child-bearing age also brings many women into a high risk category necessitating use of general as well as pharmacological antithrombotic measures.

## **Antiplatelet agents**

Increasing use of low-dose aspirin, firstly following the publication of the CLASP trial in 1994,<sup>3</sup> then the work on anti-phospholipid syndrome in recurrent miscarriage by Regan and colleagues, as well as a gradual increase in numbers of women on long-term aspirin for medical conditions, such as previous stroke, has led to guidance on aspirin use around the time of delivery.

The use of aspirin 75 mg up to the time of labor and delivery is not contraindicated on either obstetric or anesthetic grounds. At this dose there is no increased risk of bleeding either at vaginal or Cesarean delivery, nor is there evidence of any increase in the risk of vertebral canal hematoma after spinal or epidural block insertion. However, it must be remembered that, if used with either a heparin or warfarin in the postpartum period, there may be an additive effect and particular care should be taken with timing of dose administration and epidural catheter removal. There is no contraindication to breastfeeding on aspirin at 75 mg daily, in particular, there is no evidence of risk of Reye's syndrome at this dose.

The safety in pregnancy of other antiplatelet agents such as clopidogrel or ticlopidine at usual therapeutic doses has not been established and they are rarely used. Both the indication for use and a clear plan of management to minimize risk at the time of delivery, including whether to interrupt the treatment, should be made on an individual case basis with consultation among responsible obstetrician, physician, and anesthetist.

Non-steroidal anti-inflammatory drugs are largely contra-indicated in pregnancy and should not be used around the time of delivery.

# Low molecular weight heparins (LMWH)

### **Obstetric aspects**

Most of the women requiring prophylactic doses of anticoagulant will be given one of the low molecular weight heparins. This is usually given once daily, although those with a particularly high thrombotic risk, obesity, or mechanical heart valves may be on twice daily doses.

While increasing numbers of women being prescribed LMWH for thromboprophylaxis leads to increased experience for staff in managing such pregnancies, it also necessitates sufficient knowledge for safe practice, particularly around the time of labor and delivery. This would take into account the half-life, increased clearance in pregnancy and different therapeutic index of different heparins.<sup>4</sup> Underpinning all of the clinical management described below must be collaboration, clear local guidelines, knowledge and education of medical and midwifery staff, as well as written information for patients and individual care plans based on a woman's particular risk factors.

### Labor and delivery

In the presence of increased risk of venous thromboembolism, the optimum management will be to aim for a spontaneous onset of labor as these are on average shorter and have a lower risk of operative delivery. Clearly, this advantage needs to be weighed against other obstetric and medical risks if present.

A standard approach is to omit the LMWH at the onset of labor and ensure general antithrombotic measures, including adequate hydration, with early recourse to intravenous fluids if necessary, mobilization, with passive movements or massage if mobility restricted by epidural, and the wearing of graduated compression stockings. If a woman has no additional complications other than a need for LMWH thromboprophylaxis, there is no contraindication to delivering in a midwifery-led setting provided at least 8 hours has elapsed since the last dose by delivery. If women in this situation request a home confinement, this should be discussed on an individual basis.

### Induction of labor

If an induction of labor is planned, the LMWH should be omitted at the start of the process. If a morning dose is usual, the dose on the day of induction should be omitted, or if an evening dose, that on the evening before should be taken as usual, but none further until after delivery. If an omission of more than 48 hours is thought to be contraindicated, intermittent doses of subcutaneous UFH, 5000u, could be considered 8 hourly until artificial rupture of the membranes (ARM) is possible, although this is rarely needed. UFH has a half-life of about 3 hours, so that an anticoagulant effect at a level suitable for regional anesthetic blockade is possible around that point. With prophylactic LMWH this delay needs to be 8-12 hours depending on dose as discussed below. Attention should be paid to general antithrombotic measures including compression hose, hydration, and mobility.

A prolonged induction process is more likely in primigravida and those with an unfavorable cervix at the start of the induction. Thus, where possible, careful assessment should be made to try to delay induction until the cervix is more favorable. If this is not possible, there will then be the dual additional risk of a prolonged period where the woman is only covered by general antithrombotic measures and an increased risk of instrumental delivery or Cesarean section (CS) inherent in an induced labor.

### **Practical issues**

At prophylactic doses of LMWH or UFH, there is no contraindication to intramuscular analgesics during labor or to intramuscular syntometrine at delivery. The LMWH should be recommenced 3–6 hours after delivery, providing hemostasis is secured and the timing around removal of epidural catheter is considered, as described below.

It should also be emphasized that, for standard prophylactic doses of LMWH, no significant increase in the risk of intra- or postpartum bleeding, paravaginal hematoma or prolonged lochia has been shown; however, it is good practice to ensure adequate and timely use of uterotonics and early suturing of any tear or episiotomy. There is no contraindication to pudendal or perineal block for analgesia. Also, there is no increased risk of excess surgical bleeding at Cesarean section, although risk of wound hematoma may be slightly increased.

### Breastfeeding

There should be a clear plan of the length of time to continue the LMWH postpartum. The woman should be reassured that there is no contraindication to breastfeeding since, although the LMWH will be present in breastmilk, it will be broken down in the gastric acid before absorption can occur.

### Anesthetic aspects

One of the major concerns about the use of heparins in the peripartum period in relation to anesthesia is the risk of vertebral canal hematoma and its severe sequelae. This was first raised as a significant issue in publications from the USA,<sup>5</sup> and subsequently there has been much study and debate leading to some standardization and guidance.<sup>6,7</sup> Over 40 cases of vertebral canal hematoma were reported in the American literature in 1997-1998, from a 5year observation period, in patients given enoxaparin, mostly following epidural, spinal, or lumbar puncture needle insertion. However, subsequent European reports include only two such cases with vertebral canal hematoma. The incidence has been estimated at 1 in over 2 million in a European study, but about 1 in 15000 in American studies. Numerous factors including timing of LMWH in relation to needle insertion or epidural catheter removal, and dosing schedules have been implicated. Other studies have suggested that technical difficulties with needle and particularly epidural catheter insertion may also be associated with increased risk of hematoma, particularly multiple insertion attempts or blood-stained tap.<sup>8</sup> (Table 10.1)

 Table 10.1
 Estimated incidence for vertebral canal hematoma in spinal and epidural anesthesia

	Epidural	Spinal
<b>Without heparin</b> Atraumatic Traumatic	1/220 000 1/20 000	1/320 000 1/29 000
Heparin given after procedure		
Atraumatic Traumatic UFH more than 1 hr after puncture UFH less than 1 hr after puncture	1/70 000 1/2 000 1/100 000 1/8 700	1/100 000 1/2 900 1/150 000 1/13 000

### Thromboprophylaxis for elective operative procedures Single shot spinal versus epidural catheter techniques

Single shot subarachnoid anesthesia remains a popular choice amongst obstetric anesthetists to provide operative conditions for elective Cesarean section. This is primarily because of the superior nature of the quality of anesthesia produced when compared with epidural anesthesia. Because there is no catheter to be removed, this technique facilitates the use of a single agent in the post-operative period. A minimum of 2 hours should be allowed to elapse between completing the subarachnoid injection and the administration of a LMWH.

The use of an epidural catheter in isolation, for example to provide more controlled onset of anesthesia in patients with cardiovascular instability, is less common in the elective setting. The introduction of the combined spinal epidural (CSE) has allowed a flexible approach. The epidural space is located with a Tuohy needle using a loss of resistance technique, usually with a 16- or 18-gauge needle. A spinal needle, of smaller gauge such as 26, is then introduced through the Tuohy needle to pierce the dura and enter the subarachnoid space. Once this thinner spinal needle has been removed, the epidural catheter can then be threaded through the Tuohy needle into the epidural space. This technique has provided great flexibility. Administration of reduced doses of local anesthetic into the subarachnoid space, with further doses administered via the epidural catheter allows excellent control over the cardiovascular system. The presence of an epidural catheter also allows the anesthetist to provide additional doses of anesthetic in cases of inadequate anesthesia or prolonged operative delivery. However, as this technique involves a catheter in situ at the end of surgery, the operative team are presented with two options in women requiring thromboprophylaxis: (1) administration of a single anticoagulant, most commonly a LMWH or (2) a combination approach.

If a LMWH is given as a sole agent, it is preferable to wait 2–4 hours after removal of the Tuohy needle. The epidural catheter should be left in situ until the drug levels have reached a safe trough (see Table 10.2). A combination of unfractionated heparin followed by LMWH allows the epidural catheter to be removed in a highly monitored environment in the Recovery Ward and also permits more controlled reversal of heparin effects if required in cases of massive post partum hemorrhage. When unfractionated heparin is given at the end of Cesarean section, local data suggest that coagulation profiles are equal to pre-operative values at 4 hours post-operation, providing there has been no significant peripartum bleed.

### Labor analgesia

It is quite common for a "safe window" to be present to administer epidural analgesia as a result of antenatal assessment and a plan documented to omit or appropriately manage heparin once labor starts. For prophylactic dosing, there is current guidance on timings for insertion of epidural blockade. This should be utilized regularly as part of ante-natal planning, and agreed between obstetric, anesthetic, and hematology teams. The demonstrated increase in clearance of LMWH in the pregnant woman allows a slightly different regime to surgical patients in general. A scheme allowing neuraxial analgesia 8-10 hours following the administration of 2500 units and 12 hours following a dose of 5000 units of dalteparin for example, would be appropriate (see Table 10.2). The ability to predict an appropriate time is harder when higher doses of LMWH have been used, or in situations where a woman presents on full anticoagulant therapy, but in general this needs to be at least 24 hours after the last dose. An assessment based on previous anti-Xa levels if available, and on a risk-benefit analysis for each patient and situation is needed.

If anticoagulation is to commence after delivery, an adequate gap should be left after the removal of the epidural catheter before the heparin is administered, usually around 4 hours for LMWH. Whilst most anesthetists accept a 2-hour interval between catheter

**Table 10.2** Guidance for relative timings of heparin and epidural or spinal block

#### A. Subcutaneous prophylactic dose unfractionated heparin

Catheter placement or removal > 2-4 h after injection Delay next dose until > 2 h after catheter insertion or >4 h after removal

# B. Intravenous infusion of unfractionated heparin Catheter placement > 4 h after stopping infusion, when aPTT back to baseline Restart infusion >2 h after catheter insertion or >4 h after removal

### C. Low molecular weight heparin

Spinal or epidural catheter insertion > 8 h after last injection – low dose > 12 h after last injection – intermediate dose > 24 h after last injection – full anticoagulation Remove epidural catheter 12 h after any dose Delay next dose until > 2 h after catheter insertion or subarachnoid injection or > 4 h after catheter removal insertion and heparin injection, as this can easily be lengthened if the procedure is difficult or traumatic, 4 hours is preferred after removal as the catheter can pull on established clot and stir up bleeding, even when insertion had been apparently uneventful.

### **Full anticoagulation**

Women who are fully anticoagulated at the time of labor and delivery include those with significant risks of morbidity – a recent venous thromboembolic event, those normally on long-term warfarin for a variety of conditions, cardiac disease including mechanical valves, ischemic heart disease and cardiomyopathy, and symptomatic homozygous or combination heritable thrombophilias.<sup>9–11</sup>

The management of these women with a need for therapeutic levels of anticoagulation in the peripartum period involves balancing the risks of excessive bleeding and difficulties with analgesia and anesthesia against the risk of thrombosis associated with the underlying condition. This requires a careful and individualized approach and thorough forward planning, by a team including obstetrician, midwife, anesthetist, and hematologist, and in full consultation with the patient (table 10.3). This is particularly important for the small number of women in whom the usually recommended temporary peripartum reduction in level of anticoagulation may be considered unsafe.

If it has been necessary to use warfarin during the pregnancy, this should be stopped by 34–36 weeks' gestation, to allow correction of the fetal coagulopathy, which takes longer than that of the mother, and minimize the risk of intracranial hemorrhage at delivery. The most common practice is to replace it with therapeutic dose LMWH and monitor with anti-Xa levels as well as clinically. The anti Xa level is checked at 3–5 days following the first dose and, if in the desired therapeutic range does not usually need repeating.

If vaginal delivery is intended, planned induction of labor once the cervix is sufficiently favorable should be considered. This allows more accurate timing of events and minimizes the risk of delivery whilst fully anticoagulated. The LMWH should be omitted on the morning of induction. If prophylaxis needs to be continued for the day of labor, 5000iu UFH can be given subcutaneously 8 hourly. If treatment doses are necessary, an infusion of UFH at 1200 u/h should be started. APTT should be checked at 4 hours after the infusion was commenced, aiming for the therapeutic range as determined by the local laboratory. It should be noted that the aPTT is less reliable in pregnancy due to increased levels of factor VIII and heparin binding proteins.

This regime has been shown to be useful when stopped 1–6 hours (typically 4) pre-labor, with minimal obstetric or anesthetic complication.<sup>12</sup> However, if this interruption prior to labor is not appropriate, the UFH infusion should be stopped when cervical dilatation reaches 5 cm dilatation in primipara, or an appropriate pre-planned dilatation depending on previous labor experience in multipara. It should also be stopped if increased unscheduled blood loss is noted or if urgent Cesarean section is required.<sup>13</sup>

Protamine sulphate must be immediately available as should the regime for its use, and 4 units of crossmatched red cells should be available. A protamine sulphate regime is described in Table 10.4.

Graduated compression stockings should be worn throughout induction and labor and throughout the inpatient stay, mobility should be encouraged and hydration ensured.

After delivery, the third stage of labor should be actively managed with oxytocin, given by intravenous bolus 10 u followed by an infusion of 40 u over 4 hours. Perineal tears or episiotomy should be repaired immediately with careful attention to hemostasis and heparin restarted as soon as hemostasis has been secured.

A high index of suspicion must always be maintained when caring for these women with regard to hemorrhagic complications during pregnancy. The incidence of antepartum hemorrhage and abruption is not increased, but is more likely to be significant. A careful plan for investigation and management of unexplained abdominal pain or unscheduled bleeding must be available in the notes.

Other issues which must be considered are the inadvisability of pudendal block, the potential maternal risks of instrumental delivery if labor occurs spontaneously and without the lapse of time since the last dose of heparin, and the importance of careful postpartum observations for development of hematomata.

If the woman is on warfarin when labor starts, the INR must be checked urgently and if greater than 3 or if a Cesarean section is required, reversed with vitamin K and if more urgent, prothrombin complex concentrate as well. In this instance, a cord blood clotting screen must be taken after delivery as intravenous 
 Table 10.3
 Recommended thromboprophylactic and anti-hemorrhagic measures

General measures:	Optimize anticoagulation ante-natally Formulate intrapartum care plan Multidisciplinary intrapartum care Senior staff involvement in care throughout Aim for vaginal delivery whenever possible
Specific thromboprophylactic measures:	Mobilize during labor Maintain hydration Graduated compression stockings throughout labor and postpartum
Specific anti-hemorrhagic measures:	Minimize maternal soft tissue trauma (e.g. difficult instrumental delivery, perineal trauma) Active third stage with intravenous oxytocics Prompt management of complications (e.g. retained placenta, perineal trauma)

Vitamin K may be required for the neonate. Early involvement of the neonatologists is essential.

### Anesthetic considerations

Analgesia and anesthesia in this group of women is a major challenge and early involvement of senior anesthetic staff is essential in planning intrapartum care. Regional analgesia is clearly contraindicated because of the risk of vertebral canal hematoma. A review by Loo *et al.* documented an overall incidence of 0.2-0.3/100~000 following obstetric epidural analgesia, with coagulation abnormalities being identified as a major risk factor.<sup>14</sup>

### Analgesia for labor

The role of a consistent intrapartum care provider, particularly midwifery, is of high importance – one-toone care from a single carer has been shown to reduce analgesia requirements and will also reduce the many anxieties associated with labor in such a situation.<sup>13</sup> Other guidance aids decision making, concerning the need for continuity of anticoagulation, or a window to reduce the risk of hemorrhage and alter the range of analgesics available.<sup>15</sup>

Pharmacological intervention includes inhaled analgesia in the form of entonox, or administration of systemic opioids. In a fully anticoagulated woman intramuscular injection is contraindicated, so bolus or patient-controlled intravenous administration of opioid analgesia is a suitable option. Traditionally, opioid therapy used by most delivery suites across the United Kingdom was intermittent bolus administration of intramuscular drugs such as pethidine. The desire to match the pharmacokinetics of opioids to the time course of the cyclical pain associated with labor has led to the investigation of shorter-acting opioids administered in small repeated doses. Patient-controlled analgesia pumps deliver a small pre-set dose of opioid via an intravenous cannula.

Fentanyl is a synthetic phenylpiperidine derivative and is a highly selective mu opioid agonist. When given by the intravenous route, the dose is effective within 2 to 5 minutes. Fentanyl is highly lipid soluble and therefore the drug in the plasma rapidly redistributes to fat-rich areas. This accounts for the short duration of fentanyl in clinical practice. If large doses are given, in, for example, a prolonged labor, then the reservoir for redistribution becomes full. The duration of action therefore becomes exaggerated from each subsequent dose, behaving more like morphine. The time to clinical action means that it can be difficult for the laboring woman to coincide the analgesic action with the peak of each contraction.

Remifentanil is another synthetic opioid of the anilidopiperidine group. It has an ultra-short duration of action due to unique metabolism by plasma esterases. It has a peak onset of 1 to 3 minutes, thus making the timing relative to contractions easier to manage. Remifentanil can be given by bolus dose, or a combination of background infusion with supplemental bolus doses. The pharmacokinetic profile of remifentanil means that, of all the opioids available, it should most closely match the time profile of a contraction. Following a recent survey of opioid use in labor, remifentanil is now the most commonly used opioid in the UK for women laboring with a live fetus. The recommended dose varies between studies, and whilst the presence of a background infusion seems to increase analgesia, it is often at the expense of increased adverse events. The narrow therapeutic window means respiratory depression, and indeed apnea, are significant risks. The degree of monitoring required is often well in excess of that which can be offered on a delivery suite.

### Anesthesia for operative delivery

General anesthesia is associated with significant morbidity and even mortality, for example, the risk of failing to intubate and protect the trachea is increased by a factor of ten during pregnancy. This must be considered in a risk-benefit assessment for each individual woman presenting for delivery.

Advice regarding timing of regional anesthesia relative to anticoagulant dose is the same as for regional analgesia (see Table 10.2), although the use of a single shot spinal anesthetic technique with a fine gauge needle may be considered earlier than standard guidance if the woman has other significant anesthetic risk factors.

The anesthetist must be aware of the increased risk of bleeding at Cesarean section in those women taking higher doses of LMWH. The introduction of cell salvage machines in obstetric practice to collect autologous blood may help in the management of these patients.

Other potential complications of regional anesthesia include :

### Problems with blood patches

Accidental puncture of the dura mater occurs in 0.5% to 2.0% of all epidural procedures. Of these women 70% will develop a post-dural puncture headache. If this headache is severe, it is often treated with an epidural blood patch. Maternal blood is withdrawn aseptically from a suitable vein and introduced via a Tuohy needle into the epidural space. As this requires further passage of a Tuohy needle, the same time delay should be introduced after LMWH administration to avoid bleeding risk. If the woman is fully anticoagulated in the post-delivery period, it should not be done. If headache is severe, then a hiatus in anticoagulant therapy may be considered; however, it is unlikely that the risks of coming off anticoagulant therapy will be outweighed by the treatment of the headache. Review of the current literature would suggest that continuing on prophylactic doses of LMWH does not affect the ability of the epidural blood patch to treat the headache effectively.

### Cauda equina syndrome

The cauda equina is formed from the terminal nerve roots of the spinal cord, after the spinal cord has formally terminated around the L2 lumbar disc space. Compression of the cauda equina presents in a common pattern. Table 10.5 shows the symptoms and signs classically displayed by patients with a cauda equina syndrome. Patients on anticoagulant therapy whom have had regional analgesia or anaesthesia should be

Table 10.4 Treatment of sever	re heparin overdosage
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Protamine sulphate regime	<ol> <li>heparin infusion 25 mg-50 mg after stopping heparin infusion (1 mg of protamine sulphate neutralizes 80-100 units of heparin)</li> <li>heparin bolus: 1.00-1.5 mg/100 IU Heparin can be given if 30 minutes have elapsed 0.5-0.7 mg/100 IU Heparin can be given if 30-60 minutes have elapsed 0.25 mg-0.375 mg IU Heparin can be given if 2 hours have elapsed</li> <li>subcutaneous heparin injection: 1-1.5 mg/100 IU heparin. 25-50 mg by slow IV injection and the remainder by slow IV infusion over 8-16 hours (or the expected duration of absorption of heparin), or 2 hourly divided doses.</li> <li>heparin during extracorporeal circulation: 1.5 mg per 100 IU heparin. Sequential APTTs may be needed to calculate correct dosage</li> </ol>
Dose in renal/hepatic impairment.	For hepatic impairment, seek further advice No dose adjustment necessary for renal impairment
Note	Excessive doses of protamine can have an anticoagulant effect

#### Table 10.5 The cauda equina syndrome

Low back pain
Bilateral, occasionally unilateral, sciatica
Perineal numbness (saddle numbness)
Bladder dysfunction
Bowel dysfunction
Variable lower limb weakness and sensory loss

carefully monitored in the post delivery period. Imaging of a potential lesion is usually undertaken with MRI scanning. Cauda equina syndrome is a medical emergency, and in the case of hematoma, requires urgent surgical opinion to schedule evacuation of the clot, as delay is likely to increase the risk of residual neurological dysfunction.

### Thrombolysis and bypass

It has been traditional to consider pregnancy and the puerperium as contraindications to the use of thrombolytic agents. However, in the situations where they are needed, the life of the mother is likely to be at high risk, as in cardiac compromise following massive central pulmonary embolus (PE), or acute myocardial infarction. In this situation, the balance of risks needs careful consideration, but if thrombolysis is likely to be life-saving, it should not be delayed as if hemorrhage occurs it can be managed with a combination of surgical and hematological techniques. Clearly for massive central PE targeted injection via catheter is the ideal, if appropriate staffs are available, but there are reports of successful thrombolysis without this.<sup>16</sup> Life-saving treatment should not be delayed or withheld for theoretical risk which cannot be substantiated. Senior and experienced decision making is essential – for example if a Cesarean section is required as part of resuscitation in a woman collapsed from PE or MI, the timing and management of thrombolytic agents would need to be discussed carefully but swiftly.

The risk-benefit balance when cardio-pulmonary bypass is contemplated in pregnancy is different. Clearly, the seriousness of the situation giving rise to the need for bypass, usually associated with cardiac surgery, combined with prolonged and significant anticoagulation means that to facilitate optimization of both maternal condition for anesthesia and surgery and post-operative recovery, emptying of the uterus prior to bypass is advisable. There are case reports of successful prolongation of pregnancy in this situation, but also numerous reports published and unpublished of significant retroplacental bleeding, inability to maintain maternal blood pressure or oxygenation, and difficulty in maintaining good peri-operative conditions associated with attempting to continue pregnancy. Clearly, in a viable fetus these risks are unacceptable and delivery should be expedited. Prior to this, serious consideration should be given to medical or surgical termination.

### Summary

Management of women with any degree of anticoagulation in the peripartum period is often challenging. However, attention to detail, careful planning and documentation, departmental education and involving both appropriate disciplines as well as the patient, should allow optimal management to be achieved.

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# Section 4 Chapter

## Thrombophilia and fetal loss

# Antiphospholipid syndrome

Sue Pavord, Bethan Myers, and Beverley Hunt

## Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by vascular thrombosis and/or obstetric morbidity in the presence of persistent antiphospholipid antibodies (aPL)<sup>1</sup> namely, lupus anticoagulant antibodies (LAC), anti-cardiolipin antibodies (aCL) and/or anti- $\beta_2$ -glycoprotein I antibodies. There are numerous potential complications for pregnancy but with optimal management, good maternal health and a live birth rate of 80%–90% can be achieved.

The syndrome produces a spectrum of disease, both in terms of clinical manifestations and the presence of other autoimmune conditions. Arterial, venous, or small vessel thrombosis may occur, there is an array of adverse obstetric outcomes and a number of additional clinical features may be present, involving organs such as the heart, skin, and central nervous system. The disease is classified as primary (PAPS) when it occurs in the absence of any features of other autoimmune disease, and secondary where other autoimmune disease is present (SAPS). Predominantly, this is systemic lupus erythematosus (SLE), but other conditions such as inflammatory bowel disease may be involved.

## Prevalence

The syndrome occurs most commonly in young to middle-aged adults, with a mean age of onset of 31years. Women are more frequently affected, with a female to male ratio of 5:1 which is even higher in SAPS associated with SLE. There is no defined racial predominance for APS, although an increased incidence of SLE occurs in African Americans and the Hispanic population. Among patients with SLE, the prevalence of aPL is 15% to 35%, but only around half of these cases will have clinical features of antiphospholipid syndrome.

# Pathophysiology and etiology

Different pathological mechanisms may be responsible for the varying clinical manifestations. Recurrence of complications often follows a similar pattern of disease and recurrent thrombosis usually occurs in the same vascular field, although this is not always the rule.

It was originally thought that aPL were directed against negatively charged phospholipid, but it is now clear that they target plasma proteins with affinity for these anionic phospholipids. There is concordance between the LAC, aCL, and anti- $\beta_2$ -GP I, antibodies; however, they are not identical and some LAC antibodies react with phospholipids other than cardiolipin and proteins other than  $\beta_2$ -GP I, whereas some aCL and anti- $\beta_2$ -GP I antibodies have no LAC activity. In general, LAC antibodies are more specific for the diagnosis of APS, but there is no association with particular clinical manifestations and antibody type.

The main antigens involved are  $\beta_2$ -glycoprotein 1 ( $\beta_2$ GPI) and prothrombin, although many more antigenic targets have been described. Antibodies to the  $\beta_2$ GPI are persistent and associated with thrombotic complications, whereas those independent of  $\beta_2$ GPI tend to be present only transiently, in association with infectious diseases or drugs.

## Procoagulant effects

 $\beta_2$ GPI is a multifunctional apolipoprotein, which contributes to the regulation of hemostasis as well as other physiological processes. Not surprisingly therefore,  $\beta_2$ GPI-dependent antibodies have been associated with a number of different biological effects (Table 11.1). These include direct cellular effects

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Table 11.1	Procoagulant effects of	$\beta_2$ GPI-dependent aPL
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Up-regulation of the tissue factor pathway

Inhibition of the activated protein C pathway

Inhibition of antithrombin activity

Inhibition of fibrinolysis

Activation of endothelial cells

Enhanced expression of adhesion molecules by endothelial cells with increased binding of leukocytes

Activation and degranulation of neutrophilis

Potentiation of platelet activation

Enhanced platelet aggregation

Displacement of annexin V from cell membranes

caused by bound  $\beta_2$ GPI –antibody complexes, with affinity for both anionic phospholipid expressed on the surface of activated cells and heparin sulphatecontaining structures on non-activated cells. The binding of  $\beta_2$ GPI to anionic structures, through domain 5, induces the expression of new cryptic epitopes in domain 1 and may increase the antigenic density, two events that seem to be pivotal for the antibody binding. Studies show that dimerization of  $\beta_2$ GPI by anti-B2GPI antibodies causes a conformational change in the molecule increasing its affinity for phospholipids by 100-fold.  $\beta_2$ GPI can bind to the lowdensity lipoprotein receptor, ApoER2, on the surface of platelets and thus mediate platelet activation, with increased thromboxane synthesis and platelet aggregation. In vitro endothelial cells and monocytes can also be activated by aPL and  $\beta_2$ GPI binding, resulting in tissue factor expression. In addition, in vitro studies have shown some aPL cause interference with hemostatic factors such as IX, X, and XII, resistance to activated protein C, and a reduction in fibrinolysis from antiplasmin or anti-tissue-type plasminogen activator (tPA) activity. At this time, there is no clarity as to how aPL cause thrombosis, and it is the subject of much research.

### **Obstetric morbidity**

The pathophysiological mechanisms underlying fetal loss or morbidity also appear to be multiple. Due to the wide spectrum of manifestations and heterogeneous findings in placental tissue in these patients, it is unclear whether one or several aPL subgroups are responsible for the varying phenotypes and whether concurrent, aPL-independent genetic and environmental factors affecting the maternal-fetal interface, influence the potential pathogenicity of these antibodies.

Early histological studies demonstrated decidual vasculopathy and placental thrombosis. Displacement of annexin V from trophoblasts contributes to a procoagulant state through acceleration of coagulation reactions. An elegant mouse model has demonstrated activation of complement through the classical pathway, with consequent influx of inflammatory cells into tissues, mediating placental injury, and leading to fetal loss and growth restriction. In this model, heparin prevented pregnancy loss by blocking activation of complement, rather than primarily via an anticoagulant effect.<sup>2</sup>

Direct trophoblastic damage by aPL, independent of mechanisms involving thrombosis and complement activation, has also been demonstrated recently. Interaction of aPL with  $\beta_2$ GPI, exposed during trophoblast syncytium formation, has been shown to cause inhibition of the intercytotrophoblast fusion process, gonadotrophin secretion, and trophoblast invasiveness. This mechanism has been hypothesized to contribute to early pregnancy loss. There is evidence of a significant reduction in intradecidual endovascular trophoblast invasion on analysis of the products of conception (first-trimester failure) from APS patients.

The factors that determine whether aPL induce a thrombotic or non-thrombotic disease phenotype in the placenta are not known. It is likely that interplay between patient background traits and distinct aPL subgroups determines disease manifestation.

### **Clinical features**

International consensus criteria for the classification of definite APS were initially published in 1999<sup>3</sup> and updated in 2006<sup>1</sup> (Table 11.2).

### Thrombosis

Thrombosis is the most common presenting feature of APS.<sup>4</sup> Thrombosis may occur in both the venous and arterial circulation as well as the microvasculature. It can involve vascular beds that are infrequently affected by other prothrombotic states and is independent of atherosclerotic vascular disease.
Table 11.2
 Summary of the revised classification criteria for the Antiphospholipid Syndrome (APS)<sup>1</sup>

APS is diagnosed if at least one clinical and one laboratory criteria are met (although not if there is less than 12 weeks or more than 5 years between the positive aPL test and the clinical manifestation).

#### **Clinical criteria**

1. Vascular thrombosis

One or more clinical episodes of arterial, venous, or microvascular thrombosis occurring in any tissue or organ (superficial venous thrombosis is not included)

- 2. Pregnancy morbidity
  - (a) One or more unexplained deaths of a morphologically normal fetus at, or beyond, 10 weeks' gestation or
  - (b) One or more premature births of a morphologically normal neonate before 34 weeks' gestation because of eclampsia, severe pre-eclampsia or recognized features of placental insufficiency\*.
  - (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

#### Laboratory criteria

- 1. LAC present on two or more occasions at least 12 weeks apart detected according to the guidelines of the International Society on Thrombosis and Haemostasis (10)
- aCL of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA
- 3. Anti- $\beta_2$  GP-I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by standardized ELISA

\* Generally accepted features of placental insufficiency include: (i) abnormal or non-reassuring fetal surveillance test(s), e.g. a non-reactive non-stress test, suggestive of fetal hypoxemia, (ii) abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, e.g. absent end-diastolic flow in the umbilical artery, (iii) oligohydramnios, e.g. an amniotic fluid index of 5 cm or less, or (iv) a post-natal birth weight less than the 10th percentile for the gestational age.

#### Venous thrombosis

aPL are found in approximately 2% of patients presenting with acute venous thromboembolism. Often, the venous thrombosis occurs in an unusual site such as the cerebral, retinal, splanchnic or axillary, and subclavian veins and APS can account for up to 70% of such presentations. Venous thromboembolism, especially deep venous thrombosis of the legs, has been shown to occur in around 30%–50% of patients with APS during an average follow-up of less than 6 years.<sup>5</sup> Following a first episode, the risk for future venous thrombosis increases significantly.

#### Arterial thrombosis

The most common site of arterial thrombosis is the central nervous system, with strokes and transient ischemic attacks accounting for 50% of the arterial events seen with APS. Myocardial infarction accounts

for around 20% and other vascular beds may be involved including those of the lungs, retina, gastrointestinal tract, spleen, and extremities. In many cases the event is otherwise unexplained, with no other identifiable risk factors for arterial disease, such as smoking, diabetes, or hypertension.

#### **Obstetric complications**

Complications during pregnancy, in addition to maternal thrombosis, include recurrent spontaneous abortions in the first trimester as well as adverse outcomes occurring late in pregnancy. However, there are women with aPL who have no problems at all in pregnancy.

#### Early pregnancy loss

Pregnancy loss is one of the leading problems in women's health issues. Approximately one-third of all

conceptions and 15% of clinically recognized pregnancies (<6 wk of gestation) fail to result in a live birth. Of women, 5% experience two or more losses and 1%– 2% suffer with three or more. Up to half of the cases remain unexplained after gynecological, hormonal, and karyotypic analyses. Of the women who have recurrent pregnancy loss, defined as three or more first trimester miscarriages, 10% to 20% have detectable aPL.<sup>6</sup> These women potentially have a 90% risk of further fetal loss if left untreated.<sup>7</sup> The diagnostic criteria for APS suggest that evaluation should begin after the third consecutive early miscarriage, defined by less than 10 weeks' gestation (Table 11.2). However, in practice, evaluation after two early miscarriages is often initiated at the discretion of the physician.

#### Late complications of aPL in pregnancy

Complications occurring late in pregnancy relate to placental dysfunction caused by aPL. The manifestations include pre-eclampsia, prematurity, fetal distress, intrauterine growth restriction, and fetal death. Preterm delivery is associated with premature rupture of the membranes or pre-eclampsia. The median rate of gestational hypertension or pre-eclampsia is 30%-50% in untreated women with previously diagnosed APS but falls to 10% with effective management. In contrast, aPL are not found in a significantly higher proportion of general obstetric patients presenting with pre-eclampsia.<sup>8</sup> HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) may occur, being associated with pre-eclampsia/eclampsia in most cases and seems to occur earlier than in women without APS, often in the second trimester.

#### Other clinical manifestations

In addition to thrombosis and obstetric morbidity, there are a number of additional clinical manifestations which are not included in the official definition of APS. These include abnormalities of skin (particularly livedo reticularis), cardiac valves, central nervous system, kidneys, and hematological disturbances such as thrombocytopenia and a positive direct Coombs test with occasional cases of clinical hemolytic anemia.

#### Thrombocytopenia

Many patients with APS have thrombocytopenia (platelets  $< 100 \times 10^9$ /L). The pathogenic antibodies are directed towards epitopes on platelet membrane

glycoproteins and are distinct from antiphospholipid antibodies. Conversely, aPL are found in approximately 25% of patients with chronic autoimmune thrombocytopenia. They do not confer a different clinical phenotype initially, but the persistence of lupus anticoagulant in these patients has been found to be an important risk factor for subsequent development of APS.<sup>9</sup>

#### **CNS** affects

A variety of neurological manifestations may occur, mostly secondary to cerebrovascular infarcts. The clinical features depend upon the caliber and location of the vessels occluded and include multi-infarct dementia, psychomotor agitation and insomnia, movement disorders such as chorea, dystonia, oral dyskinesias and speech impairment, transverse myelitis, seizures, migraine, psychosis, and optic neuritis.

#### Valve defects

Up to 30% of patients with APS have minor valvular abnormalities, which usually do not cause hemodynamic disturbance. Non-bacterial thrombotic endocarditis (Libman–Sacks endocarditis) is a rare disorder characterized by sterile, thrombotic vegetations of the heart valves and can occur rarely in APS. These thrombotic lesions carry significant embolic potential.

# Catastrophic antiphospholipid syndrome (CAPS)

This term defines a severe accelerated form of APS that results in multi-organ failure from widespread thromboses, which are usually microvascular rather than large vessel occlusions. The pathogenesis appears dependent on a multi-hit phenomenon, with infection, trauma or surgery, drug administration, or warfarin withdrawal exacerbating an already procoagulable state. In 50% of cases no triggering factor is identified and in some it may be relatively minor such as a biopsy. Around one-quarter suffer with disseminated intravascular coagulation (DIC), contributing to "thrombotic storm" and end organ damage. Severe thrombocytopenia is common. Acute adult respiratory distress syndrome (ARDS) occurs in one-third of patients and death in around 50%, mainly from cardiac or respiratory failure, despite treatment with anticoagulation and plasma exchange.

#### Laboratory evaluation

Limitations to laboratory testing include lack of laboratory standardization for aPL and the heterogenous nature of the antibodies resulting in low specificity of the assays. Many healthy individuals can have aPL without thrombosis or obstetric morbidity; indeed aPL are found in 3%–5% of the normal population. They are often transient and associated with infection or drugs. The clinical importance of these aPL is uncertain. To satisfy the APS laboratory classification criteria, a patient has to be persistently positive for either one of the assays – anticardiolipin antibody, lupus anticoagulant, or  $\beta_2$ GPI antibody, for at least 12 weeks. Testing should occur away from the acute event.

#### Lupus anticoagulant (LAC)

These antibodies are detected by their ability to prolong phospholipid-dependent coagulation reactions, not corrected by mixing patient and normal plasmas. As aPL showing LAC activity are heterogeneous, it is recommended that at least two methods are performed; APTT and a direct antiXa assay such as the dilute Russell viper venom assay (dRVVT). It should be confirmed that the anticoagulant is directed against protein bound to negatively charged phospholipids.

The International Society for Thrombosis and Haemostasis has identified the following criteria for the confirmation of a LAC.<sup>10</sup>

- (1) Prolongation of a phospholipid-dependent clotting assay
- (2) Evidence of an inhibitor demonstrated by mixing studies
- (3) Confirmation of the phospholipid-dependent nature of the inhibitor (platelet or other phospholipid neutralization procedure).

Most LACs are directed against either  $\beta_2$ GPI or prothrombin and recently methods to distinguish those associated with anti  $\beta_2$ GPI have been developed but whilst these are highly specific, their sensitivity is low. LAC has been shown to be the most relevant assay in relation to vascular events and obstetric morbidity. The odds ratios for thrombotic risk ranges from 5 to 16.

#### Anticardiolipin antibodies (aCL)

Anticardiolipin antibodies are measured by ELISA, although, again, concordance amongst laboratories is

poor and it is difficult to distinguish between the significant antibodies associated with  $\beta_2$ GPI from those bound to other plasma proteins or directly bound to cardiolipin. The correlation between aCL titer and thrombotic risk is well established, with the IgG subtype having stronger association than IgM or IgA.<sup>11</sup> The revised classification criteria for APS uses an IgG aCL cut off of 40 U. Low levels of aCL, although statistically abnormal, may not be associated with a significant risk of thrombosis and in a systematic review of the literature, Galli *et al.* observed no correlation with venous thrombosis and only a weak correlation with arterial thrombosis.<sup>12</sup>

#### Anti-beta 2 glycoprotein 1 antibodies

Anti- $\beta_2$ GPI antibodies are now included in the revised criteria for the diagnosis of APS<sup>1</sup> (Table 11.2). They show better correlation with thrombosis than aCL but there is a high false-positive rate. Recently, new guidelines have been published for the performance of an anti- $\beta_2$ GPI antibody ELISA, which might improve standardization of the assay. However, the specificity remains low as there are non-pathogenic antibodies that bind  $\beta_2$ GPI. Indeed, of the five domains of  $\beta_2$ GPI involved, only those antibodies directed against domain 1 correlate with thromboembolic complications, with an odds ratio of around 18.

#### **Principles of management**

Individual treatment strategies for the management of the antiphospholipid syndrome in pregnancy in part depends on the assessment of a number of different factors. These include:

- history of prior thrombosis;
- whether the thrombotic event was provoked or spontaneous;
- whether the thrombotic event was venous or arterial;
- history of obstetric morbidity alone;
- evidence of any organ damage;
- the presence of SLE or other autoimmune disease;
- other maternal risk factors, such as obesity and maternal age.

#### Background

The first treatment used and studied for pregnant patients with APS, was a combination of corticosteroids and low dose aspirin. Low-dose aspirin is known to be safe in pregnancy, in the first and second trimesters, and also recognized to reduce risk of preeclampsia.

Corticosteroids were an obvious choice as an immunosuppressant to suppress the antibodies present. Small, early studies were encouraging. Subsequent studies comparing heparin and prednisolone concluded that low dose heparin was preferable, since, although effective, steroids induced significant maternal morbidity, and more premature deliveries.<sup>13</sup> Heparin (either unfractionated or low molecular weight) is the standard anticoagulant in pregnancy for prophylaxis and treatment of VTE. With improved understanding of the mechanisms of action of heparins and the pathophysiology of APS, it is a logical drug of choice in this condition. In addition to anticoagulant activity, it has anti-inflammatory and anti-complement effects, both of which may be involved in APS pathogenesis. In vitro heparin also appears to enhance trophoblast development, apparently limiting aPL attack on trophoblasts. Two systematic reviews of small studies recommended a combination of aspirin and heparin to reduce fetal loss, concluding that this regime may reduce pregnancy loss by 54%.<sup>14,15</sup> Some authors, however, question the role of pharmacological treatment in improved live birth rate, as some studies showed no difference between treatment and placebo arms, in low-risk patients. Problems in interpretation are due to the small size of studies, variable entry criteria, lack of placebo arms, and absence of blinding.

#### Pre-pregnancy management

Pre-pregnancy counseling should be offered, taking all factors into consideration. Where necessary, recommendations should be made to improve general health and reduce risk before a pregnancy is undertaken, such as the need for weight loss, to wait at least 6 months following an acute thrombotic event or until SLE has been quiescent for 3 months. There may be circumstances where pregnancy should be actively discouraged, for example, if pulmonary hypertension is present the risk of maternal death is estimated at greater than 35%.

During this review, a clear proposed plan for pregnancy management should be outlined, both verbally and in writing. The following issues need to be addressed:

- Review detailed medical and obstetric history.
- Document and confirm persistant aPL, assess renal function and presence of thrombocytopenia and/or anemia.
- Optimize the patient's clinical state and pharmacological treatment before pregnancy. Advise postponing pregnancy if a thrombotic event has occurred within the last 6 months, SLE has been active or hypertension uncontrolled.
- Assess individual additional risk factors such as obesity and maternal age and give a clear indication to the patient regarding the degree of risk for both thrombosis and obstetric complications.
- Assess for the presence of anti-Ro or La antibodies, even if no evidence of SLE. These antibodies are associated with a 2% risk of complete heart-block in the fetus and up to a 10% risk of neonatal lupus. If found, fetal cardiology assessment should be offered and any pregnancy affected by complete heart block should be managed by a specialized centre where there is a pediatric cardiologist to manage the neonate.
- Provide contact information for prompt, early referral at the onset of pregnancy and ensure a clear understanding of the need to substitute heparin for warfarin at the time of the first missed period. Ideally, the woman can be provided with a supply of LMW heparin and lessons in self-injection so should they get pregnant, they can switch quickly from warfarin.

#### Management of thrombosis

The immediate management of thrombosis should be the same in those with or without the antiphospholipid syndrome. It may, indeed, be the first indication of underlying APS. Samples should not be sent for thrombophilia testing at the time of an acute event. The results may be misleading for several reasons, particularly during pregnancy, and the laboratory results do not change initial management.

#### Management of women with antiphospholipid antibodies and a previous thrombotic event

These women may be on long-term anticoagulants, although this depends on the circumstances of the thrombotic event; if it was a single venous event with a clear temporary provoking factor, a limited duration of anticoagulation may have been given.

In the former case, a change from warfarin to heparin can be made once a pregnancy test is positive. This requires the woman to be well motivated to check carefully in order to ensure that the substitution occurs before 6 weeks' gestation, to minimize risk of teratogenicity of warfarin. In the UK, it is usual to recommend a pregnancy test on the first or second day of a missed period and then to switch to low molecular weight heparin (LMWH) either at intermediate or full therapeutic doses, depending on the extent of risk when all factors are taken into account. Low dose aspirin, at 75 mg daily, is also given.

The patient requires regular, frequent review throughout the pregnancy, and scans to assess fetal growth should be performed throughout the second half (monthly or more often as indicated). Uterine artery Doppler flow measurements (between 20 and 24 weeks onwards) are a further useful tool to assess platelet dysfunction. The absence of bilateral notching is a good prognostic sign for fetal outcome.

Post-natally, the patient may be re-established on warfarin or continued on LMWH for at least 6 weeks.

# Management of women with multiple previous venous events, or venous plus arterial events

This group of women will likely be on long-term warfarin, possibly at a higher INR range (3–4s), and are at very high risk during pregnancy. In this group, pre-pregnancy counseling is particularly important, to assess the extent of risk on an individual basis, and this risk clearly conveyed to the patient and partner prior to embarking on pregnancy. Low molecular weight heparin should be substituted for warfarin before 6 weeks' gestation, in intermediate or full dose. Some groups monitor anti-Xa levels, although they are not clearly predictive of anti-thrombotic effect. Other management is as above, i.e. low dose aspirin, fetal growth assessment by regular ultrasound scanning, and warfarin reintroduced post-natally.

# Management of women with APS and pregnancy morbidity

A Cochrane systematic review in 2005 assessed 13 trials published (between 1991 and 1999) on recurrent pregnancy loss associated with aPL. They commented that the quality of the studies was not good, which limited useful conclusions.

#### Aspirin

In obstetric patients, low dose aspirin has been used to improve pregnancy outcome in those with hypertension, pre-eclampsia, preterm birth, and intrauterine growth restriction. The Cochrane review and meta-analysis summarized the studies with aspirin.<sup>16</sup> Three trials with aspirin alone showed no significant reduction in pregnancy loss; two studies using unfractionated heparin and aspirin showed a significant improvement in fetal outcome compared with aspirin alone; but in a further randomised controlled trial, whilst high success rates were achieved with low dose aspirin, the addition of LMWH did not provide further benefit.<sup>17</sup> This latter study has been criticized as the laboratory criteria for APS were not met.

However, these studies were done at a time when LMWH was just being introduced, and it is difficult to draw firm conclusions from this collection of data. Subsequently obstetric hematology groups, have accumulated a large volume of experience with LMWH, and it is considered safer and as effective as unfractionated heparin, and more convenient with a oncedaily dosing regimen. The risk of osteoporosis which is as high as 2% with unfractionated heparin, is rarely described with LMWH and prophylactic dose LMWH and low dose aspirin has become standard practice. Improved outcomes for women with previous late fetal loss or early delivery due to placental insufficiency have been confirmed and a recent metaanalysis supports the efficacy of this approach for recurrent pregnancy loss.18

#### Ultrasonography

In patients with poor obstetric history, pre-eclampsia or evidence of fetal growth restriction, fetal growth scans every 4 weeks, from 20 weeks is recommended, in addition to pharmacological treatments. Studies have shown uterine artery Doppler to be valuable in predicting placental dysfunction, i.e. pre-eclampsia and intrauterine growth restriction and the discovery of bilateral uterine artery notching can allow the obstetrician to monitor the pregnancy more closely. Multivariate analysis of data on 100 pregnancies demonstrated that a notched uterine artery at the second trimester was the only predictor for adverse pregnancy outcome. Uterine artery Doppler assessment should be performed with the fetal scan at 20 weeks and 24 weeks. Le Thi Huong *et al.*<sup>19</sup> showed the predictive value of the umbilical artery Doppler ultrasound examination for late pregnancy outcome, together with clinical examination and laboratory tests in women with SLE and/or APS.

Table 11.3	Summary of pharmacological management of APS
in pregnanc	ý

Clinical feature	Management
APS with prior fetal death or recurrent pregnancy loss	Aspirin 75 mg od LMWH prophylactic dosage Doppler ultrasound for fetal assessment
APS with prior venous or arterial thrombosis	Low molecular weight heparin at intermediate or therapeutic dosage, plus aspirin
Antiphospholipid antibodies without clinical features and healthy previous pregnancies	No treatment, or low dose aspirin
Primigravida with isolated aPL	Low dose aspirin and fetal monitoring
APS with recurrent thrombotic events	Full therapeutic dose LMWH; consider warfarin

#### Other treatment modalities

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A summary of pharmacological management of APS in pregnancy is provided in Table 11.3.

If there is continued pregnancy loss despite prophylactic-dose heparin and low dose aspirin, the following options should be considered.

- (a) Increasing the dose of heparin to therapeutic levels may be effective, although there are no trials that have demonstrated this.
- (b) There are anecdotal case reports of use of intravenous immunoglobulin in refractory cases

with success, although several studies have not demonstrated its benefit.<sup>20</sup> It may also be useful in APS cases who have additional indications for its use, for example, in auto-immune thrombocytopenia or Guillain–Barré syndrome.

(c) Successful use of plasma exchange to remove antibodies temporarily has been reported, in high risk pregnancies where plasma exchange was administered.

# Management of thrombocytopenia associated with APS in pregnancy

This may be due to pre-eclampsia, HELLP syndrome or worsening maternal idiopathic thrombocytopenic purpura (ITP). This should be managed in the same way as those complications occurring without APS (see Chapters 4,17, and 18).

#### Management dilemmas

- (1) Management of women who have isolated aPL, with no prior pregnancy loss or thrombo-embolic phenomena, do not generally merit ante-natal pharmacological treatment, although low dose aspirin is often used. The best predictor of maternal and fetal outcome in APS pregnancies is the previous obstetric history. Mothers with a previously normal obstetric history despite aPL can be reassured that any future pregnancy has a low risk of complications.
- (2) For women in an ultra-high risk group, such as those with multiple unprovoked venous and arterial event, or patients who develop a new thrombotic event during pregnancy despite anticoagulation, consideration should be given for warfarin usage from the second trimester, or even all trimesters. The risks of warfarin to the fetus must be explained – including the teratogenic risk in the first trimester and the ongoing risk of fetal loss, hemorrhage and subtle neurological changes, which have been described after its use in the second and third trimester.
- (3) Where in vitro fertilization (IVF) or other assisted reproductive techniques are planned, LMWH should be substituted for warfarin at the time at which assisted reproductive procedure is performed, i.e. at the time of egg transfer; if the woman is not on anticoagulation prior to IVF,

then prophylactic LMWH and aspirin should be used.

- (4) For the rare seronegative APS, or SNAPS, where typical clinical features occur in the absence of measurable standard antibodies – expert clinical judgment is required to make this diagnosis and to determine need for treatment.
- (5) Management of women with SLE in pregnancy is one of the few indications for the use of glucocorticoids during the pregnancy. SLE may flare during pregnancy and increasing or starting small doses of prednisolone is appropriate. Hydroxychloroquine and azathioprine, standard drugs for the management of SLE, are safe in pregnancy and should be continued if the disease is stable. Stopping such medications may lead to a flare of SLE which could be harmful to mother and fetus.
- (6) Chorea gravidarum is a rare complication in pregnancy and may be associated with primary or secondary APS. It is thought to be due to development of antibodies against components of

the basal ganglia, or rarely due to infarction of this area. It is usually self-limiting and resolves following pregnancy, although may recur in subsequent pregnancies. When severe, a variety of treatments have been described, including low dose haloperidol, steroids, anticoagulants, antiplatelet medication, or a combination of treatments.<sup>21</sup>

#### **Neonatal issues**

Neonatal APS has been described, although the existence of this syndrome has not been fully accepted. It is a rare occurrence, characterized by neonatal thrombosis thought to be due to the transplacental passage of maternal aPL.<sup>22</sup> Ischemic stroke is the main event described. In comparison to a high incidence of thrombotic and obstetric complications in women with APS, the aPL-associated thrombotic events in neonates are extremely rare. There is no benefit from routine screening for aPL in neonates born to mothers with APS.

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# Section 4 Chapter

#### Thrombophilia and fetal loss

### **Thrombophilia and pregnancy loss**

Isobel D. Walker

#### Introduction

Pregnancy loss is psychologically and emotionally extremely difficult for the mother, her partner and wider family. Couples who have had such an event, have many questions including, what caused the pregnancy to fail, will it happen again, and what can be done to minimize the risk of a recurrence?

It has been postulated that, in some cases, pregnancy failure may be, at least in part, due to inadequate placental circulation and that thrombophilia, by increasing the risk of fibrin deposition or thrombosis within the placental circulation, may increase the risk of pregnancy loss. This postulate has led to the hypothesis that, for women with a history of pregnancy loss with no identifiable cause other than an underlying thrombophilia, intervention with antithrombotics may improve the outcome in subsequent pregnancies.

#### Epidemiology

Sporadic pregnancy loss is very common. It has been estimated that 30%–50% of fertilized ova are spontaneously aborted with around 15% of clinically recognized pregnancies being lost before 24 weeks' gestation. Around one in 20 women will suffer two or more consecutive pregnancy losses and 1% suffers the loss of three or more consecutive pregnancies (Table 12.1). The observed incidence of recurrent pregnancy loss is greater than the 0.34%, which may be expected by chance, suggesting that some women are predisposed to pregnancy loss.

The World Health Organization's definition of miscarriage is a pregnancy which fails to progress, resulting in the death and expulsion of an embryo or fetus weighing no more than 500 g (which corresponds to a gestational age of 20 weeks or less). Unfortunately, this definition is not used consistently and a huge range of "definitions" have been employed in the many studies examining potential associations between thrombophilia and pregnancy loss. Recurrent pregnancy loss is defined as the occurrence of three or more consecutive miscarriages. This includes women with primary recurrent pregnancy loss (with  $\geq$  3 consecutive pregnancy losses and no pregnancy proceeding beyond 20 weeks' gestation) and women with secondary recurrent pregnancy loss (with  $\geq$  3 consecutive pregnancy losses following a pregnancy which proceeded beyond 20 weeks' gestation and resulted in a live birth, stillbirth, or neonatal death). Some investigators include within the definition of recurrent pregnancy loss, women who have had  $\geq$  3 non-consecutive pregnancy losses. To add further confusion, because reproductive practice has changed and many women nowadays do not embark on their first pregnancy until they are in their mid to late 30s, there has been an increasing tendency to consider intervention for women who have a history of only two consecutive miscarriages and to "label" these women as having a history of recurrent pregnancy loss.

#### Pathogenesis

#### Thrombophilia

By definition, thrombophilias are disorders of hemostasis which predispose to thrombosis. Included are heritable deficiencies of the natural anticoagulants antithrombin, protein C, and protein S and common mutations in the genes encoding clotting factor V, factor V Leiden which results in increased resistance to activated protein C and clotting factor II, the prothrombin G20210A mutation. Also included are acquired abnormalities such as antiphospholipid antibodies and some disorders of mixed genetic and

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Table 12.1 Incidence of pregnancy loss

Spontaneous abortion of fertilized ova	30%-50%
Spontaneous loss of clinically recognized pregnancy before 24 weeks	15%
Spontaneous loss of two or more consecutive pregnancies	5 %
Three or more consecutive pregnancy losses before 20 weeks	1%

**Table 12.2** The prevalences of heritable thrombophilias inEuropean populations

Thrombophilia	Prevalence (%)
Antithrombin deficiency	0.25-0.55
Protein C deficiency	0.20-0.33
Protein S deficiency	0.03-0.13
Factor V Leiden (heterozygous)	2–7
Prothrombin G20210A (heterozygous).	2

environmental etiology such as hyperhomocysteinemia. Around 10% of Caucasians carry an identifiable heritable thrombophilia (Table 12.2).

#### Placentation in normal pregnancy

Successful pregnancy requires trophoblast invasion into the maternal uterine spiral arteries converting them into large dilated vessels, which lack a functioning contractile smooth muscle wall. Prior to this remodeling, the spiral arterioles are occluded by endovascular trophoblasts. It is postulated that this plugging protects the early intervillous spaces from maternal systemic arterial pressure and protects the developing intervillous trophoblasts from high oxygen tension and oxidative damage. Although the blood flowing through the spiral arteries and the placental intervillous spaces is maternal, the cells lining these spaces are embryonic trophoblasts. Thus the hemostatic balance within the placenta may be disturbed as a result of hypercoagulability of the maternal blood or as a result of abnormality of cellular regulatory mechanisms of fetal origin operating at the feto-maternal interface. Since the fetal blood is separated from the trophoblasts by fetal endothelial cells, the fetal hemostatic balance is influenced only by components of fetal origin.

#### Placental pathology in pregnancy loss

Thrombi in the spiral arteries or fibrin deposition in the intervillous spaces on the maternal side of the placenta may result in inadequate placental perfusion. Microthrombi are frequently found in the vessels of the placentas from women who have experienced pregnancy loss and placental infarction has been described in the placentas of some, but not all, women who have a pregnancy loss and who have thrombophilia. Placental thrombosis and infarction are, however, not uncommon in fetal loss cases in the absence of any identifiable thrombophilia and no placental lesion is specific for thrombophilia. Most of the studies that have reported on the placental pathology in women with thrombophilia and a history of pregnancy loss have concentrated on women with antiphospholipid syndrome. There is limited information about the placental pathology in women with pregnancy loss and an underlying heritable thrombophilia. Furthermore, there are methodological problems with many of the published studies. Some studies have compared the placentas from women with thrombophilia and pregnancy loss with the placentas from non-thrombophilic women with normal gestations - others with placentas from non-thrombophilic women with pregnancy loss. Others have included no control group at all.

# Is heritable thrombophilia associated with pregnancy loss?

#### **Observational studies**

It has long been accepted that antiphospholipids in maternal plasma increase the risk of both early and late pregnancy loss. More recently, attention has turned to the question of the potential role of heritable thrombophilias in the causation of pregnancy loss. Associations between heritable thrombophilias and pregnancy loss were first noted in families in which the probands had presented with venous thrombosis. One such study of family members, the European Prospective Cohort on Thrombophilia (EPCOT), reported the incidence of pregnancy loss in a cohort of 571 women with heritable thrombophilia who had experienced 1524 pregnancies and 395 age-matched controls who had had 1019 pregnancies and reported a significantly greater percentage of women with thrombophilia had a history of pregnancy loss (29.4% vs. 23.5%).<sup>1</sup> The

Table 12.3 Pregnancy loss in	women with heritable
thrombophilia (identified beca	use of a family history of venous
thrombosis). Data from EPCOT	Study <sup>1</sup>

	Pregnancy loss at <28 weeks Odds Ratio (95% CI)	Pregnancy loss at ≥ 28 weeks Odds Ratio (95% CI)
Antithrombin deficiency	1.7 (1.0–2.8)	5.2 (1.5–18.1)
Protein C deficiency	1.4 (0.9–2.2)	2.3 (0.6–8.3)
Protein S deficiency	1.2 (0.7–1.9)	3.3 (1.0–11.3)
Factor V Leiden	0.9 (0.5–1.5)	2.0 (0.5–7.7)
<b>Combined defects</b>	0.8 (0.2–3.6)	14.3 (2.4–86.0)

Odds Ratio (OR) for fetal loss associated with thrombophilia was 1.35, 95% Confidence Interval (CI) 1.01-1.82. When the data for all thrombophilic women and the controls were stratified according to the stage of gestation at which the pregnancy losses occurred, the odds ratio was statistically significant only for fetal losses after 28 weeks' gestation (OR 3.6, 95% CI 1.4-9.4). For pregnancy loss at, or before, 28 weeks the odds ratio was 1.27 (95% CI 0.94-1.71). When the data for fetal losses were stratified according to the specific thrombophilic defects, the odds ratios for individual thrombophilias were significant only for antithrombin deficiency and protein S deficiency for pregnancy loss after 28 weeks' gestation (Table 12.3). The odds ratio for pregnancy loss after 28 weeks' gestation in women with more than a single identifiable heritable thrombophilia was 14.3 (95% CI 2.4-86.0), suggesting a possible dose-response effect.

#### Meta-analyses

Following the early studies of families, numerous studies have examined possible associations between heritable thrombophilias and pregnancy loss. Within the past 5 years, two meta-analyses have been published. Both noted significant heterogeneity between studies. Rey et al., following analysis of 31 case-control, cohort, and cross-sectional studies, reported that factor V Leiden and the prothrombin G20210A mutation are significantly associated with recurrent early fetal loss and with non-recurrent late fetal loss, and that protein S deficiency was associated with late non-recurrent fetal loss but not with recurrent fetal loss (Table 12.4).<sup>2</sup> Rev also found that maternal factor V Leiden was associated with recurrent late pregnancy loss - odds ratio 7.83 (95% CI 2.83-21.7). The meta-analysis by Robertson et al. confirmed<sup>3</sup> that factor V Leiden and the prothrombin G20210A mutation are associated with recurrent early fetal loss and non-recurrent late fetal loss, and reported that both factor V Leiden and the prothrombin G20210A mutation are associated with non-recurrent second trimester loss (Table 12.4). As in the Rey meta-analysis, Robertson et al. found that protein S deficiency is associated with an increased risk of late pregnancy loss. This meta-analysis also reported an association between hyperhomocysteinemia and early pregnancy loss (odds ratio 6.25, 95% CI 1.37-28.42).

#### Very early pregnancy loss – embryo loss

Most reports do not separate very early pregnancy losses (before 10 weeks' gestation) from later first trimester losses. In a cohort study, 491 patients with a history of adverse pregnancy outcome, maternal thrombophilia was associated with an increased risk of pregnancy loss after 10 weeks' gestation (odds ratio 1.76, 95% CI 1.05–2.94 for women with one thrombophilia and odds ratio 1.66, 95% CI 1.03–2.68 for women with more than one identifiable thrombophilia) (Table 12.5).<sup>4</sup> Paradoxically, the presence of

Table 12.4 Heritable thrombophilia and pregnancy loss. Data from two meta analyses\*<sup>2</sup> and\*\*<sup>3</sup>

	Factor V Le	iden	Prothromb	in G20210A	Protein S de	eficiency
	Odds Ratio (9	5% CI)	Odds Ratio (9	5% CI)	Odds Ratio (9	5% CI)
	Rey*	Robertson**	Rey*	Robertson**	Rey*	Robertson**
Recurrent 1 <sup>st</sup> trimester loss	2.01 (1.13–3.58)	1.91 (1.01–3.61)	2.56 (1.04–6.29)	2.70 (1.37–5.34)	14.7 (0.99–218)	-
Non recurrent 2nd trimester loss	-	4.12 (1.93–8.81)	-	8.60 (2.18–33.95)	-	-
Late pregnancy loss	3.26 (1.82–5.83)	2.06 (1.10–3.86)	2.30 (1.09–4.87)	2.66 (1.28–5.53)	7.39 (1.28–42.6)	20.09 (3.70–109.15)

Table 12.5	Heritable	thrombophilia	and embr	yo or fetal loss <sup>4</sup>
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	<b>1 thrombophilia</b> Odds Ratio (95% Cl)	>1 thrombophilia Odds ratio (95% Cl)
<b>Embryo loss</b> <10 weeks' gestation	0.55 (0.33–0.92)	0.48 (0.29–0.78)
Fetal loss >10 weeks' gestation > 14 weeks' gestation	1.76 (1.05–2.94) 3.41 (1.9–6.1)	1.66 (1.03–2.68) 3.86 (2.26–6.59)

one or more maternal thrombophilias seemed to be protective of recurrent very early (less than 10 weeks' gestation) pregnancy loss (odds ratio 0.55, 95% CI 0.33–0.92 for one and odds ratio 0.48, 95% CI 0.29– 0.78 for multiple thrombophilias).

#### Fetal thrombophilia

It has been suggested that fetal carriage of thrombophilic mutations may have adverse clinical consequences. In one case control study a twofold increase in factor V Leiden carrier frequency was noted in abortuses compared with unselected pregnant women, but most studies have not shown a significant association between fetal carriage of the most prevalent heritable thrombophilias (factor V Leiden and prothrombin G20210A) and feto-placental thrombosis.

## Does maternal heritable thrombophilia cause pregnancy loss?

The majority of published studies have been too small and therefore inadequately powered to detect odds ratios of 2 or more for heritable thrombophilias which usually have prevalences of less than 5% in the general population. Meta-analyses support the hypothesis that at least some heritable thrombophilias are associated with pregnancy loss but, where the data are mature and the confidence intervals are narrow (i.e. for factor V Leiden and prothrombin G20210A), the point estimates of the odds ratios are small, suggesting that the associations, if they truly exist, are weak.

Even if an association exists, it may not be a causal association. However, a few studies have shown that, compared with heterozygotes carrying a single thrombophilic variant, homozygous patients or patients with combinations of thrombophilic variants have increased odds ratios for pregnancy loss. This apparent dose effect would support the hypothesis of causality but needs further evidence. Evidence that pregnancy outcome could be improved in thrombophilic women with a history of pregnancy loss by reducing the hypercoagulability with anticoagulant treatment would offer indirect support to the hypothesis that maternal thrombophilia may cause pregnancy loss.

Many factors including chromosomal abnormalities, endocrine disorders, anatomical aberrations, and infections have been shown to cause pregnancy loss, but around 40% of cases of recurrent pregnancy losses are unexplained after gynecological, hormonal, immunological, microbiological, and karyotypic investigations. There is an increasing risk of pregnancy loss as the number of previous losses increases. Recurrent pregnancy loss is recognized to be a multi-causal disorder. Whilst heritable thrombophilias may not alone cause pregnancy loss, it is possible that carriage of a thrombophilic variant may contribute to a complex network of factors, which together result in pregnancy failure.

It is generally assumed that the mechanism of pregnancy failure associated with maternal thrombophilia involves fibrin deposition or thrombosis secondary to hypercoagulability but, although it is biologically plausible that placental thrombosis may have a role in the causation of fetal loss after 10 weeks' gestation, it is not plausible that this mechanism would cause embryo loss (before 10 weeks) prior to development of the placental vasculature. The vast majority of recurrent pregnancy losses occur early in pregnancy. In women with antiphospholipid syndrome in addition to hypercoagulability, a non-prothrombotic mechanism has been postulated. Antiphospholipid antibodies have been shown to inhibit extravillous trophoblast differentiation and subsequent placentation. Studies of trophoblast differentiation and early placental development are lacking in heritable thrombophilias, but experiments in mice have shown that maternal protein C is activated following binding to thrombomodulin on the trophoblast surface. Activated protein C then binds to endothelial protein C receptor also on the trophoblast surface and with protein S as a cofactor down-regulates local coagulation activation. Tight regulation of thrombin generation is essential for the regulation of trophoblast cell growth and limits the production of fibrin degradation products, which trigger trophoblast apoptosis. It is therefore possible that, in early pregnancy in humans, some maternal heritable thrombophilias may exert an adverse effect on normal trophoblast development.

#### Diagnosis

#### Thrombophilia testing

#### Who should be tested?

Routine testing for thrombophilias in unselected populations is not recommended. There are important issues relevant to the clinical utility and cost effectiveness of testing that must be addressed in considering who should be tested. Positive tests are not sensitive predictors of poor pregnancy outcome in women with no history of pregnancy complications. There are a number of published guidelines which suggest that women with a history of recurrent pregnancy loss and women with a history of unexplained late pregnancy loss be tested for antiphospholipids, testing for both lupus anticoagulant activity and elevated anticardiolipins.<sup>5</sup> Some authors have extended this guidance and have suggested that women with a history of recurrent early pregnancy loss or an unexplained late pregnancy loss should, in addition, be tested for heritable thrombophilia.<sup>5</sup> Others take an opposing view suggesting testing for heritable thrombophilia is at present not indicated, since there is insufficient evidence on which to base any intervention in women with a history of pregnancy loss with no other identified abnormality apart from a heritable thrombophilia.<sup>6</sup>

#### What tests?

Currently, not only is there a lack of consensus about which individuals (if any) merit thrombophilia testing, but there is also no universal agreement regarding which tests should be included in the "thrombophilia screen." Most diagnostic laboratories would include functional assays of antithrombin, protein C and an immunologic assay of free protein S along with tests to detect factor V Leiden and the prothrombin G20210A mutation (Table 12.6). A few centers include an assay of homocysteine in the panel of tests they offer for women with a history of pregnancy loss.

#### Pitfalls

If testing for heritable thrombophilia is pursued, managing clinicians should be aware that there are numerous potential pitfalls in the interpretation of "thrombophilia screens" particularly in pregnant or recently pregnant women. Antithrombin activity falls slightly towards the end of a normal pregnancy, but usually

Table 12.6	Thrombophilia	screening tests
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Heritable thrombophilias	Preferred test method
Antithrombin deficiency	Heparin co-factor activity
Protein C deficiency	Chromogenic activity
Protein S deficiency	Free protein S antigen
Factor V Leiden	Activated protein C resistance after predilution of test plasma in factor V depleted plasma or DNA based
Prothrombin G20210A	DNA based
Acquired thrombophilia	Preferred test method
Lupus anticoagulant	Clotting based tests*
Anticardiolipins	Immunologic assays of IgG and IgM anticardiolipin
* See Chapter 11	

levels remain within the reference range for non pregnant subjects. Protein C activity is unaffected by gestation, although an elevation of protein C activity occurs in the early puerperium. Even in non-pregnant women there is considerable overlap of protein S levels between "normals" and subjects with heritable protein S variants. The levels of both free and total protein S are reduced by 60%-70% in uncomplicated pregnancy. A diagnosis of possible protein S deficiency made on a sample collected during pregnancy or the puerperium requires confirmation when the woman is no longer pregnant, puerperal or using hormonal contraception. Pregnancy is also associated with a progressive increase in resistance to activated protein C (APC) due to the physiological rise in clotting factor VIII levels and fall in protein S levels. Using the original APC resistance test, around 40% of pregnant women in their third trimester have an APC sensitivity ratio below the general population reference range. Testing for factor V Leiden therefore requires the use of a modified APC resistance test with predilution of the test sample in factor V deficient plasma or genetic testing. Thrombophilia test results should always be interpreted by staff experienced in the reporting of thrombophilia tests and in the light of clear clinical information about each particular patient.

#### Management

#### **General measures**

First, primary prevention of vascular placental complications using antithrombotics is not indicated, so routine screening of asymptomatic women cannot be justified on this basis. Second, the prognosis for future pregnancies in women with a heritable thrombophilia who have a history of recurrent pregnancy may be better than generally expected. The EPCOT investigators reported that the prognosis in subsequent pregnancies of women with recurrent pregnancy loss and underlying heritable thrombophilia was a live birth rate of 63%.<sup>1</sup>

In women with a history of previous pregnancy loss, ante-natal surveillance to assess placental function is useful. Given the possible association between hyperhomocysteinemia and pregnancy loss, it would seem prudent to suggest that women with a history of pregnancy loss take prophylactic doses of folic acid in subsequent pregnancies

#### Are antithrombotics useful?

Studies published in the 1990s reported improved pregnancy outcome in women with antiphospholipid syndrome and a history of recurrent pregnancy loss, given prophylactic doses of heparin combined with low dose aspirin compared with those given aspirin alone, but there is a paucity of data to indicate whether antithrombotic therapy is beneficial in women with heritable thrombophilia and pregnancy loss.

In a prospective study, 131 women with heritable thrombophilia (identified because of a family history of venous thrombosis) were followed through their first pregnancy. Only 7 of 83 (8%) given thromboprophylaxis to prevent venous thrombosis had a pregnancy loss compared with 10 of 48 (21%) who received no thromboprophylaxis (relative risk 0.3; 95% CI 0.1–1.0).<sup>7</sup>

#### Open, non-controlled studies

In women with heritable thrombophilia and a previous history of pregnancy loss, low molecular weight heparin has been tested in open, non-controlled studies in which outcomes were compared with the outcome of the subjects' previous pregnancies or with outcomes in controls who were either untreated or treated differently. In studies in which pregnancy outcome in women with thrombophilia and a history of pregnancy loss treated with once daily prophylactic doses of a low molecular weight heparin was compared with their past obstetric history, low molecular weight heparin use was associated with an increase in the live birth rate from 20% to 75%.<sup>8</sup>

#### Randomized studies

Although some randomized controlled studies have been reported, they lack a no treatment or placebo group. In one, women with factor V Leiden, prothrombin G20210A or protein S deficiency and a history of unexplained pregnancy loss after 10 weeks' gestation, live births were recorded in 86% of 80 women given daily prophylactic doses of a low molecular weight heparin from 8 to 37 weeks' gestation and in only 29% of the 80 women given daily low dose aspirin (odds ratio 15.5, 95% CI 7–34; *P*<0.0001).<sup>9</sup> The randomization and "blinding" in this trial have been criticized. There is no evidence that aspirin improves fetal outcome in women with heritable thrombophilias and a history of fetal loss.<sup>8</sup>

#### Purist vs. pragmatic management

From a purists' standpoint there is currently insufficient evidence on which to base antithrombotic intervention in women with a history of pregnancy loss with no other identified abnormality apart from a heritable thrombophilia. This is the position adopted by many authors, by the British Committee for Standards in Haematology<sup>6</sup> and by the authors of a recently published Cochrane Review.<sup>10</sup> In support of this position it has to be reiterated that the use of antithrombotic drugs during pregnancy is not without risk for mother and fetus and, in general, empirical intervention during pregnancy should be discouraged.

Pragmatists, on the other hand, argue that there is at least some observational evidence that women with heritable thrombophilia who have suffered pregnancy loss may benefit from intervention with antithrombotic drugs in future pregnancies and they point out that low molecular weight heparins are used increasingly in pregnant women and are, in general, considered safe. Based on extrapolation from the evidence of benefit from intervention with heparin and low dose aspirin in women with antiphospholipid syndrome and recurrent pregnancy loss, the limited evidence in women with heritable thrombophilia, and the relative safety of prophylactic doses of low molecular weight heparin in pregnancy, an increasing number of clinicians are willing to prescribe antithrombotic agents to women with heritable thrombophilia and a history of two or more otherwise unexplained miscarriages or one unexplained later intra-uterine fetal death. The American Consensus of Chest Physicians suggested for women with heritable thrombophilia and

recurrent miscarriage or a second-trimester or later loss, prophylactic doses of low molecular weight heparin (or minidose unfractionated heparin) with low dose aspirin therapy during pregnancy and following delivery.<sup>5</sup>

#### Dilemmas

Women who have suffered pregnancy loss have many questions and will seek information about the possible cause, the likelihood of recurrence, and the possibility of intervention to try to reduce the chances of further pregnancy loss. At present, however, there is a lack of solid evidence on which to base advice about the appropriateness or otherwise of testing these women for heritable thrombophilias or on the management of those who may be found to have a heritable thrombophilia.

#### Lack of evidence

Studies on the management of pregnancy loss are frequently flawed. The subjects included are often poorly selected and form a heterogeneous group lacking stratification for important factors such as maternal age, past obstetric history, and stage of gestation. Some studies have compared pregnancy outcome in patients subjected to a new intervention with the outcome in their own previous pregnancies. This strategy ignores the fact that some of these women will have suffered previous pregnancy loss merely by chance and will, as a result of the phenomenon of "regression to mean," have a high chance of having a successful pregnancy outcome without any additional intervention. Reports of studies in which the pregnancy outcome in women with a history of pregnancy loss subjected to some experimental intervention is compared with pregnancy outcome in historical controls who were either untreated or treated differently are subject not only to the phenomenon of "regression to mean" in the treated patient group but also to problems ascertaining the control information.

#### Randomized trials are needed urgently

Proper evaluation of interventions in women with a history of pregnancy loss requires randomized, double-blind, controlled trials in which patients are carefully selected to ensure that the treated and control groups are similar with respect to all of the important determinants of pregnancy outcome. Randomized, controlled trials have proven difficult to complete because many women do not wish to risk being randomized to the control group. A number of randomized double-blind studies are, however, nearing completion. It has to be hoped that these studies will provide more solid evidence on which to base information and advice for women with a history of unexplained late pregnancy loss or recurrent early loss.

In the meantime, many clinicians choose to treat patients on an individual and pragmatic basis with prophylactic daily doses of low molecular weight heparin (e.g. enoxaparin 40 mg daily or dalteparin 5000 units daily) throughout pregnancy and the puerperium. Some also advocate the addition of low dose aspirin (<150 mg) daily. The pros and cons of intervention should be discussed with the patient and the lack of proof of efficacy of thromboprophylaxis made clear. Ideally, this discussion should take place during preconception counseling.

#### Summary

- Many studies have examined the association between heritable thrombophilias and fetal loss, but the results are frequently contradictory, populations heterogeneous, and the absolute risk (if any) small.
- Published meta-analyses suggest that factor V Leiden, prothrombin G20210A, and protein S deficiency are associated with an increased risk of recurrent early pregnancy loss and non-recurrent late pregnancy loss.
- Women with a history of pregnancy loss merit increased surveillance in subsequent pregnancies and should be given folic acid during pregnancy.
- Currently, there is a lack of evidence on which to base any pharmacologic intervention in women with a history of pregnancy loss with no other identified abnormality apart from a heritable thrombophilia.
- Despite the lack of evidence from randomized, double-blind, placebo-controlled trials, many clinicians are offering women with a history of pregnancy loss found to have a heritable thrombophilia self-administered prophylactic doses of low molecular weight heparin +/- daily low dose aspirin in subsequent pregnancies.

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# Section Hemorrhagic disorders

# Section 5 Hemorrhagic disorders Image: Description 1 Management of obstetric hemorrhage: obstetric management obstetric management Annette Briley and Susan Bewley

#### Introduction and epidemiology

Obstetric hemorrhage (OH) is the leading cause of maternal mortality worldwide. In the UK, mortality rates are relatively low, with 17 deaths per 100 000 maternities recorded in the Confidential Enquiry into Maternal and Child Health (CEMACH) report 2000–2002.<sup>1</sup> However, morbidity remains high, and timely recognition and management is of the utmost importance.

Antepartum hemorrhage (APH) is defined as bleeding from the genital tract after 24 weeks' gestation and affects approximately 3%-4% of all pregnancies. The most common cause of APH is due to the presence of placenta previa, where the placenta is abnormally located in the lower uterine segment, covering or partially covering the internal os. As pregnancy progresses, especially as the lower segment forms or the cervix dilates, the woman is prone to episodes of bleeding that may be profuse. Another common cause of APH is placental abruption, when the placenta prematurely separates either partially or totally. It may be a single episode or recurrent, small or large, and the features may be typical and multiple (bleeding and pain, tender and woody Couvelaire uterus with stillbirth) or atypical and isolated (bleeding, premature labor, fetal growth restriction, abnormal CTG). However, the cause of many cases of APH is often unknown.

Primary postpartum hemorrhage (PPH) is the most common obstetric hemorrhage and is defined by the World Health Organization (WHO) as the loss of blood estimated to be >500 ml from the genital tract within 24 hours of delivery. After this, and until 6 weeks' postpartum, abnormal bleeding from the genital tract is defined as secondary PPH. Hemorrhage is considered severe when blood loss exceeds 1000 ml.<sup>2</sup> The major cause of postpartum

hemorrhage is uterine atony, when the uterus fails to contract fully after delivery of the placenta. PPH complicates 11% of deliveries worldwide, and is annually responsible for 132 000 maternal deaths.<sup>3</sup>. Even with appropriate active management, around 3% of women will experience a PPH<sup>2</sup> following vaginal delivery and a recent study in low risk Australian women suggested it was as high as 12%.<sup>4</sup> Hemorrhage is a direct cause of around 30% of all maternal deaths worldwide, the majority occurring in the poorest countries.<sup>5</sup> Substandard care has been highlighted as a factor in 60% of maternal deaths in the UK Confidential Enquiry into Maternal Deaths 2003–2005 report.<sup>6</sup>

Table 13a.1 shows the estimated time to death for obstetric emergencies, highlighting APH and PPH, in particular, and revealing obstetric hemorrhage as the most dangerous complication of pregnancy for the mother.<sup>7</sup>

#### Prevention

Prevention of PPH is via the recognition of any risk factors present either ante-natally or during the intrapartum period, and the subsequent implementation of preventative management/strategies.

Although there are a host of risk factors (see Table 13a.2 below), postpartum hemorrhage often occurs in women with no identifiable predictors and therefore clinicians must be prepared for this eventuality at each and every delivery.<sup>8</sup>

The degree of risk will influence the management of these women from place of birth to mode of delivery and post-natal care. Women at higher risk of hemorrhage should be advised to have their babies in consultant-led units with an on-site blood bank. It is important to involve the woman and her family in the multi-disciplinary plan for her delivery, which must

*The Obstetric Hematology Manual*, ed. Sue Pavord and Beverley Hunt. Published by Cambridge University Press. © Cambridge University Press 2010.

 Table 13a.1
 Estimated time to death for obstetric emergencies

Cause	Time to death
Postpartum hemorrhage	2 hours
Antepartum hemorrhage	12 hours
Uterine rupture	1 day
Eclampsia/severe PET	2 days
Obstructed labor	3 days
Infection	6 days

be well documented and reviewed as the pregnancy progresses and risk factors change. CEMACH recommends planned management, particularly in cases of placenta percreta.<sup>6</sup>

Ultrasound localization of the placenta in all women, especially those who have had previous Cesarean section,<sup>9</sup> should be reported and documented clearly in the handheld notes. Ante-natal assessment of full blood count and treatment of anemia is essential.

The importance of communication with all members of the multi-disciplinary team, and early involvement of senior medical and midwifery staff, have been highlighted in successive Confidential Enquiries and CEMACH Reports to improve prognosis. The Scottish Audit has found that reporting morbidities and the resultant review of management has consistently reduced the incidence of substandard care.<sup>10</sup>

If a woman is at risk of PPH, there are preventative and predictive measures which can be implemented in the intrapartum period. Such interventions include giving oral ranitidine (150 mg), gaining intravenous access with two large bore cannulae and taking blood to send for a full blood count, group, and save.

Active management of the third stage of labor is recommended for any woman at increased risk of PPH. This shortens the time between delivery of the baby and the placenta and membranes with no significant increase in retained placenta.<sup>11,12</sup> Active management involves the administration of oxytocin (or other uterotonic drug) with, or shortly following, delivery

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	Factors	RISK (IF KNOW
Pre-pregnancy	Maternal age >35 years Nulliparity Grand multiparity Asian ethnicity Obesity Previous Cesarean section Previous PPH Uterine fibroids Factor VIII deficiency – hemophilia A carrier Factor IX deficiency – hemophilia B carrier	× 3 × 2 × 2 × 3
Pregnancy acquired	Multiple pregnancy Placenta praevia Abnormal placental implantation – accreta, increta, and percreta APH in current pregnancy Polyhydramnios Pre-eclampsia or pregnancy induced hypertension Sepsis (including chorioamnionitis and/or endometritis)	× 5 × 15 × 4
Delivery acquired	Elective cesarean section Precipitate labor Maternal pyrexia in labor Oxytocin administration for induction or augmentation of labor Labor lasting >12 hours Operative vaginal delivery Emergency Cesarean section Fetal macrosomia (Baby weight >4 kg) Ruptured uterus	× 4 ×2 × 2 × 2 × 9 × 2
Third stage	Tissue – Retained placenta (causes 10% of PPH) Tone – Uterine atony (causes 70% of PPH) Trauma – laceration to perineum, vagina, or cervix (causes 20% of PPH) Thrombin – coagulopathies (causes 1% of PPH) Infection	

Table 13a.2 Risk factors for postpartum hemorrhage<sup>4,7,20</sup>





of the anterior shoulder of the baby. Controlled cord traction may reduce the risk of retained placenta and subsequent need for medical intervention. There have been no reported adverse effects of controlled cord traction.<sup>13–15</sup> More recently, international guidelines include uterine massage following delivery of the placenta as the last part of active management of the third stage,<sup>16</sup> although there is little evidence of the effective-ness of this.<sup>17</sup>

#### **Pathogenesis of PPH**

The most common cause of PPH, accounting for approximately 70% of occurrences is uterine atony. There are numerous reasons for the uterus failing to contract effectively; including exhaustion, sepsis, and retained products. Other causes of PPH include perineal trauma, uterine inversion, clotting disorders, pelvic hematomas, and cervical tears. An abnormally implanted placenta (see Fig 13a.1) (placenta accreta, increta or percreta) can remain in situ and hence prevent the uterus from contracting properly. Placenta previa and accreta are becoming an increasing problem, attributed to abnormal adherence of the placenta in subsequent pregnancies following Cesarean section.

If obstetric hemorrhage is not managed efficiently and effectively, this will lead to shock, hemostatic failure from disseminated intravascular coagulation (DIC), and ultimately death.

#### Diagnosis

Diagnosis of obstetric hemorrhage is typically by the visualization of blood loss from the genital tract. In the case of APH, bleeding can be concealed, and the only

sign may be evidence of maternal compromise and/or fetal distress. With PPH, the volume of blood loss is usually estimated visually, although this is notoriously inaccurate. In the acute situation before hemodilution, hemoglobin will not represent the amount of blood lost and fit, young women may appear to compensate and maintain vital signs until a late stage. Alertness and attention to clinical symptoms and signs are vital. Some units attempt to measure blood loss by weighing blood-soaked items, for example, sanitary pads and sheets. CEMACH suggest that an Early Warning Score chart be used to assess maternal compromise and so give a more accurate representation of maternal condition compared with visual estimation of blood loss, to prevent delay in emergency management.6

#### **Obstetric management**

In the case of APH, management will depend on the amount of bleeding, maternal compromise and/or degree of fetal distress. A concealed APH large enough to cause intra-uterine death is probably at least 1.5 liters and DIC and PPH should both be assumed and anticipated.

#### Immediate management of PPH

Once PPH has been diagnosed, action must be rapid. Figure 13a.2 is an effective tool in identifying what needs to be done by whom, as often in the case of a PPH several actions need to be taken simultaneously.

Whilst constantly assessing maternal resuscitation requirements (pulse, blood pressure, respiration, temperature), the uterus should be massaged to stimulate a contraction, which may assist stemming of the



Move to theater early if bleeding persists

Fig. 13a.2 Management of PPH: organizing the team (adapted from PersePhone/Pingirl).<sup>2</sup>

bleeding should the cause be atonic. This massaging action also helps expel retained products or blood clots. A full bladder could prevent the uterus from contracting properly by impeding on the space, and therefore catheterization is recommended (Table 13a.3).

Other uterotonics have been suggested with limited anecdotal evidence. These include:

- Dinoprostone; however, this is not suitable in hypovolemic situations.
- Gemeprost (cervogem)
- Sulproston a Prostaglandin E<sub>2</sub> widely used in France as a second line drug after oxytocin (before ergometrine). Can cause coronary spasm, hypertension, pyrexia, nausea, and vomiting.
- Vasopressin (R) 5 iu in 19 ml normal saline given by subendothelial infiltration. Avoid intravenous administration as it causes severe hypertension.
- Tranexamic acid a lysine derivative, which appears well tolerated. There is no evidence of

increased thrombosis and this drug is probably underused. I g intravenously with, if necessary, repeat dose 4 hours later.

 Methotrexate – prevents DNA replication and may be useful in conservative management of placenta accreta.

#### Volume maintenance in PPH

Initially, while blood is being cross-matched, volume replacement with crystalloid should be instituted. Close attention to fluid balance is required to avoid the perils of hypoxia-hypovolemia, on the one hand, and cardio-pulmonary overload on the other. In massive hemorrhage, fluid replacement can be controlled with central venous and arterial lines and anesthetic and hematology input is vital both during the event and subsequently on high-dependency or intensive care units (see Chapter 13b).

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Name of drug	How it works	Administration	Side effects
Oxytocin Prevention	Stimulates rhythmic upper uterine segment contractions	IM as part of syntometrine (acts in 2–3 minutes, lasts up to 60 mins) IV bolus 5 i.u. (acts in 1 min, has half life of 3 mins) IV 5 i.u. bolus can be repeated Infusion- 40 units/500 mls over 4 hours	<ul> <li>Hypotension, due to vasodi- latation, especially in cardiac patients</li> <li>Administer slowly</li> <li>In cardiac patients infuse 10 units over 30 mins</li> <li>Anti-diuretic hormone effect</li> <li>Fluid overload – can lead to pulmonary edema</li> <li>Hyponatremia</li> </ul>
Ergometrine Recognition	Sustains uterine contraction via alpha receptors in the upper and lower uterine segment of the uterus Combined with oxytocin as Syntometrine Acts in 2–5 mins lasts up to 3 hours If atony persists give 0.5mg IV		Potent agonist causes blood vessels to constrict Vomiting+ + + most women WILL vomit Hypertension- <i>do not give</i> to women with pre-existing high BP, Pre-eclampsia or PIH or cardiac disease
Carboprost (Hemobate <sup>®</sup> ) <i>Treatment</i>	This is a prostaglandin F2 alpha	Not for IV administrationIntramyometrially into the fundus of the uterus to avoid blood vessels (but there are very large vessels in the uterus)Intramuscularly, 250 μg (microgram) every 15 mins (maximum of 2mg)In practice most women are not given more > 2 doses85% women respond to the first dose	Has predelection for smooth muscle of the bronchi and therefore <b>caution is</b> <b>required with asthmatics</b> Bronchospasm Significant intrapulmonary shunt Hypoxia
Microprostol (Cytotec <sup>®</sup> ) <i>Treatment</i>	This is a prostaglandin E <sub>1</sub> analog It is thermostable and does not require refrigeration. This drug is cheap and therefore useful in resource limited countries.	Multiple routes of administration Orally, sublingually, rectally 800–1000 mcg (effective within 3 mins)	Shivering Pyrexia

#### Table 13a.3 Drug Management of PPH



Fig. 13a.3 Bimanual uterine compression.

#### Surgical management of PPH

• Manual removal of placenta – This is an emergency procedure to separate the placenta manually that should be considered if it has not delivered within an hour of birth. Partial separation and delays can be associated with very heavy bleeding.

- **Bimanual uterine compression** This is an effective way of stemming bleeding by compressing the uterus with both hands (Fig 13a.3)
- Examination under anesthesia (EUA) and evacuation of retained products of conception (ERPC) This should be performed in theater with appropriate conditions, personnel, and instruments and in preparation for further procedures. It is important to explore the whole of the uterus, cervix, vagina, and perineum in a rigorous way even if one cause is found or excluded. The aim of EUA is to assess the cause of bleeding and take action accordingly. The cause may be found, for example, retained cotyledon, pelvic hematoma (common after a normal vaginal

delivery and often requiring surgery) or cervical tears. ERPC for secondary PPH, especially if associated with sepsis, must be performed with great care as it can lead to perforation of the uterus.

- Balloon tamponade can be used. This involves placing a balloon in the uterus and inflating it. Most commonly around 800–1000 ml are used to ensure the balloon does not fall out after a vaginal delivery, but less is required if only compressing the lower segment after elective Cesarean; the balloon is then left in situ for 24 hours after which time it is gradually deflated. This is a cost-effective method. In an emergency a condom could be filled with fluid and inserted into the uterus to apply pressure to stop the bleeding.
- **Packing with surgical gauze**. This is a traditional and effective way to stop surgical bleeding and ooze from a raw or sutured surface, although the disadvantage is that a second procedure may be required for removal. Packs have to be placed under pressure, and can be left in the uterus, the vagina, or in the abdomen.
- The B-Lynch brace suture Although not popular in some units, this has revolutionized practice in recent years. The brace suture has not been evaluated in a RCT, but the case history evidence is compelling, and any speculated effect on fertility has to be compared with hysterectomy, which would otherwise be the next surgical option. It has been suggested that the B-Lynch brace suture may indent the uterus or cause necrotic uterus. Prophylactic brace sutures can be advocated in Jehovah's Witnesses and in others who will refuse transfusion who require Cesarean section and are assessed as at increased risk of PPH (although risk assessment is difficult).

- Internal iliac vessel ligation this is an old-fashioned technique and less familiar to obstetricians nowadays, though more often used by gynecological oncologists. The principle has evolved into an interventional radiology technique of **uterine artery embolization** to stop bleeding. The collateral circulation is adequate to protect the uterus, but the equipment is not available in all units, and there is a risk to future fertility.
- Hysterectomy Women may die if the decision to do a hysterectomy is not made or made too late, but practitioners must be prepared to defend their decision making in the legal process, as unnecessary loss of fertility is devastating. This must be the treatment of last resort, having attempted conservative measures first. The UKOSS study of hysterectomy did show a failure rate both for brace suture and interventional radiology embolization.<sup>17</sup>

All women, and their companions, deserve a contemporaneous explanation, and a discussion afterwards about what happened, so that any questions can be answered. After a PPH, women can make a remarkable physical recovery. However, unrecognized or undocumented PPH may lead to dizziness, fainting, or collapse in the immediate postpartum period. All women with symptoms or a recognized PPH should have a postpartum or day 2-3 hemoglobin in case iron supplements should be prescribed. A prolonged recoverv may be associated with fatigue, exhaustion, and interference with breast feeding and bonding. Massive hemorrhage can be very traumatic, for women, their families, and for staff, and the need for explanation and reflection must not be underestimated. Staff skills must be constantly updated.

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#### Hemorrhagic disorders

### Management of obstetric hemorrhage: anesthetic management

Vivek Kakar and Geraldine O'Sullivan

#### Introduction

Section 5 Chapter

Once the diagnosis of obstetric hemorrhage has been made, early senior anesthetic involvement (experienced registrar or a consultant) is vital. The UK Confidential Enquiry into Maternal and Child Health 2000– 2002 (Why Mothers Die<sup>1</sup>) and 2003–2005 (Saving Mothers Lives<sup>2</sup>) show that hemorrhage is still one of the commonest causes of direct maternal deaths. In Why Mothers Die 1999–2002, 17 maternal deaths were caused by hemorrhage; care was considered suboptimal in 5 of these 17 cases. In the Saving Mothers Lives 2003–2005, hemorrhage caused 14 deaths and was a complicating factor in 9 others. In as many as 10 of these 14 deaths, the patient received suboptimal care.

#### Communication

Early and clear communication between obstetricians, midwives, anesthetists, hematologists, and the porters is essential. A "leader" should coordinate the ongoing management of the hemorrhage. Arguably, this leader should be the senior anesthetist. Extra help, surgical, and/or anesthetic, should also be summoned.

#### Access

Several large bore intravenous (IV) cannulae (14G/16G) should be sited. Central venous catheterization may be needed at a later stage, but should not delay resuscitation in emergent situations, in otherwise healthy patients. Ultrasound guidance is recommended by NICE<sup>3</sup> for the insertion of a central venous catheter in the internal jugular vein. Subclavian vein cannulation should specifically be avoided in established or suspected coagulopathy, as occurs in concealed abruption, sepsis, severe pre-eclampsia and massive transfusion.

#### Monitoring

Blood pressure, oxygen saturation, and electrocardiogram (ECG) should be continuously monitored. There should be a relatively low threshold to insert an arterial line in bleeding patients. A central venous pressure (CVP) monitor may be required in cases of massive hemorrhage, although not as a part of the initial resuscitation. A urinary catheter should be inserted in all cases to measure the hourly urine output. Resuscitation should be guided by clinical parameters, arterial blood gases, lactates, CVP, and urinary output. In cases with cardiovascular and/or renal problems, some form of cardiac output monitoring (LiDCO, PiCCO, or esophageal Doppler in intubated patients) can provide useful information. Accurate assessment of blood loss is essential and can be achieved by weighing the surgical swabs and measuring the volume of blood in the surgical suction. The Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines<sup>4</sup> for monitoring should be followed during surgery, recovery and transfer of these patients, should that be required. Other recommendations<sup>2,5-6</sup> are that some form of track and trigger scoring system (such as Modified Early Warning Scores (Table 13b.1)) should be used in high risk patients monitored on the labor ward to facilitate early identification of patients with ongoing hemorrhage.

#### Oxytocics (see also Chapter 13a)

(a) Oxytocin: Five to ten units should be administered as a slow IV bolus. Rapid IV administration can cause profound hypotension and tachycardia. Cardiac arrest has also been reported. It works within 2–3 minutes but due to its short half-life it needs to be administered as an infusion, e.g. 40 IU in 40ml of normal saline over 4 hours.

*The Obstetric Hematology Manual*, ed. Sue Pavord and Beverley Hunt. Published by Cambridge University Press. © Cambridge University Press 2010.

	3	2	1	0	1	2	3
HR (bpm)		<40	40-50	51-100	101-110	111–129	≥130
BP	>45%↓	30%↓	15%↓	Normal	15%↑	30%↑	>45%↑
RR (/min)		<u>≤</u> 8		9–14	15–20	21–29	≥30
Temp (°C)		<35.0		35.0-38.4		>38.5	
CNS				Α	v	Р	U
Urine Output	Nil	<1 ml/kg/2 h	<1 ml/kg/h		>3 ml/kg/2 h		
A = Alert $V =$ Responds to Verbal commands $P =$ Responds to Pain $U = U$ nresponsive.							

 Table 13b.1
 Modified early warning scoring system<sup>5</sup>

- (b) Ergometrine: It is an extremely effective second-line drug for an atonic uterus. The IV dose is 100–300 mcg. Uterine contraction occurs within 5 min of an intramuscular (IM) injection and 1 minute after an IV injection. Its effects last at least 1 hour.
- (c) **Carboprost (methyl prostaglandin**  $F_{2\alpha}$ ): It is an extremely potent drug and is administered by IM or intramyometrial injection. It should be administered in 250 µg increments, repeated at 15-minute intervals up to a maximum of 2 mg. The majority (85%) of patients will usually respond to the first or second dose, and in practice the full 2 mg dose will rarely be employed as ongoing severe hemorrhage usually necessitates further surgical/radiological intervention.
- (d) **Misoprostol:** This is a prostaglandin  $E_1$  analog. It is supplied as 200 µg tablets and 800–1000 µg should be administered rectally.

#### Fluids

Immediate resuscitation should begin with crystalloids and colloids. There is no evidence of superiority of one over the other in non-septic obstetric patients.<sup>7</sup> In an emergency, the choice of fluid is immaterial. Hartmann's solution is the most physiologically balanced solution; normal saline can also be used, although it can itself cause metabolic acidosis after several liters have been used.

Commonly available colloids include starches (*Voluven*), gelatins (*Haemaccel*, *Gelofusine*), and albumin. There have been concerns about the effect of starches on platelet function and renal function. A

recent large study<sup>8</sup> found significantly increased renal failure and blood transfusion requirements in septic patients who required more than 22 ml/kg of 10% hetastarch (0.5/200). This study did not include the obstetric population. Gelatins can interfere with blood grouping, cross-matching, and cause allergic reactions. A recent Cochrane review failed to establish any difference between different colloids in terms of outcome.<sup>9</sup>

Blood pressure, heart rate, and urine output are good endpoints in assessing adequate resuscitation. In fit and healthy young patients, tachycardia will usually represent uncorrected hypovolemia. Blood pressure will generally not fall until 30% of the blood volume ( $\sim$ 1500 ml) has been lost (Table 13b.2).

# Preventing the "lethal triad" of hypothermia, acidosis and coagulopathy

It has been demonstrated in trauma patients with massive bleeding, that if they are allowed to become hypothermic and acidotic, their coagulopathy worsens or is refractory to correction.<sup>10</sup> This has also been shown to be true in other cases of hemorrhagic shock (Fig. 13b.1).

Evidence suggests that a fall in temperature from  $37 \,^{\circ}$ C to  $33 \,^{\circ}$ C reduces rFVIIa activity by 20%, whilst a fall in pH from 7.4 to 7.0 reduces rFVIIa activity by 90%. Platelet function is also inhibited to a varying degree. It seems that acidosis alone does not seem to affect the clotting, but increases the effect of hypothermia on clotting.<sup>11</sup> Therefore, the prevention

#### Table 13b.2 Classification of hemorrhagic shock

	Class 1 (Compensated)	Class 2 (Mild)	Class 3 (Moderate)	Class 4 (Severe)
Blood loss (% Circulating blood volume)	750 ml (<15%)	800 – 1500 ml (15%–30%)	1500 – 2000 ml (30%–40%)	>2000 ml (>40%)
Systolic blood pressure	No change	Orthostatic Fall	Low	Very low
Diastolic blood pressure	No change	Raised	Reduced	Very low
Pulse rate	<100	>100	>120 (weak)	>140 (very weak)
Capillary refill	Normal	Slow (>2 s)	Slow (>2s)	Prolonged (>5 s)
Respiratory rate	Normal	Normal	Raised (>20/min)	Raised (>20/min)
Urine output	>30 ml/h	20 – 30 ml/h	10 – 20 ml/h	0 – 10 ml/h
Extremities	Normal	Pale	Pale	Pale and cold
Complexion	Normal	Pale	Pale	Ashen
Mental state	Alert, thirsty	Anxious, thirsty	Anxious, aggressive or drowsy	Drowsy, confused or unconscious

Adapted from ATLS manual.



Fig. 13b.1 The lethal triad

of hypothermia and acidosis is an essential component in the successful management of massive hemorrhage.

Patients should be kept warm using forced air warming blankets. All fluids should be warmed using any of the commonly available fluid warmers (Fig. 13b.2). When the fluid needs to be infused rapidly, normal fluid warming devices may not be able to perform efficiently, when pressurized fluid is run through them. Therefore, every obstetric unit should have access to a Level 1 infusor (Fig. 13b.3) which can both pressurize and warm blood and fluids rapidly.



Fig. 13b.2 Fluid warmer.

## Blood and blood component therapy<sup>12</sup> (see Chapter 13c)

Blood replacement should be guided by bedside and/or laboratory hemoglobin testing. When hemorrhage is first diagnosed, blood should be sent to the laboratory for a group and cross match, full blood count (FBC) and coagulation screen (INR, aPTT, fibrinogen). The hemoglobin, coagulation screen, and platelet count will need to be repeated at regular



Fig. 13b.3 Level 1 Infusor.

intervals in order to facilitate the logical use of coagulation factors. Alternatively, if available, a thromboelastogram (TEG) can be used to guide the replacement of coagulation factors.

#### Cell salvage<sup>13–18</sup>

Intraoperative cell salvage and auto transfusion has been available for many years and has been very useful in cardiac surgery, major vascular surgery, orthopedic surgery, and trauma. Cell salvage is now increasingly considered in massive obstetric hemorrhage as recent research has shown it to be safe in obstetrics.

#### Indications

Cell salvage is a technique for re-cycling operative blood loss. It is particularly appropriate for elective surgery where massive blood loss is anticipated, e.g. placenta previa/acreta/percreta and for mothers who refuse blood and blood products, e.g. Jehovah's witnesses. Once skill has been acquired with the technique, it can be rapidly set up, even in an emergency.

# Principles of cell salvage (Figs 13b.4 and 13b.5)

Blood is aspirated from the surgical site through heparinized tubing and a filter into a collecting reservoir. The cells are separated by hemoconcentration and differential centrifugation in 0.9% saline, and washed in 1-2 L of 0.9% saline. This process removes circulating fibrin, debris, plasma, micro-aggregates, complement, platelets, free hemoglobin, circulating pro-coagulants, and most of the heparin. At the end of the salvaged process, the hematocrit of the salvaged blood is usually between 55% and 60%.

#### Problems

Cell salvage was until recently considered to be contraindicated in obstetrics because of the following two theoretical risks:

- Amniotic fluid embolism: In the literature, only one death has so far been reported after the use of salvaged blood. However, the patient was a Jehovah's Witness with severe pre-eclampsia and HELLP syndrome (Hemolysis, elevated liver enzymes and low platelet count), and a leukocyte depletion filter was not used. It has now been shown that use of a 40 µ leukocyte depletion filter (Fig. 13b.6), on the return limb to the patient, effectively depletes or entirely removes fetal squames, white blood cells, and platelets from the salvaged blood. To date, no case of amniotic fluid embolism has been reported in patients who received salvaged blood during Cesarean section where a leukocyte filter was used. In addition, amniotic fluid embolism is now considered to be more of an immunological phenomenon rather than actual physical embolism. Nevertheless, any contamination of the salvaged blood with amniotic fluid should be avoided as far as possible.
- Allo-immunization: Despite the use of several wash cycles and filters, it is still not possible to avoid contamination of the salvaged blood with fetal red blood cells. This is because the machine cannot distinguish between fetal and maternal red blood cells. The amount can vary between 2 ml and 19 ml and Kleihauer counts should be routinely performed in the postpartum period. All rhesus negative mothers should be immunized with anti-D. A second dose may be required if the Kleihauer suggests heavy contamination with fetal cells.

#### Cost

Although the machines can be very expensive, most hospitals lease them from the manufacturer. Typically,



Fig. 13b.4 Cell salvage schematic diagram.<sup>17</sup>

it costs approximately £100–170 per patient (towards disposables) to setup and use the cell salvage machine. So, the cost of disposables is covered as soon as you need to transfuse more than one unit. A systematic review of over 600 studies comparing various transfusion strategies to reduce allogenic blood transfusion found that the relative risk of requiring allogenic blood transfusion with cell salvage was 0.59 and it was more cost effective than all other strategies except acute normovolemic hemodilution. Every unit with cell salvage facilities should have a protocol for the use of cell salvage in obstetrics.

#### Investigations

FBC and clotting should be checked frequently. In cases of ongoing blood loss, resuscitation should be guided by bedside hemoglobin estimation (e.g. HemoCue, Fig. 13b.7) and/or arterial blood gas estimation. Liver and renal function should also be assessed at baseline and, once the patient has been stabilized, especially in patients with complex co-morbidities, multiple medications, massive transfusion, or prolonged period of intraoperative hypotension.

#### **Regional Vs general anesthesia**

In an elective situation, where significant blood loss is anticipated, such as with anterior placenta praevia, regional anesthesia can still be considered, although the patients should be warned of the occasional need to convert to general anesthesia (GA) intra-operatively. Baseline hemoglobin, venous access, invasive monitoring and a cell salvage unit should be established prior to starting such cases. Two to four units of blood should also be cross-matched.

In an emergency situation, anesthetic management will be determined by both fetal and maternal considerations. GA is usually considered in cases of severe hemodynamic instability, sepsis, and suspected or confirmed coagulopathy. If GA is used in severely hypovolemic patients, the anesthetic induction agents, ketamine or etomidate should be used instead of thiopentone or propofol, as they do not cause the profound hypotension commonly seen when the latter two agents are used in hypovolemic patients. If a bleeding patient needs to be transferred to the interventional radiology suite, it might be worth securing the airway prior to transfer, especially if the radiology department is not very close to the obstetric unit. In addition, adequate anesthetic facilities and assistance should be available in the radiology suite.





Fig. 13b.6 Leukocyte filters.

Fig. 13b.5 Cell salvage machine.

#### Post-hemorrhage care

Post-operative care will usually be on a high dependency unit, but transfer to an intensive care unit may be necessary particularly if the patient requires mechanical ventilation. If possible, cardiovascular and metabolic parameters should be stabilized prior to transfer. Acceptable standards of monitoring should be maintained during the transfer as mentioned earlier.

Once the bleeding has been controlled and the patient is stable, regular thromboprophylaxis should be commenced.

#### Documentation

Accurate and complete documentation of the sequence of events is very important. In cases of poor outcome, poor documentation is indefensible even if excellent care was provided. One person can be assigned the job of keeping a record of all the drugs and fluids



Fig. 13b.7 Hemocue.<sup>TM</sup>

administered and of the personnel involved in the resuscitation.

#### Drills/protocols

A multidisciplinary massive hemorrhage protocol must be available in all units and should be updated and rehearsed regularly. Women known to be at high risk of bleeding should be seen by a consultant anesthetist in the ante-natal period. These patients should ideally be delivered in centers with facilities for blood transfusion, cell salvage, intensive care, and interventional radiology, and plans for their management should be made in advance.

#### **Debriefing and counseling**

Supportive counseling of all the team members involved is vital, should the hemorrhage result in maternal death. Such an event represents a tragedy not only for the woman's family, but also for the carers. Debriefing after such episodes can be a very good opportunity to reinforce learning points and seek improvements for future.

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#### Hemorrhagic disorders

## Management of obstetric hemorrhage: hemostatic management

Eleftheria Lefkou and Beverley Hunt

#### **Blood loss**

Section 5 Chapter

**Obstetric hemorrhage** (OH) is defined by the World Health Organization (WHO)<sup>1</sup> as a blood loss of more than 500 ml in the first 24 hours after birth, or of more than 1000 ml when Cesarean section has been performed. A more comprehensive definition could be any blood loss which can provoke a physiological change threatening the woman's life. According to the American College of Obstetrics and Gynecology, OH is defined as either a 10% change in hematocrit between admission and postpartum, or the need for a blood transfusion.<sup>2</sup>

Current best practice for the hematological management of obstetric hemorrhage (OH) emphasizes the need for speedy and appropriate use of blood components with close monitoring of blood loss. However, best practice is not always followed. This seems, in part, to be due to poor understanding in the appropriate use of blood components and pharmacological agents to reduce bleeding.

In this chapter we give practical guidelines for the hematological management of OH. Table 13c.1 shows the available blood components and their derivatives used in hemostatic replacement therapy.

#### Hemostatic replacement therapy

#### Red cell products

Red blood cell (RBC) transfusion is a first-line intervention to treat the inadequate oxygen delivery (but not the volume loss) seen in OH. In the UK whole blood is not usually available.

One unit of packed red cells increases the hemoglobin by approximately one g/dl and the hematocrit by 3%. There are no evidence-based guidelines for transfusion of RBC into hemodynamically unstable women with OH. According to the British Committee for Standards in Hematology guidelines on the management of massive blood loss, red cell transfusion is likely to be required when 30%-40% blood volume is lost; when 40% blood volume loss is immediately life-threatening.<sup>3</sup> As a general rule, the target hemoglobin levels should be greater than 8 g/dL.

Ideally, all pregnant women should be transfused with red cells of the same ABO and Rhesus group.<sup>4</sup> In an urgent situation where blood is required immediately, with unknown patient's blood group, all women under 50 years must be given group O Rhesus negative red cells, in order to avoid sensitization and hemolytic disease of the newborn in subsequent pregnancies. Every obstetric unit should have 2 units of O-Negative blood in the fridge for emergency use. However, antenatal ABO and rhesus grouping and sending a sample to the blood transfusion laboratory to confirm ABO grouping allows the release of matched blood. The physicians should be mindful that blood grouping takes less than 10 min and so ABO group-specific red cells should be administrated as soon as possible.

#### Platelet transfusion

In the UK platelets are usually obtained by plateletpheresis from one donor- single donor plateletpheresis and stored in polyolefin packs with a viability of about 5 days; or they are removed from a unit of blood and bagged togethers known as pooled random donor platelets.

In massive OH after a  $1.5-2 \times$  blood volume replacement, a platelet count  $<50 \times 10^9$ /l should be anticipated. The target of platelet transfusion is to maintain platelet count  $>50 \times 10^9$ /l (70–110  $\times 10^9$ /l). In cases with qualitative platelet abnormalities, as in

 Table 13c.1
 Blood components and their derivatives used in hemostatic replacement therapy

- Red cells
- Platelet pools
- Fresh frozen plasma
- Cryoprecipitate or fibrinogen concentrates
- Recombinant Factor VIIa
- Antithrombin, Protein C and activated Protein C concentrates
- Prothrombinase concentrates (II, VII, IX and X)
- Plasma-derived and Recombinant Factor VIII and IX
- von Willebrand Factor concentrates

some inherited diseases such as Glanzmann's thrombasthenia or Bernard–Soulier syndrome, or acquired disorders such as liver or kidney disease, or druginduced platelet dysfunction, the trigger for platelet transfusion should be higher, depending not on the number but on the function of platelets. In the UK one platelet apheresis concentrate will increase the platelet count by  $50 \times 10^9$ /L in most adult patients. Ideally, the platelet count should be checked 10–15 minutes after platelet infusion to ensure the adequacy of therapy. A poor increment of less than  $20 \times 10^9$ /L after 15 minutes in a patient without ongoing bleeding to suggest the presence of antiplatelet antibodies, usually human leukocyte antigen (HLA) antibodies.

#### Fresh frozen plasma (FFP)

Fresh frozen plasma (FFP) is separated within 6–8 hours of whole blood collection, frozen at -18 °C and stored for up to 1 year. The volume of a typical unit is 200 to 250 ml. FFP contains normal levels of all coagulation factors, except FVIII, which rapidly decays, leaving around 60% levels. The indications for use of FFP in massive transfusion and disseminated intravascular coagulation with significant bleeding is PT or APTT ratio >1.5. There is no evidence base for the dose that should be used, however 15 mL/kg is widely accepted. Solvent detergent prepared FFP has a lower risk of transfusion transmitted infection but has reduced levels of macromolecular von Willebrand factor (VWF), which is of little concern in the management of bleeding.

#### Fibrinogen

There are two sources of fibrinogen available in the UK: cryoprecipitate and fibrinogen concentrate. Cryoprecipitate is made from donor plasma by placing the plasma in a fridge at  $4^{\circ}$ C. This allows all the large molecules such as fibrinogen, von Willebrand factor, and Factor VIII to precipitate out. These are separated off and they are redissolved in a small residue of plasma, as it is warmed. A typical adult dose is two five-donor pools (equivalent to 10 single donor units) containing 3–6 g fibrinogen in a volume of 200 to 500 ml. As a rule of thumb, 10 bags of cryoprecipitate will increase a normal adult's fibrinogen by 1 g/L.

Fibrinogen concentrate is available but not licensed for use in massive transfusion in the UK. Its potential side effects include hypertension, anaphylaxis, and arterial thrombosis. It is licensed for use in patients with congenital a- or hypo-fibrinogenemia.

In normal pregnancy fibrinogen levels are elevated as part of the hemostatic response to pregnancy, with levels at term between 5 and 7 g/L. So even normal non-pregnant levels (range: 1.5–4.0 g/L) of fibrinogen mean that significant consumption of fibrinogen has occurred.

In OH fibrinogen levels are often very low. With a poorly contractile uterus or intra-abdominal bleeding, large volumes of clot form and rapidly consume all the available fibrinogen. Often, fibrinogen levels are as low as 0.1 g/L. In this situation there is not enough fibrinogen for normal coagulation to occur. Infusion of fresh frozen plasma is not enough to replete the deficiency and so 20 bags of cryoprecipitate should be used as soon as possible to elevate fibrinogen by approximately 2 g/dL.

# Pharmacological agents that reduce bleeding

#### Antifibrinolytics

The two agents which have been used in the UK are tranexamic acid and aprotinin. Aprotinin has been suspended from marketing in the UK with concerns about its safety.<sup>5</sup>

Tranexamic acid binds to plasminogen and thus inhibits its binding to fibrin. It has a plasma half-life of 2 hours. It is contraindicated in renal tract bleeding and in renal failure.

Tranexamic acid has been used extensively to reduce perioperative bleeding, whether or not there is evidence of hyperfibrinolysis. A recent Cochrane review<sup>6</sup> shows it is safe in that it is not associated with an increased risk of venous thromboembolism with short-term use. However, there are no studies of the efficacy and use of antifibrinolytics in OH, but theoretically the hemostatic changes of obstetric hemorrhage should be little different from surgical bleeding and trauma. We know that massive bleeding will stimulate epinephrine, which will cause release of fibrinolytic activators. If there is a low fibrinogen, clot formation will be defective and the clot is open and more liable to being penetrated by fibrinolytic activators. The use of tranexamic acid in traumatic bleeding is being investigated in the CRASH-2 (clinical randomization of antifibrinolytic therapy in significant hemorrhage), which aims to randomize 20 000 patients to tranexamic acid vs. placebo and will report in 2010. The same group plan to do a similar randomized controlled trial of tranexamic acid in obstetric hemorrhage (the WOMAN study).

The authors suggest in the interim that tranexamic acid in a 1-2 g bolus should be strongly considered in the management of OH in view of its safety and efficacy in other settings.

#### Recombinant VIIa

Recombinant FVIIa is not adequately studied in OH. It is licensed in Europe for treatment of hemophilia patients with inhibitors to factors VIII and IX, and for patients with Glanzmann's thrombasthenia, and FVII deficiency. It has no other licensed indication for any other group of patients but it has been used "off license" in the management of bleeding.

There are no prospective, randomized placebocontrolled studies in the use of rFVIIa in OH, but many case reports. Unfortunately, case reports can lead to considerable reporting bias with a tendency towards reporting only positive outcomes. There are, however, three major studies reporting data in the use of rFVIIa in this setting. The first study comes from the Northern European Registry 2000-2004, and gives data from the use of rFVIIa in primary postpartum hemorrhage (PH), from nine European countries.<sup>7</sup> A total of 113 individual cases are presented and the authors conclude that there was some improvement in more than 80% of women and few adverse effects. But it is not clear that best practice for blood components was applied prior to use of rFVIIa, i.e that the use of blood components appropriately would not have resulted in the same improved outcome. The second study, from Finland, reports retrospectively the one-center experience on the administration of rFVIIa to 38 parturients.8 The authors conclude that there is no evidence that the use of rFVIIa was better than standard management with blood components. The last study from Ireland, reports massive OH in 28 cases, with rFVIIa use in six patients, in a 3-year period at one institution.9 The authors concluded that there is a need for resuscitation, surgical intervention and appropriate use of blood products and no place for the routine use of rFVIIa. Haynes et al.<sup>10</sup> summarizes 44 reported cases with rFVIIa in OH and added four cases from their experience. Data from this study showed that, despite the administration of rFVIIa, invasive surgery or procedures, such as hysterectomy or embolization, remained necessary. From the 48 patients, seven responded only partially to treatment and three died despite treatment. A relatively recent systematic review on the efficacy and safety of rFVIIa for treatment of severe bleeding conclude that more randomized controlled trials are required to assess the use of rFVIIa for patients without a pre-existent coagulation disorder and with severe bleeding.<sup>11</sup> A recent Cochrane review did not find real evidence of its off license use but there was a trend towards reduced mortality and increased thromboembolic events.<sup>12</sup> The review did not include any studies of obstetric hemorrhage.

There is current concern about the safety of rFVIIa in "off licence" indications. A recent meta-analysis showed an arterial thrombosis rate of 5.6% in those receiving rVIIa compared with 3% in the placebotreated patients.

Thus the use of rVIIa in OH should ideally be limited to clinical trials or in intractable hemorrhage in carefully selected patients, where there are adequate levels of platelets and coagulation factors and bleeding has not resolved despite optimal management and good transfusion practice.

The current recommended dose is  $90 \mu g/kg$  repeated up to every 2 hours. Currently, no monitoring is available for rFVIIa therapy. It is important to remember that the success of rFVIIa is dependent on several pre-conditions that include:

- (a) the presence of adequate platelets (> $50 \times 10^9/L$ ) and coagulation factors (fibrinogen levels >1g/L), and
- (b) the absence of acidemia and hypothermia.

#### **Other products**

Prothrombinase complexes contain Factors II, VII, IX, and X isolated from thousands of units of blood and stored as a powder that requires rehydration for use. They are used for the emergency reversal of vitamin K antagonists, an unlikely prospect in pregnant women.
Their use in OH has been restricted to cases with inherited or acquired deficiency of coagulation factors.

DDAVP (1-deamino-8-D-arginine vasopressin, desmopressin) is a non-blood-derived alternative (a synthetic analog of vasopressin) that retains the antidiuretic action of the natural hormone and also stimulates the release of tissue plasminogen factor (tPA). These effects are used to elevate the plasma factor VIII and vWF level two- to fourfold above the baseline, by its release from storage sites. It can correct the hemostatic defect in mild hemophilia A or von Willebrand disease (VWD) sufficiently to cover minor surgery or at a minor bleeding episode. DDAVP should be used with caution in women with pre-eclampsia, due to the antidiuretic effect and to the potential risk of hyponatremia that can lead to convulsions. Therefore, restriction of fluid intake is required to accompany its use. Other side effects comprise mild facial flushing and headache.

There are insufficient data about the efficacy and safety of DDAVP for prophylaxis and treatment of OH. It has been used safely during pregnancy in women for other indications (see Chapter 14). DDAVP does not pass into breast milk in significant amounts and so it may be used in labor and in the postpartum period.

# Hematological monitoring and management

Regular full blood counts (FBCs) and coagulation screens should be used to guide therapy, with regular (up to hourly) requests with massive loss. The turnaround time in an average hospital makes nearpatient testing an attractive option. A thromboelastogram (TEG) is an alternative, but is poorly validated in this setting.

In general, if the bleeding continues and no bleeding point can be found:

- Keep hemostatic monitoring going.
- Consider an antifibrinolytic agent.
- Consider the bleeding history and the possibility of undiagnosed von Willebrands disease or other bleeding disorder.

Speedy responses are required to prevent a cycle of failure to catch up e.g. excessive hemorrhage  $\rightarrow$  depletion of hemostatic factors  $\rightarrow$  further bleeding  $\rightarrow$ , etc.

#### Table 13c.2 Use of Blood components in OH

#### Red blood cells:

- Maintain Hb > 8 g/dL
- One unit of packed red cells increases the hemoglobulin by 1 g/dL and the hematocrit by 3%.

#### **Platelet transfusion:**

- Maintain platelet count > 50  $\times$  10<sup>9</sup>/L (70  $\times$  10<sup>9</sup>–110  $\times$  10<sup>9</sup>/L).
- If platelet count  ${<}50\times10^9{\rm /L}$  give one adult therapeutic dose of platelets

#### FFP:

If INR/APTT ratios > 1.5 give FFP 15ml/kg

#### Cryoprecipitate:

- Maintain fibrinogen >1.0 g/L
- 10 bags of cryoprecipitate will increase a normal adult's fibrinogen by 1.0 g/L

Ideally, a blood warmer should be used to help prevent hypothermia, and regular blood gases should be performed (see Chapter 13b).

#### Disseminated intravascular coagulation

DIC is not a usual direct consequence of OH but rather a complication of appropriate, delayed or inadequate treatment. Delayed and inappropriate treatment will lead to prolonged hypoxia, hypovolemia, hypothermia or extensive muscle damage and thus to a DIC-like syndrome. A prolonged PT and aPTT, thrombocytopenia and low fibrinogen levels (<1.0 g/l), are highly suggestive of a developing DIC-like syndrome.

#### Post-hemorrhage care

Once bleeding has stopped, it should be remembered that, in the UK, the most common cause of maternal direct deaths in UK is thromboembolism.

Mothers that hemorrhage and have operative intervention will have excellent acute phase responses postpartum that will make the blood more prothrombotic and the patients at high risk of venous thromboembolism. Therefore, thromboprophylaxis with a low molecular weight heparin should be started as soon as possible postpartum, according to current guidelines.

Table 13c.2 summarizes the suggested guidelines for the management of OH. Current best practice emphasizes the need for speedy and appropriate use of blood components with monitoring if bleeding continues.

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#### Section 5 Chapter

Hemorrhagic disorders

# Management of obstetric hemorrhage: radiological management

Ash Saini and John F. Reidy

# Introduction

Those rare cases of obstetric hemorrhage that do not respond to conservative measures such as the use of uterotonics, correction of coagulopathies, laceration repair, evacuation of retained products, and uterine packing have traditionally been treated by more invasive surgical methods. These include: application of a uterine compression suture, ligation of the arterial supply to the uterus and, if all else fails, hysterectomy.

The use of interventional radiology (IR) to treat postpartum hemorrhage (PPH) was initially described in 1979.<sup>1</sup> Since then, uterine artery embolization (UAE) to treat fibroids has become common practice and interventional radiologists have been able to apply the technique to the treatment of obstetric hemorrhage. UAE plays a vital role once conservative treatments have failed, avoiding the trauma of major surgery, reducing transfusion requirements and importantly preserving fertility. Although there are no randomized controlled trials, there are a large number of case series which have established arteriography and embolization for PPH to be safe and effective, with a success rate of 90% and very low complications.<sup>2</sup> In the United Kingdom recommendations have been made that all hospitals with delivery units should have access to an emergency IR service and to consider early or prophylactic embolization as an important tool in the prevention and management of obstetric hemorrhage.3,4

The main indications for embolization are in the emergency treatment of PPH and electively, in high risk cases. Embolization has also successfully been used to treat hemorrhage secondary to ectopic pregnancy, gestational trophoblastic disease, and acquired uterine arterio-venous malformations.<sup>5-9</sup> Contraindications are all relative and include coagulopathy, renal failure, and severe contrast allergy.

### The role of interventional radiology in the management of emergency postpartum hemorrhage

There are a variety of indications for the use of embolization, but it is most commonly used following a vaginal delivery to treat primary PPH secondary to uterine atony (Table 13d.1). Obstetric units should have protocols to guide referral (Fig. 13d.1).

Although embolization should ideally be performed on a hemodynamically stable patient, some leeway exists depending on anesthetic support and the speed and experience of the local IR service. Early liaison with interventional radiology and referral for embolization is critical. In this respect obstetricians should be aware of the potential delay in treatment whilst the patient is transferred to an angiographic suite and plan accordingly. It is often the case that, if conservative treatments are unsuccessfully employed for such prolonged periods, the patient is then too unstable to be transferred to the radiology department for embolization.

It is essential that the procedure is performed by an experienced interventional radiologist. As with other more invasive surgical procedures, it is imperative that the patient is resuscitated by another practitioner, preferably an anesthetist. The procedure is minimally invasive, carried out under local anesthetic. Standard transfemoral arterial access is obtained and specialized catheters inserted into the anterior

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Table 13d.1Indications for the use of interventional radiologyin the treatment of emergency postpartum hemorrhage

#### Primary postpartum hemorrhage due to:

- atonic uterus post-vaginal delivery (most common, usually following prolonged labor)
- uterine, cervical, or vaginal tears
- hemorrhage post-Cesarean delivery
- pelvic bleeding in a surgically challenging location, e.g. broad ligament, pelvic, or vulval hematoma
- undiagnosed placenta previa or accreta

#### Other indications for the use of emergent embolization:

- hemorrhage following therapeutic or accidental abortion or interstitial ectopic pregnancy
- secondary post-operative PPH
- acquired uterine arterio-venous malformations caused by instrumentation after delivery

division of each internal iliac artery. Arteriography is performed, but it is not essential that bleeding is demonstrated. If the source of bleeding is identified (usually the uterine or vaginal arteries), selective catheterization is performed and the vessel embolized with small particles (1–2 mm) of Gelfoam (Upjohn) until the antegrade flow of contrast stops (Fig. 13d.2). Gelfoam is the embolic agent of choice as it creates a temporary occlusion and is small enough to stop flow in distal branches but unlikely to reach capillary level and cause uterine necrosis. If the source of bleeding remains undetected, or if time and patient anatomy does not allow selective catheterization, then empiric embolization of the anterior division of the internal iliac artery is performed.

### The role of interventional radiology in the elective or prophylactic management of postpartum hemorrhage

Even rarer than those cases of unexpected emergency obstetric hemorrhage treated by embolization, are a high risk group of patients with abnormalities of placentation in whom massive bleeding at the time of delivery may occur. In these patients the elective use of embolization has been advocated.

Placenta accreta occurs when there is abnormally firm attachment of the placental villi to the uterine wall and remains a formidable clinical challenge, with patients most at risk of emergency hysterectomy. Although previously extremely rare, there has been a tenfold increase in cases, thought to be secondary to the rise in Cesarean deliveries, in which the uterine incision acts as the nidus for abnormal placentation.<sup>10,11</sup> Placenta accreta most commonly occurs in patients with placenta previa. Three variants are



**Fig. 13d.1** Example of a protocol for the management of emergency postpartum hemorrhage.



(C)



Fig. 13d.2 Persistent massive primary PPH following Cesarean section and uterine packing (\*). Right transfemoral arterial access has been obtained and a catheter placed in the origin of the right internal iliac artery. Angiography demonstrates active pelvic hemorrhage (*arrow*), however the precise source is not demonstrated (a). Selective arteriography identifies hemorrhage arising from a vasoconstricted right uterine artery (b), (c) which was successfully embolized with particles of Gelfoam.

recognized, depending on the depth to which the placenta extends through the myometrium (Fig 13a.1). In its most severe form the placenta extends beyond the serosal surface of the uterus to invade neighboring structures, usually the bladder (placenta percreta).

Effective management starts with a high index of clinical suspicion and accurate pre-natal diagnosis. Pelvic ultrasound by a skilled ultrasonographer is reliable in excluding a diagnosis of placenta accreta. In cases with suspicious but inconclusive ultrasonographic findings, magnetic resonance imaging (MRI) may be used to optimize diagnostic accuracy.<sup>12</sup> Once diagnosed, it is vital that a multi-disciplinary approach is adopted, with appropriate anesthetic, hematologi-



Fig. 13d.3

cal, IR, and urological support as necessary. Patients are treated either by elective Cesarean hysterectomy or, if possible, by Cesarean delivery, for example, in cases of placenta percreta where attempts to perform a hysterectomy would lead to further blood loss. Although based on very small numbers of cases, IR has an important role in helping to minimize hemorrhage.<sup>5,13–16</sup>

Bilateral transfemoral arterial access is obtained and pre-delivery catheterization of the anterior division of both internal iliac arteries with occlusion balloons performed (Fig. 13d.3). The balloons are deflated throughout the delivery and then inflated immediately afterward, thus allowing time to better control the hemorrhage surgically. Alternatively, Gelfoam embolization can then be performed non-selectively or selectively through a micro-catheter passed co-axially through the lumen of the occlusion balloon catheter and into the uterine arteries. Although the efficacy of this technique remains to be fully determined, it is likely to represent the safest form of combined management in a group of patients that have a higher risk of hemorrhage and are more likely to undergo an emergency hysterectomy.<sup>17</sup>

# Complications of embolization and effects on fertility

Minor complications related to the puncture site include hematoma or pseudoaneurysm formation, but are uncommon since patients are usually young and free of vascular disease. Major complications are even rarer with anecdotal reports of pelvic sepsis, uter-ine necrosis, bladder necrosis, and transient buttock ischemia.<sup>2</sup>

A prime advantage of embolization is that it avoids the need for hysterectomy. Although no large prospective studies have been completed, several case series have reported a return to normal menses with no significant adverse effects on future fertility.<sup>18–20</sup>

#### **Summary**

The techniques of selective arterial embolization to treat emergency obstetric hemorrhage, and balloon occlusion used electively in high risk patients are proven safe and effective methods of treatment for obstetric hemorrhage. They can reduce transfusion requirements, preserve fertility and thus have the potential to reduce maternal morbidity and mortality. Obstetric departments should have protocols for management that include early referral to IR and consideration of embolization prior to surgery.

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#### Hemorrhagic disorders

# Inherited disorders of primary hemostasis

Sue Pavord

# Introduction

The management of inherited bleeding disorders during pregnancy, delivery, and the postpartum period is particularly challenging. Consideration should be given to the inheritance risk to the fetus and the bleeding risk to the mother, with appropriate multidisciplinary management plans to minimize complications for both. Good communication among the haematologists, obstetricians, anesthetists, neonatologists, and labor ward staff is required, as well as full information for the patient. This should begin prior to conception and be reviewed as pregnancy advances. Guidelines for management have been provided by a task force of the UK Haemophilia Centre Doctors' Organization.<sup>1</sup>

### **Von Willebrand disease**

Von Willebrand disease (VWD) is the most common of the inherited bleeding disorders. It is characterized by a deficiency of Von Willebrand factor (VWF), a large multimeric glycoprotein, which plays a crucial role in the first steps of thrombus formation. Pregnancy, delivery, and the postpartum period pose significant challenges to the hemostatic system, and women with VWD need to be carefully managed during these at-risk times.

### **VWF** activity

The functions of VWF are twofold:

 It mediates platelet adhesion and aggregation at sites of vascular damage, initially by forming a bridge between the platelet Gp1b receptor and the subendothelial collagen fibers, exposed by the injured vessel. • It acts as a carrier for FVIII, protecting it from proteolysis and facilitating its cofactor activity by transportation to the site of vascular injury.

The synthesis by endothelial cells and subsequent secretion from its storage site in the Wiebel Palade bodies determines the plasma concentration of VWF. A separate supply is synthesized by megakaryocytes and stored in the alpha granules of platelets, from where it is released during platelet activation, providing a rapid and local increase to levels during vessel repair. These actions are particularly important in sites of fast flowing blood and high shear forces, as occurs in the arterial circulation and the microvasculature. In these conditions, the globular VWF molecule is dragged into an elongated shape, exposing its platelet binding sites, whilst in the venous system where blood flows more slowly, fibrinogen-dependent clot formation predominates.

# **Clinical features**

The principal clinical manifestations of VWD reflect the dual function of VWF. Reduced activity of VWF, leading to impaired platelet plug formation gives rise to bleeding from mucosal surfaces, typical of the thrombocytopathies, whilst the rapid clearance of the unprotected factor VIII impedes fibrin clot formation, causing symptoms characteristic of the coagulopathies, such as prolonged bleeding after surgery. Both these effects have potentially serious implications for women in pregnancy.

### **Disease prevalence**

VWF is encoded by a gene spanning 178 kb of genomic DNA on the short arm of chromosome 12. Numerous genetic mutations, affecting VWF production, have been described<sup>2</sup> and VWD has an estimated frequency

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Subclassification	Multimeric pattern	VWF function	Specific characteristics
Type 1	Normal	Normal	Quantitative deficiency of VWF. Accounts for about 70% of all cases.
Type 2a	Absent HMW multimers	Abnormal	Impaired platelet adhesion
2b	Loss of HMW multimers through increased platelet binding	Abnormal	Increased affinity for platelets causing thrombocytopenia
2M	Normal	Abnormal	Impaired platelet adhesion
2N	Normal	Abnormal FVIII binding	Reduced affinity for FVIII with low FVIII levels due to short half-life
Type 3	Absent	Absent	Severe bleeding phenotype
HMW = high molecular	r weight.		

in the population of around 1%, based on the number of people with bleeding symptoms, low VWF, +/a positive family history. Clinical penetrance of the genetic abnormalities is variable;<sup>3</sup> in some cases they are fully penetrant, accounting for the low VWF levels and bleeding phenotype, but in others the VWF mutation may simply act as a risk factor for bleeding in combination with other modifying factors, such as platelet dysfunction or the presence of blood group O, which is typically associated with 25% lower levels than the other blood groups.<sup>4</sup> In other cases, classic VWD mutations have not been identified but VWF may still play a role. Thus, those with a clinically significant bleeding phenotype amount to only about 0.02% of the population. These patients are usually diagnosed in childhood, whereas the milder forms may not present until after significant hemostatic challenges, such as menstruation and childbirth. This probably explains the misconception in the original reports by Erik von Willebrand, describing women as twice as likely to be affected than men.

#### Classification of VWD

VWF is present in the plasma as a series of multimers, assembled from varying amounts of identical subunits. The composition of multimers, which range from 150 000 to 20 000 000 Daltons, has been used to classify VWF into its different subtypes (Table 14.1). Its adhesive function is largely dependent on the high molecular weight (HMW) multimers, which are released during platelet and endothelial cell activation.

Type 3 disease is characterized by unmeasurable VWF levels and consequently, severely low FVIII levels, with median FVIII levels being around 4%. Thus,

in addition to clinical features of impaired primary hemostasis, these patients behave like those with moderate hemophilia, with potential for spontaneous joint and muscle bleeds. Transmission is autosomal recessive with patients being homozygous or double heterozygous for the abnormal VWF gene, inherited from asymptomatic parents. Prevalence in the UK is around 1 per million, being most frequent in communities where consanguinous marriages are common.

#### Laboratory evaluation

Routine coagulation screening tests including the prothrombin time (PT) and activated partial thromboplastin time (APTT) do not detect VWD unless the factor VIII level is below normal, prolonging the APTT. Specific assays for FVIII activity and VWF antigen and activity are available, the latter including Ristocetin cofactor activity and collagen binding assay. Platelet function can be assessed by PFA-100, which measures the time taken for platelets to close over a hole in a collagen membrane coated with ADP or epinephrine. However, all assays are limited in their specificity and sensitivity and none show good correlation with the severity of bleeding. Furthermore, levels can be influenced by external factors such as physical and mental stress. Thus, despite the numerous tests available, the diagnosis of VWD and its subclassification is often difficult.

#### Hormonal influences on levels in pregnancy

Levels of von Willebrand factor and factor VIII start to rise from 6 weeks' gestation, increasing progressively throughout pregnancy to three to five times baseline levels by delivery.<sup>5</sup> This is due to increased synthesis of VWD, although the cause for the increase in FVIII is not entirely clear but in part reflects improved stabilization by VWF. This rise is beneficial to many patients with type 1 VWD, in whom normal levels are often reached by delivery. However, those with starting baseline levels of <15 IU/dL may fail to reach normal values<sup>6</sup> and in patients with type 2 disease, where the molecule functions abnormally, the condition may not improve and may even deteriorate.<sup>7</sup> This is particularly evident in type 2b where the rise in dysfunctional VWF protein enhances abnormal platelet binding and exacerbates thrombocytopenia. In patients with type 2N disease, factor VIII levels tend to remain low because of impaired binding by the abnormal VWF and patients with type 3 disease show little or no rise in VWF.<sup>8</sup>

A study of VWF levels in 248 healthy women, showed that they remained elevated for 1-3 days post-partum and then returned to baseline by day 7-21.9

Factor VIII and VWF levels are also influenced by thyroxine, which shows a physiological rise in its bound form during pregnancy. Hypothyroidism may be associated with clinical and laboratory features of VWD which corrects with thyroid replacement. <sup>10</sup>

#### **Obstetric complications**

#### Maternal bleeding

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Women with VWD have an increased risk of bleeding events and even death during childbirth.<sup>11</sup> Although the physiological rise in VWF and FVIII protects many women with mild type 1 disease during delivery, they remain vulnerable in early pregnancy and in the postpartum period. Studies have found:

- One-third of women with VWD have bleeding during their first trimester.
- 15%–30% of women with VWD have primary postpartum hemorrhage.
- Delayed postpartum bleeding occurs in 20%–25% of women with VWD.
- There is a relatively high frequency of perineal hematoma, a normally rare complication of vaginal birth.
- The risk of receiving a blood transfusion is increased fivefold
- Maternal mortality rate is ten times higher than that for women without the condition.

 Table 14.2
 Pre-pregnancy management of WWD

- Reassess severity of clinical bleeding tendency including previous responses to hemostatic challenges.
- Check baseline investigations if not already known
- Establish response to DDAVP
- Obtain consent for use of plasma products after full counseling of risks
- Where plasma-derived products have been received in the past, the presence of transfusion transmitted infection should be excluded.
- Vaccinate against hepatitis A and B if not already immune
- Check hemoglobin and serum ferritin and give oral supplements as necessary
- All should receive counseling about risks of increased bleeding, particularly in the postpartum period and particularly for women with type 2 or 3 VWD
- A management plan should be discussed with all patients.
- All patients should be offered genetic counseling as they are at risk of delivering an affected child
- All should receive explanation regarding evaluation of the infant after delivery

#### Pregnancy outcomes

Women with VWD are no more likely to experience premature labor, placental abruption, fetal growth restriction or intrauterine fetal death.<sup>11</sup> Early miscarriage has not been shown to be any more frequent than in the general population, but can be complicated by significant bleeding.<sup>8,12</sup>

# Pregnancy management for women with VWD

The safe management of women with VWD requires good communication between the hematologist, obstetricians, anesthetists, neonatologists, and labor ward staff. The patient should be fully informed of potential bleeding risks and the plan for management of pregnancy, delivery, and the postpartum period. This should begin prior to conception and should be reviewed as pregnancy advances (Table 14.2).

#### Ante-natal management

In view of the physiological rise in factor VIII and VWF during pregnancy, most women with mild type 1 VWD achieve levels above 50 IU/dL, the lower limit of the normal range outside of pregnancy, and can be safely managed in standard obstetric units in collaboration with hemophilia center staff. Women with types 2 and 3 VWD, or moderate or severe type 1, or a history of severe bleeding, should be referred for pre-natal care and delivery to a center where there are specialists in high risk obstetrics, as well as a Hemophilia Center. Laboratory, pharmacy, and blood bank support is also essential.

For all types of VWD, levels should be checked routinely at booking, 28 weeks and if still abnormal, 34 weeks' gestation. If an adequate rise is demonstrated, only a third trimester sample may be necessary for subsequent pregnancies, unless earlier interventions are required.

Levels are always needed prior to invasive procedures such as chorionic villus sampling, amniocentesis, or cervical cerclage. If VWF activity or FVIII levels are <50 IU/dL, women should receive prophylaxis. DDAVP should be used in preference to plasma derived products in type 1 VWD, to avoid potential for transfusion transmitted infections (Table 14.3).

#### **DDAVP** in pregnancy

DDAVP (1-deamino-8-D-arginine vasopressin) a synthetic derivative of antidiuretic hormone that acts specifically through type 2 vasopressin receptors, stimulates release of ultralarge VWF multimers from storage in the Wiebel Palade bodies of the endothelial cells. This is not a direct stimulatory effect, but is mediated through intracellular calcium mobilization and cyclic adenosine monophosphate. Administration has traditionally been by slow intravenous infusion, over 20 minutes, of 0.3 µg per kilogram of body weight, although a subcutaneous preparations are now commonly used, with similar efficacy and fewer side effects. Intranasal preparations are also available. Administration results in a three to fivefold increase in both VWF and factor VIII, within 30-60 minutes, lasting for 8-10 hours. To assess the response to DDAVP, VWF activity levels and factor VIII should be measured before administration and again at 1 and 4 hours after, to determine peak levels and clearance rate, respectively.

#### Table 14.3 Ante-natal management of VWD

- Check VWF antigen and activity and FVIII levels at booking, 28 and if still abnormal, 34 weeks' gestation and prior to any invasive procedure.
- In patients with type 2B VWD, the platelet count should also be monitored. Platelet transfusions, as well as VWF factor replacement may sometimes be required for bleeding or to cover surgical procedures and spontaneous miscarriage.
- Aim for FVIII and VWF:RCo activity levels of ≥ 50% to cover surgical procedures or spontaneous miscarriage.
- Treat with desmopressin in preference to coagulation factor concentrates whenever possible, checking pre- and post-treatment VWF activity levels and factor VIII.
- Distribute action plan for acute bleeding events, to hematology and obstetric staff and ensure patient is given an emergency number for contact.

DDAVP is generally thought to be safe for mother and fetus<sup>13</sup> and previous concerns regarding the potential risk of uterine contractions or neonatal hyponatremia have diminished, in view of its selective effect on V2R receptors. Fluid intake should be restricted to 1 liter for the following 24 hours, to prevent maternal hyponatremia caused by water retention from the antidiuretic effect. An in vitro placenta model showed that DDAVP, at therapeutic dose, did not cross the placenta in detectable amounts.<sup>14</sup>

The advantages of DDAVP are its low cost, unlimited availability, and most importantly, the avoidance of blood products. However, there are many situations where DDAVP will be contraindicated or ineffective and plasma products necessary (Table 14.4). In these patients, prophylactic treatment with a clotting concentrate containing Factor VIII and von Willebrand Factor should be considered to raise levels >50 IU/dL for ante-natal procedures and childbirth. Patients with type 2B disease may also require platelet transfusion if thrombocytopenia is severe.

### Coagulation factor replacement

There are several licensed plasma-derived VWF/FVIII products available. The spectrum of VWF HMW

Table 14.4 Situations where DDAVP may not be suitable

Patients with insufficient baseline levels	Patients with baseline VWF or FVIII levels of less than 15 IU/dI may not achieve post-infusion levels, which are sufficient to control or prevent bleeding.
Some subtypes of Type 1, including Vicenza subtype	Some subtypes of type 1 VWD show decreased survival of endogenously produced VWF following DDAVP compared with normal survival of exogenously administered VWF.
Previous intolerance or severe adverse effects	During intravenous infusion, hypotension, headache and facial flushing are common but generally mild. Blood pressure should be monitored during and after infusion.
Known cardiovascular disease, pre-eclampsia or unstable blood pressure	There are anecdotal reports of myocardial and cerebral infarction and DDAVP should be avoided in patients known to have arterial disease.
Tachyphylaxis after repeated doses	The response to DDAVP diminishes after repeated doses.
Type 2 VWD (except some cases of 2M)	DDAVP is less likely to correct the abnormality in type 2 VWD, although there may be a transient shortening of the bleeding time. Because the molecule is abnormal, the usual increase in the amount of VWF protein following DDAVP is unlikely to improve function.
Type 2B	The heightened and spontaneous binding of the abnormal VWF molecule to normal platelets may be aggravated by the rise in VWF levels after DDAVP, increasing platelet clearance from the circulation and exacerbating thrombocytopenia.
Type 2N	DDAVP also causes release of Factor VIII from stores. However, due to the abnormal VWF : FVIII binding, the response to DDAVP is shortened to a median of 3 hours.
Type 3 VWD	These patients lack releasable stores of VWF and do not respond to DDAVP.

multimers and ratio of VWF:RCo/FVIII activity differs between them, but this does not appear to cause a difference in efficacy.<sup>15</sup> They are available as lyophilized powders and, after reconstitution in water, can be administered by slow bolus intravenous injection. Treatment is usually given 1 hour pre-operatively. Pre-and post-levels should be checked and therapeutic levels of FVIII and VWF:RCo >50 IU/dL maintained until hemostasis is secure. For most ante-natal procedures, a single pre-operative treatment is sufficient, but in some cases a second dose may be required at 12–24 hours, depending on the nature of the procedure and the measured levels.

#### Intrapartum management

Although there are no large prospective studies that correlate VWF:RCo and FVIII levels with the risk of bleeding at the time of childbirth, the opinion of experts is that levels above 50 IU/dL should be achieved before vaginal delivery or Cesarean section.<sup>1,16</sup>

Neonates are at risk of intracranial hemorrhage and cephalhematomas during labor and delivery. The increase in FVIII and VWF, induced by the stress of labor, provides some protection for babies with mild type 1 disease but in more severe types, trauma to the baby should be minimized by avoiding extracephalic

#### Table 14.5 Intrapartum management

- Allow spontaneous labor and normal vaginal delivery, if no other obstetric concerns, to minimize risk of intervention.
- If FVIII or VWF:RCo activity levels <50 IU/dl at the last check, the test needs to be repeated.
- If levels <50 IU/dL, treat with DDAVP if known responder, otherwise plasma-derived factor concentrate. Treatment should be given at the onset of established labor and pre- and post-treatment levels should be obtained.
- Avoid prolonged second stage of labor, with early recourse to Cesarean section if necessary, to reduce risk of trauma to mother and baby and risk of uterine atony.
- For fetuses at risk of having type 2 or 3 disease or moderately severe type 1, avoid fetal blood sampling, fetal scalp monitoring, Ventouse delivery and mid-cavity or rotational forceps.
- Avoid aspirin and consider alternatives for NSAIDs. Intramuscular injections may be suitable if FVIII and VWF activity and PFA-100 are in the normal range.
- Active management of the third stage of labor and early suturing of episiotomy and lacerations.

version, Ventouse delivery, fetal blood sampling, scalp electrodes, and rotational forceps.

#### Analgesia

There is no consensus on the levels that are safe for regional anesthesia but if FVIII and VWF activity levels are > 50 IU/dL, regional anesthesia may be undertaken. Consideration should also be given to the levels at the time of catheter removal and repeat treatment given beforehand if necessary. Intramuscular injections are not contraindicated if FVIII and Von Willebrand activity are shown to be normal, but attention should be given to the prolonged antiplatelet effect of non-steroidal anti-inflammatory drugs, being 2-3 days for indomethacin and diclofenac. Aspirin has an irreversible effect on platelets, but following ibuprofen normalization of platelet aggregation occurs within 24 hours. Before delivery, all women with VWD should have the opportunity to discuss analgesia with an anesthetist.

#### Table 14.6 Postpartum management

- Ensure careful surgical hemostasis and effective uterine contraction in all cases.
- Repeat VWF activity levels and Hb prior to discharge.
- Give prophylactic tranexamic acid.
- For patients with significantly low pre-pregnancy levels, consider DDAVP if known responder.
- For types 2 and 3 disease or severe type 1, ensure VWF activity levels are maintained at >50 IU/dL for 3 days following vaginal delivery or 5 days if Cesarean section has been performed.
- Maintain regular contact with the patient after discharge and encourage them to report excessive blood loss.
- Consider use of combined oral contraceptive pill if excessive bleeding is ongoing despite prophylaxis. This is particularly beneficial to patients with type 1 disease due to the associated increase in functional VWF protein.

### Postpartum management (Table 14.6)

The postpartum fall in FVIII and VWF levels is variable, occurring between 24 hours and 2 weeks after birth. In normal pregnancies, the median duration of bleeding after childbirth is 21 to 27 days, with delayed or secondary postpartum hemorrhage occurring in fewer than 1% of cases. In women with VWD this is much more common, affecting 20%-25% of cases. In addition, there are multiple cases of postpartum hemorrhage that have occurred despite prophylaxis. The average time of presentation of postpartum hemorrhage in women with VWD is 10-20 days after delivery.<sup>17</sup> Women with mild type 1 disease should be encouraged to report excessive bleeding but, for more severe cases, hemoglobin should be monitored and regular contact with the patient maintained for several weeks

#### Tranexamic acid

Patients with mild type 1 disease can usually be safely managed with tranexamic acid alone. This is a lysine analog, which saturates lysine binding sites on plasminogen and prevents them from interacting with the fibrin surface, thus inhibiting fibrinolysis. It has proven efficacy in reducing blood loss, without increasing thrombotic risk. It is contraindicated in patients with hematuria and doses should be reduced in renal failure.

Tranexamic acid crosses the placenta and should generally be avoided during pregnancy, although it has been used to treat ante-natal bleeding in a limited number of cases without adverse fetal effects reported. Traces have been found in breast milk but this has not been associated with changes to neonatal fibrinolytic activity.

#### DDAVP and plasma products

For patients with significantly low pre-pregnancy levels, DDAVP can be given at the time of cord clamping, although as the peak effect is 40 to 60 minutes after administration, it may be more beneficial if administered during the second stage of labor or immediately before Cesarean section. DDAVP may be used to raise factor levels in responders, but care must be taken in its administration at the time of childbirth and extra fluids should be avoided. Tranexamic acid is a useful adjunct to desmopressin, particularly as it counteracts the mild fibrinolytic effect of DDAVP related to the associated rise in tissue plasminogen activator.

All patients with type 3 and most with type 2 disease require plasma derived VWF concentrates, to maintain levels >50 IU/dl for at least 3 days after vaginal delivery and 5 days following Cesarean section.<sup>1</sup> These patients also usually require prolonged administration of tranexamic acid and close monitoring (Table 14.6).

# Potential complications of factor replacement

#### Transfusion transmitted infections

To minimize risk of viral transmission, two independent and effective steps which complement each other in their mode of action, are incorporated into the plasma product manufacturing process. These include dry heat treatment at  $80 \,^{\circ}$ C for 72 h, pasteurization at  $60 \,^{\circ}$ C for 10 h, or solvent detergent (SD) treatment with tri(n-butyl) phosphate and Tween-80 or Triton X. A third step of nanofiltration has been introduced for some products. No cases of HIV, hepatitis B, and hepatitis C have occurred with products inactivated by the currently used processes; however, some viruses, such as parvovirus B19, are relatively resistant to all these inactivation techniques. Parvovirus infection can have serious consequences in pregnancy, being associated with hydrops fetalis and intrauterine fetal death. In addition, new emerging infections as well as those such as vCJD, capable of crossing between species, will remain potential infective risks.

#### Inhibitor formation

Alloantibodies to exogenous VWF are a rare complication of treatment and more likely to occur in patients with type 3 disease, associated with large or complete VWF gene deletions or stop codons. The prevalence in these patients is around 8%. The antibodies render replacement therapy ineffective and can cause severe anaphylactic reactions.

#### Thrombosis

Excessive accumulation of FVIII may arise after repeated administration of Von Willebrand factor containing concentrates. Resulting thrombosis has been reported but mostly these cases were peri-operative without use of monitoring.

It is advised that when using VWF containing concentrates peri-operatively, monitoring of FVIII:C and VWF:RCo should be used in deciding dosing of therapy and excessive FVIII levels avoided. Mobilization and hydration should be encouraged and anti-embolic or stockings considered. Pharmacological thromboprophylaxis should generally be avoided, particularly with type 3 disease.

#### Neonatal management

Being an autosomal dominant condition in most cases, the risk of transmission is 50%. However, the variable penetrance of type 1 VWD results in only around one third being clinically affected. Type 3 disease is autosomal recessive giving a 25% risk if a previous sibling has been affected. The risk of peri-natal intracranial hemorrhage is low, even in neonates with VWD type 3. Nevertheless newborns at risk of moderate and severe types need to be tested for VWD using cord blood and assessed to exclude intracranial hemorrhage. For diagnostic purposes, however, levels are unreliable in most cases, being artificially low due to the gestational age or increased from the stress of labor and delivery and need repeating at 6–12 months when adult values are reached (Table 14.7).

#### Table 14.7 Neonatal management

- If severe disease phenotype is expected, a cord sample should be tested for FVIII level and VWF activity. The limitations of testing at this stage should be understood.
- Babies with type 2B disease may require platelet transfusion if there is severe thrombocytopenia or bruising/ bleeding manifestations.
- Intramuscular vitamin K should be avoided until results are known and given orally if necessary. Any heel prick tests should have pressure applied afterwards for 5 minutes.

# Inherited disorders of platelet function

There are a number of platelet function disorders and for most cases management requires assessment of maternal bleeding phenotype with consideration given to use of platelets to cover ante-natal procedures and delivery, DDAVP may be used if response has been previously demonstrated. Patients with bleeding histories should be given tranexamic acid for 5–14 days postpartum. If there is a neonatal risk of platelet dysfunction, traumatic delivery should be avoided and if thrombocytopenia is a feature of the condition, a cord sample should be taken at birth. Special mention is given to Glanzmann's thrombasthenia and Bernard– Soulier syndrome.

#### Glanzmann's thrombasthenia

Glanzmann's thrombasthenia is a congenitally acquired platelet disorder with an autosomal recessive mode of inheritance. Platelets are normal in number, but their ability to aggregate is reduced due to loss of the surface receptor glycoprotein IIbIIIa. Pregnancy and delivery are rare in these patients but have been associated with a high risk of severe postpartum hemorrhage.

Recombinant activated factor VIIa is licensed for use in patients with this disorder. In pharmacological concentrations, FVIIa is capable of binding to the surface of activated platelets and improving thrombin generation to enhance adhesion and aggregation of platelets lacking GPIIb/IIIa. The usual dose given is 90 mcg/kg 2–3 hourly. Bleeding can also be successfully prevented by transfusion of platelets before and after delivery. However, platelet transfusion can stimulate isoantibody formation against glycoprotein IIb–IIIa, resulting in a decreased efficacy of subsequent transfusions. A single donor platelet preparation should be used in preference to pooled platelet transfusion to reduce this risk and where possible should be HLA matched.

Delayed bleeding up to 2–3 weeks postpartum has been reported and in these circumstances, DDAVP and tranexamic acid are useful to reduce platelet transfusion requirements.

#### Neonatal management

Unless the father has the same condition, the fetus is heterozygous, with platelets carrying specific paternal antigens that are not present on the maternal platelets and thus are capable of causing maternal alloimmunization. Transplacental transfer of the maternal antiplatelet immunoglobulin G antibodies can lead to severe isoimmune neonatal thrombocytopenia and a risk of intracranial hemorrhage in the fetus. Women should be monitored for the development of platelet specific antibodies.

#### Bernard–Soulier Syndrome

The Bernard–Soulier syndrome (BSS) is a rare autosomal recessive bleeding disorder, characterized by impaired platelet aggregation with ristocetin and a normal to decreased number of unusually large platelets whose membranes lack glycoprotein complex GP Ib/IX/V. In some patients the disease can go unrecognized until the third or fourth decade.

Four different features of BSS may contribute to the hemorrhagic diathesis: thrombocytopenia, abnormal platelet interaction with vWF, impaired platelet interaction with thrombin, and abnormal platelet coagulant activity. BSS is caused by genetic defects in the genes of GPIb $\alpha$ , GPIb $\beta$ , GPIX or GPV. This variety of mutations could explain the heterogeneity of the syndrome; however, the clinical manifestation may even differ in consecutive pregnancies of the same patient.

The main complications encountered in reported cases have been antepartum hemorrhage excessive intra-operative bleeding and immediate and delayed postpartum hemorrhage, development of maternal antiplatelet antibodies leading to fetal intracranial hemorrhage and neonatal alloimmune thrombocytopenia.

#### Management

Management is similar to that for Glanzmanns thrombasthenia and includes the judicious and timely use of platelet transfusions to prevent bleeding whilst minimizing the risk of platelet refractoriness. Regional anesthesia should be avoided and postpartum tranexamic acid and DDAVP prescribed as necessary.

#### **Neonatal management**

The risk to the fetus is unpredictable but thrombocytopenia can occur due to heterozygosity of the platelet function disorder and, more significantly, fetomaternal alloimmunization, which may be encountered even in the absence of demonstrable antibodies. Thus the management may follow that for fetal/neonatal alloimmune thrombocytopenia. (See Chapter 5.)

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# Section 5 Chapter

#### Hemorrhagic disorders

# **Inherited coagulopathies**

Sue Pavord

# Hemophilia

# Introduction

Hemophilia is characterized by a deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B), both key components of the intrinsic pathway of the coagulation cascade. The gene is carried on the long arm of the X chromosome, so males are clinically affected and females are carriers. Female carriers may also have low factor levels due to skewed X chromosome inactivation, giving rise to an increased tendency to bleed. Thus management of pregnancy requires the assessment of bleeding risk for both mother and baby, with particular attention given to multidisciplinary planning and co-ordination of healthcare professionals at the time of, and after, delivery.

# **Disease incidence**

Hemophilia A and B occur with an incidence of around 1:5000 and 1:10 000 male births, respectively. The severity of the disease runs true in families and, if the family history is known, the bleeding risk to male offspring can be largely predicted (Chapter 16). However, 40%–50% of cases are sporadic and unexpected with no family history of the condition.

# **Clinical features**

The hallmark of the condition is hemarthrosis, resulting in progressive arthropathies requiring joint fusions or joint replacement to alleviate pain. The bleeding risk correlates with the level of coagulation factor (Table 15.1). Patients with severe hemophilia or those with recurrent joint bleeds require prophylaxis with factor concentrate twice (factor IX) or thrice (factor VIII) weekly with an aim to keep trough levels at, or above, 5% and avoid spontaneous bleeds. Acute bleeds require immediate treatment to minimize joint and soft tissue damage. After a period of training and assessment of competency, factor concentrate can be selfadministered using home stocks, although many children on prophylaxis have difficulty with venous access and require insertion of portacaths, which are often complicated by recurrent infections.

# Hormonal influences on levels in pregnancy

Levels of factor VIII increase from 6 weeks' gestation, to two to three times baseline by term. Factor IX levels are relatively unaltered.<sup>1</sup>

# **Obstetric complications**

# Maternal bleeding

Female carriers of hemophilia typically have half levels of factor VIII/IX. Unbalanced lyonization, where there is uneven X chromosome inactivation, may result in significantly lower levels. For carriers of hemophilia A, the pregnancy-induced rise in factor VIII level alleviates any potential problems for childbirth, although they remain vulnerable in early pregnancy and those with baseline levels <15 IU/dL may not achieve normal levels by delivery. Women with low factor IX levels remain at risk of bleeding throughout pregnancy.

### **Pregnancy outcomes**

Miscarriage and placental insufficiency syndromes are not increased. The main risk is to the neonate at the time of delivery, as well as the maternal bleeding risk, particularly postpartum, for those mothers with low factor levels.

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۲able 15.1	Severity o	f hemophilia	according to	o factor level
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Factor level (% activity)	Severity of clinical condition	Bleeding risk
<1	Severe	Spontaneous joint and muscle bleeds
1–5	Moderate	Joint and muscle bleeds mainly after trauma. Occasional spontaneous bleeds
>5	Mild	Trauma/surgery induced bleeding

#### **Neonatal risk**

The most significant potential complication for the neonate is intracranial hemorrhage (ICH), particularly following instrumental or traumatic birth. The risk is approximately 50 times greater than for the general population and affects around 4% of all hemophilia boys,<sup>2</sup> although it is clearly highest in those with severe hemophilia or where the disease is unexpected and no preventative strategies, neonatal surveillance, or considered management plan are in place.

ICH is most often associated with extracranial hemorrhage (ECH) after trauma and any significant ECH in a newborn should raise the suspicion of underlying coagulopathy and ICH. Common complications are cephalhematomas and abnormal bleeding after injection or venepuncture. Other reported events are umbilical bleeding, hematuria and retro-orbital bleeding.

#### **Pre-pregnancy management**

All women with a family history of hemophilia should be assessed for carrier status, including pedigree profile and calculation of statistical risk, baseline factor levels and genetic mutation analysis where possible. (See Chapter 16.)

- Carriers should receive effective counseling regarding their risk of
- (a) bleeding, particularly in the postpartum period;
- (b) delivering an affected male.

These risks need to be determined and fully discussed with the patient, including options for pre-natal diagnosis. Appropriate multidisciplinary management plans should be agreed to minimize complications for both mother and baby. Table 15.2 Ante-natal management of hemophilia carriers

- Check factor levels at booking, 28 and if still abnormal, 34
   weeks' gestation or prior to any invasive procedure.
- Aim for FVIII /FIX levels of ≥ 50 U/dL to cover surgical procedures or spontaneous miscarriage.
- For carriers with low factor VIII levels DDAVP may be used but recombinant factor concentrate is required to raise factor IX levels.

# Ante-natal management (Table 15.2)

- All women should be offered pre-natal diagnosis (Chapter 16), but women who do not wish for this should to have the fetal sex determined by ultrasound when the anomaly scan is performed.
- Factor levels should be checked at booking, 28 and if still abnormal, at 34 weeks' gestation. Factor VIII levels usually rise in pregnancy, but factor IX tends to remain constant. If an adequate rise in Factor VIII is demonstrated, only a third trimester sample may be necessary for subsequent pregnancies, unless earlier interventions are required.
- Factor levels should also be checked prior to potentially hemorrhagic events such as invasive diagnostic procedures, spontaneous abortion, or termination of pregnancy. If levels are <50 IU/dL, women should receive prophylaxis.
- DDAVP can be used to raise factor VIII levels by around three times, but recombinant clotting factor concentrate is needed for factor IX deficient women and may be required for those with factor VIII levels below 15 IU/dL, as the response to DDAVP may be insufficient. Pre- and post-treatment levels should be checked and therapeutic levels maintained for a suitable time period depending on the procedure.

### Intrapartum management (Table 15.3)

Although there are no large prospective studies that correlate FVIII or IX levels with the risk of bleeding at the time of childbirth, the opinion of experts is that levels should be above 50 IU/dL. If treatment is required, the level should be brought to 100 U/dL pre-delivery and maintained at >50 U/dL for at least 3–5 days. Excessive treatment should be avoided due to the risk of thrombosis and thus careful titration and monitoring of levels is required. Table 15.3 Intrapartum management of hemophilia carriers

- If FVIII/IX levels <50 IU/dL at the last check, the test needs to be repeated on arrival in labor
- Recombinant factor concentrate is required to raise factor IX levels. Treatment should be given at the onset of established labor and pre and post treatment levels should be obtained.
- Allow spontaneous labor and normal vaginal delivery, if no other obstetric concerns, to minimize risk of intervention.
- Avoid prolonged second stage of labor, with early recourse to Cesarean section if necessary, to reduce risk of trauma to the baby.
- Avoid fetal blood sampling, fetal scalp monitoring, Ventouse delivery, and mid-cavity forceps, or forceps involving rotation of the head.
- Active management of the third stage of labor and early suturing of episiotomy and lacerations for patients with low factor levels.
- Regional anesthesia has been shown to be safe if the coagulation screen is normal and factor levels are >50 IU/dL treatment is required but levels must be checked prior to removal of the catheter as they may fall rapidly in the postpartum period.
- If maternal FVIII/IX levels < 50 IU/dL, caution with non-steroidal anti-inflammatory drugs and intramuscular injections.

Neonates are at risk of intracranial hemorrhage and cephalhematomas during labor and delivery. The risk is not increased by vaginal delivery but the second stage of labor should not be prolonged and early recourse to Cesarean section may be required. Trauma should be minimized by avoiding extra cephalic version, Ventouse delivery, fetal blood sampling, scalp electrodes, and rotational forceps. The cut-off value for predicted factor VIII or IX, above which no birth restrictions are necessary, has not been defined, although mild hemophilia is unlikely to be associated with severe bleeding at birth. Furthermore, the increase in FVIII, induced by the stress of labor, provides some protection for babies with mild hemophilia A. Female carriers have a small risk of extreme lyonization and low factor levels, but this needs to be weighed up against the possibly greater risks of withholding instrumental delivery and invasive fetal monitoring. As Factor IX levels are lower at birth and are not increased by the stress of delivery, female carriers of severe Hemophilia B are theoretically at higher risk.

#### Analgesia

There is no consensus on the levels required for regional anesthesia but this is generally considered to be safe if FVIII /IX levels are > 50 IU/dL.<sup>3,4</sup> Consideration should also be given to the levels at the time of catheter removal and repeat treatment given beforehand if necessary. Intramuscular injections and nonsteroidal anti-inflammatory drugs are not contraindicated if factor levels are normal. All women with low factor levels should have the opportunity to discuss analgesia with an anesthetist prior to delivery.

#### Postpartum

Postpartum blood loss should be assessed as factor levels may fall rapidly after delivery. Levels should be maintained at >50 IU/dL for at least 3 days, or for 5 days if Cesarean section has been performed.<sup>5</sup>

DDAVP and/or tranexamic acid may be useful to prevent excessive postpartum bleeding. These agents are described in Chapter 14.

#### Neonatal management

Affected babies may suffer bruising and bleeding at venepuncture and heel prick sites and even spontaneous organ or joint bleeding. To identify neonates at risk, a cord sample should be taken for coagulation factor assay and the result must be known before the patient leaves hospital. Female babies at risk of being carriers for severe hemophilia may also require a cord sample, as very low levels may occur due to severely unbalanced lyonization. However factors VIII and IX from the newborn do not reflect the true baseline level and may need repeating at 6 months of age, when adult values are reached.

Venepunctures and intramuscular injections, including vitamin K should be avoided until the cord factor level is known. Vitamin K could be given orally if the results are delayed. Severely affected babies should receive an ultrasound scan of the head to assess for signs of intracranial hemorrhage (ICH), particularly if delivery was traumatic or labor prolonged. This investigation is non-invasive, but lacks sensitivity, particularly for subdural bleeds, which is the commonest site of ICH in the neonate. The mean age for occurrence of ICH is 4.5 days,<sup>2</sup> when the baby is likely to be at home. Hence parents and midwives should be informed of the early signs of ICH; poor feeding, listlessness, vomiting, and seizures, so that treatment can be administered without delay. To date, there is no evidence for the benefit of prophylactic factor concentrate, about which the risk of inhibitor development is debated. However, it may be justified in selected cases, such as prematurity or traumatic delivery, where the risk of ICH is greater.

#### **Factor XI deficiency**

#### Introduction

Factor XI is an important component of the intrinsic coagulation pathway, playing a key role in the amplification of initial thrombin production, via activation of factor IX. The additional amount of thrombin activates thrombin-activatable fibrinolysis inhibitor (TAFI), which consolidates the fibrin clot and protects it from degradation by fibrinolysis. Thus deficiency of Factor XI is manifest mostly by injury or surgery-related bleeding at sites which are prone to local fibrinolysis, such as the nose and genitourinary tract. Women with factor XI deficiency are at risk of menorrhagia and bleeding in relation to childbirth.

#### **Disease incidence**

The inheritance of Factor XI deficiency is autosomal. It is most common amongst Ashkenazi Jews, where the estimated heterozygosity rate is as high as 8%.<sup>6</sup> The incidence in the non-Jewish population is reported to be around 1:100 000, although this is likely to be an underestimate, as it may frequently remain undetected as routine coagulation assays may be normal in heterozygotes and there may be no bleeding history.

The predominant mutations in Ashkenazi Jews are a Glu117stop codon in exon 5 designated type II, and a Phe283Leu mutation in exon 9 designated type III. Homozygotes for type II and type III mutation have factor XI activities < 1 U/dL and 8–15 U/dL, respectively, with compound heterozygotes for type II and III having factor XI levels between these values.<sup>7</sup> In non-Jewish populations, rapidly increasing numbers of mutations and polymorphisms have been reported, now reaching over 80. For the majority of these, the level of FXI antigen has not been reported. **Table 15.4** Pre-pregnancy management of women withFactor X1 deficiency

- Assess clinical bleeding tendency and coexistence of confounding factors such as VWD or platelet dysfunction.
- Offer pre-natal diagnosis where there is a risk of severe deficiency and the mutation is known.
- Discuss potential maternal bleeding risk and options for management.
- Consent for use of blood products if necessary and ensure hepatitis A and B immunity.

#### **Clinical features**

The bleeding tendency in FXI-deficient individuals is highly variable.<sup>8</sup> Factor XI activities < 15 U/dL have been designated as severe deficiency, although bleeding is not closely correlated with factor levels<sup>9</sup> as it is with hemophilia A and B. Neither does the abnormal genotype causing the condition seem to bear any relationship to bleeding tendency, which is inconsistent amongst family members. Indeed, in most patients spontaneous bleeding, as well as bleeding after hemostatic challenge, does not occur and phenotype may depend on other associated factors, such as coexistence of mild von Willebrand disease.

#### Hormonal influences on factor levels

Factor XI levels usually remain constant in pregnancy, but studies have shown inconsistencies in levels with increases or decreases as pregnancy advances.<sup>10</sup>

#### **Obstetric complications**

The main risk in pregnancy is of uterine hemorrhage during invasive procedures, miscarriage, or postpartum. Patients with FXI levels  $<15 \text{ IU dL}^{-1}$  have a 16%– 30% risk of peripartum bleeding<sup>11</sup> and this has been confirmed to almost exclusively affect those with a predetermined bleeding phenotype.<sup>10</sup> Thus it is important to attempt to ascertain, by thorough history taking, which patients are at risk of bleeding, so that ante-natal procedures, childbirth, and the postpartum period can be managed appropriately (Table 15.4).

#### Ante-natal management

As it is often not feasible to check levels in an acute situation, routine monitoring should be carried out

 Table 15.5
 Ante-natal management of women with Factor X1

 deficiency
 Image: Comparison of the second secon

- Check levels at booking, 28 and 34 weeks' gestation and prior to invasive procedures.
- Patients with severely low levels or a positive bleeding history should be given prophylaxis to cover invasive procedures.
- Other patients can be managed expectantly with close observation and treatment available on standby should bleeding occur.

at booking, 28, and 34 weeks. Whilst low factor levels cause prolongation of the APTT, test reagents vary in their sensitivity to factor XI levels and a normal APTT does not exclude mild deficiency. This is particularly so in pregnancy where the increase in factor VIII may normalize the APTT even when factor XI is reduced. Thus a specific coagulation factor assay is required (Table 15.5).

#### Treatment options to cover delivery and ante-natal procedures

Most patients can be managed expectantly,<sup>12</sup> but those with severely reduced levels or a positive bleeding history require prophylaxis for invasive ante-natal procedures, miscarriage, and delivery.

Factor XI concentrate provides effective cover and has a mean half-life of 52 hours, so a single dose is usually sufficient. However, it is associated with a potential risk of transfusion transmitted infections, common to all plasma products, as well as an increased risk of thrombosis due to coagulation activation.<sup>13</sup> The increased thrombotic risk may be further exaggerated in pregnancy where there is already activation of coagulation and increased thrombin generation.

Fresh frozen plasma contains variable amounts of factor XI and patients with severe deficiency are unlikely to achieve levels above 30 IU dL<sup>-1</sup>. However, it is helpful for milder cases and involves less donor exposure than factor XI concentrate. A dose of 15–20 mL/kg is effective, but the risk of fluid overload must be considered.

Monitoring of the response to FFP or factor XI concentrate is important and, due to the thrombogenicity of the latter, levels should not be allowed to exceed 70 IU dL<sup>-1</sup>. A recent study found inhibitor development, after transfusion of plasma derived factor XI, in **Table 15.6**Intrapartum management of women with FactorX1 deficiency

- An on-demand policy can be advocated, including for those with severely low levels, during and after vaginal delivery.
- Most patients undergoing Cesarean Section can be managed expectantly, but those with severe deficiency should be given prophylaxis.
- Measures should be taken to avoid unnecessary trauma to the baby during delivery.
- The third stage of labor should be actively managed.

33% of patients with severe factor XI deficiency due to homozygous type II mutation (which accounts for approximately 25% of Jewish patients with severe factor XI deficiency).

Recombinant factor VIIa (rFVIIa, NovoSeven<sup>®</sup>, Novo Nordisk Ltd, Bagsvaerd, Denmark) is currently being assessed as a possible alternative to plasmaderived FXI replacement and avoids the risk of bacterial or viral infections, transfusion-related lung injury and development of inhibitors to factor XI. It is as yet unlicensed for use in this setting and the optimal dose has not been ascertained. A suggested dose for minor procedures is 90  $\mu$ g/kg administered intravenously before surgery and 4 h later. For major surgery, 2 hourly infusions are necessary due to the short half-life of the product.

#### Intrapartum management

Around 70% of patients do not experience bleeding problems at delivery. This may be due to increased levels of coagulation factors, including factor VIII and fibrinogen, at term. Also, the pregnancy-associated reduction in fibrinolytic activity, due to decreased levels of tissue plasminogen activator and urokinase and an increased level of plasminogen activator inhibitor-2, contributes to hemostasis. Thus, even for those with severe factor XI deficiency an on-demand policy can usually be adopted for vaginal delivery.<sup>14</sup> However, it is important that the patient is closely observed and that all relevant staff is aware of the management plan.

It may be that a similar policy can be adopted for patients with severe deficiency undergoing Cesarean section, but until further studies are done, these patients should probably receive prophylaxis with one of the agents described above (Table 15.6).

#### **Regional anesthesia**

Epidural anesthesia should be avoided in patients with low factor XI levels. If the procedure is necessary, it should be covered with factor XI concentrate and an adequate response demonstrated. FFP is not recommended due to the variable levels of FXI. Recombinant factor VIIa may provide effective cover, but further evaluation is required in this area.

#### **Postpartum management**

The incidence of primary and secondary postpartum hemorrhage, in patients with untreated factor XI deficiency, has been reported to be 16% and 24%, respectively. Tranexamic acid is effective, although its use with factor XI concentrate should be avoided. The standard dose is 1g 6–8 hourly for 3–5 days, with the first dose being administered in labor.

#### **Neonatal management**

Neonatal hemorrhage due to peripartum events is rare but nevertheless care should be taken during delivery to avoid unnecessary trauma to the baby, including avoidance of Ventouse extraction, rotational forceps, and invasive monitoring techniques. Spontaneous bleeding or intracranial hemorrhage has not yet been reported in neonates, but a cord blood sample should be taken to determine the potential for bleeding during high risk procedures such as circumcision. Neonatal levels are approximately half that of adults and repeat testing after 6 months of age is required to provide an accurate baseline level.

### **Rare coagulation factor deficiences**

The rare coagulation disorders include deficiencies of coagulation factors II, V, VII, X, V, and VIII, combined vitamin K-dependent factors, FXIII, and disorders of fibrinogen. The spectrum of bleeding manifestations in individuals with these disorders is variable, but some may present with severe bleeds, including intracranial hemorrhage and hemarthroses. With the exception of dysfibrinogenemia, these disorders have autosomal recessive inheritance and their prevalence, in the severe form, varies between 1:500 000 and 1:2,000 000. Pregnancy in women with these disorders or couples at risk of having an affected child, should be managed in an obstetric unit with close links to a Hemophilia Center.

### Hormonal influences on factor levels

Factors II, V, and XIII tend to remain constant throughout pregnancy or show a slight increase but there is a progressive rise in factors VII, X, and fibrinogen, particularly in the third trimester. This is beneficial to heterozygous women with mild or moderate factor deficiency, but in homozygous women, with severe deficiency, levels remain low.

#### **Pre-pregnancy management**

The clinical bleeding tendency and response to hemostatic challenges should be ascertained. Women should be counseled about their potential bleeding risk in relation to pregnancy, ante-natal procedures, delivery, and the postpartum period. Consent for use of blood products should be obtained and immunity to hepatitis A and B ensured. Genetic counseling should be given and pre-natal diagnosis offered where possible.

### **Ante-natal management**

Levels should be checked at booking and repeated at 28 and 34 weeks' gestation. Depending on the factor level and clinical bleeding tendency, prophylaxis may be required for ante-natal procedures and delivery. There is little evidence to guide therapeutic decisions but in general, relatively low levels of factors II, V, VII, and X, of around 20 IU/dL, are sufficient for normal hemostasis.<sup>12,15</sup> Therefore, patients with partial deficiencies and no history of bleeding can be managed expectantly. Otherwise, replacement therapy should start at the onset of established labor and the factor half-life should be considered to determine the need for, and timing of, repeat doses. Pre- and post-treatment factor levels should be obtained and effective levels maintained for 3–5 days after delivery.

### **Treatment options**

Prothrombin complex concentrates can be used for patients with factors II or X deficiency. These are pooled plasma-derived products containing known quantities of factors II, IX, and X, with or without factor VII. The strength of the concentrate is expressed in terms of units of FIX, but this is approximately equal to the units of prothrombin. Concomitant use of tranexamic acid should be avoided because of the risk of thrombosis.

FFP is the only available product for FV deficiency and may also be used for patients with prothrombin and FX deficiency. A virally inactivated product should be used. An initial dose of 15 mL/kg should be given, with repeat doses dictated by factor levels and clinical response. Women with factor V deficiency failing to respond to FFP may benefit from platelet transfusions, which provide a concentrated supply of platelet factor V.

Recombinant FVIIa is the treatment of choice for surgery or childbirth in women with FVII deficiency, at a dose of 20–25 mcg/kg administered every 4–6 hours.

Tranexamic acid is useful in preventing postpartum bleeding, although should not be used in conjunction with prothrombin complex concentrates.

Patients with combined vitamin K-dependent factors can be treated with daily vitamin K, although FFP may be needed in the event of bleeding.

#### Early pregnancy failure

Maternal FXIII plays a critical role in uterine hemostasis and maintenance of the placenta during gestation. The risk of miscarriage in women with severe factor XIII deficiency is around 50%, depending on the subtype. These women should receive prophylactic infusions of FXIII at monthly intervals, aiming for a trough level of >3 U/dL, although higher Factor XIII levels may be needed for delivery. <sup>16</sup>

Fibrinogen is important for implantation and patients with afibrinogenemia or hypofibrinogenemia have a high rate of early miscarriage occurring at 6–8 weeks' gestation. Regular infusions of fibrinogen concentrate, to maintain trough levels >0.6 g/L, should be started as soon as pregnancy is confirmed and continued throughout pregnancy and the peripartum period.<sup>17</sup> Fibrinogen consumption tends to increase as

pregnancy advances. Repeated ultrasounds should be carried out to detect concealed placental bleeding and monitor fetal growth.

Dysfibrinogenemia has been associated with a high incidence of miscarriage and stillbirth<sup>18</sup> but clinical phenotypes vary and management should be individualized, depending on the fibrinogen level and the clinical presentation of the disorder in the family. Thromboprophylaxis with low molecular weight heparin is required for those with personal or family history of thrombosis and fibrinogen replacement for bleeding phenotypes, but many cases are asymptomatic without the need for specific treatment.

#### Thrombosis

The potential for thrombosis following factor replacement must be considered and attention given to simple thromboprophylactic measures such as adequate hydration, compression stockings, and early mobilization. Patients with afibrinogenemia- or dysfibrinogenemia are at particular risk of thrombosis due to impaired regulation of thrombin generation. Loose platelet thrombi form and are susceptible to embolization, therefore careful consideration should be given to the balance of bleeding and thrombotic risk. For these patients, a continual infusion of fibrinogen concentrate to maintain levels above 1.5 g/L during the peripartum period allows for fine control.

#### Neonatal management

Perinatal trauma such as Ventouse delivery, rotational forceps, and fetal blood sampling should be avoided. Severe and moderate deficiencies can be diagnosed on a cord blood sample. Severely affected babies require cranial ultrasound to detect any ICH.

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Section 5 Chapter Hemorrhagic disorders

# Genetic counseling and pre-natal diagnosis in hemophilia

Andrew Mumford

# Introduction

Hemophilia is the most common severe genetic bleeding disorder and presents significant risk to the fetus at delivery. Hemophilia is also associated with significant morbidity later in life and may require intensive long-term treatment, which may be a considerable burden to affected families. High quality obstetric care of women with a family history of hemophilia is therefore paramount but presents particular management challenges.

# Genetic counseling in hemophilia

Genetic counseling refers to the process of communication of information to women and families to enable informed decision making about the consequences of carrying a fetus with hemophilia. Genetic counseling for hemophilia should encompass the issues of carrier testing and pre-natal diagnosis.

Successful genetic counseling should be supportive and requires careful two-way discussion between families and healthcare professionals who are familiar with hemophilia management and with the techniques available for carrier testing and pre-natal diagnosis. Since genetic counseling often raises complex ethical and moral issues, this process may require multiple face-to-face consultations supported by clear and objective written information. Ideally, genetic counseling should be initiated before pregnancy is planned.<sup>1</sup>

Genetic counseling is a step-wise process and may require discussion about the following issues:

- family diagnosis of hemophilia and clinical severity;
- inheritance pattern of hemophilia within the family to exclude carriership or to identify "possible" and "obligate" carriers;

- pattern of transmission and consequences of hemophilia in future offspring;
- benefits and hazards of carrier detection techniques;
- Options available for management of pregnancy, including pre-natal diagnosis.

# Heritability of hemophilia

As hemophilia A and B are sex-linked disorders, affected families may contain males with hemophilia and female hemophilia carriers who usually do not have abnormal bleeding, but may transmit hemophilia to males in the next generation (Fig. 16.1). Analysis of an accurate family pedigree is essential to establish the probability of hemophilia carriership and transmission risk.

- Sons of female hemophilia carriers have a 50% chance of having hemophilia.
- Daughters of female hemophilia carriers have a 50% chance of being carriers.
- Sons of males with hemophilia will not inherit hemophilia.
- Daughters of males with hemophilia will always inherit hemophilia and will therefore be obligate hemophilia carriers.
- Approximately 50% of individuals newly diagnosed with hemophilia have no family history of hemophilia.

Some women can be excluded as being hemophilia carriers by analysis of the family pedigree. Although these women do not have the gene change responsible for hemophilia elsewhere in their families, they retain a small risk, as in the general population, of being carriers of a different hemophilia gene change that has arisen by spontaneous mutation. For hemophilia A,

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**Fig. 16.1** Pedigree of a family with hemophilia showing possible patterns of transmission of hemophilia over three generations. The offspring of a female hemophilia carrier (I.2) can include males with hemophilia (II.1), males without hemophilia (II.2), female hemophilia carriers (II.3), and females who are not hemophilia carriers (II.4). The offspring of males with hemophilia (II.1) can either be males without hemophilia (III.1) or female obligate hemophilia carriers (II.2).

this background risk of carriership is approximately 1 in 20 000 women.

# Prediction of carrier status by pedigree analysis

For women from families with hemophilia, the probability that a pregnancy will yield a fetus that is a male with hemophilia can be calculated from the family pedigree using simple rules of Mendelian inheritance (Fig. 16.2).

For families in which there is hemophilia in one individual but no antecedent history of hemophilia (sporadic hemophilia), calculating the risk of hemophilia in subsequent members of the same generation is more difficult (Fig. 16.3). Sporadic hemophilia usually arises because of new mutations in the F8 or F9 genes (hemophilia A and B, respectively) occurring during gametogenesis in either the mother or a maternal ancestor of an affected male. However, spontaneous mutations occur more readily during spermatogenesis than oogenesis. Therefore, the causative mutation in a male with sporadic hemophilia is more likely to have arisen during spermatogenesis in the maternal grandfather than in oogenesis in the mother. It follows that mothers of males with sporadic hemophilia are likely to be constitutional hemophilia carriers. Observational population studies confirm this prediction and show that approximately 90% of mothers of males with sporadic hemophilia are carriers and therefore, have significant risk transmitting hemophilia to future male offspring.<sup>2</sup>



**Fig. 16.2** Example pedigree allowing calculation of the probability of carriership and transmission of hemophilia. The female proband (III.2-arrowed) has a maternal grandfather (I.1) with hemophilia. Since I.1 is a male with hemophilia, the mother of the proband (II.2) is an obligate carrier of hemophilia. The proband III.2 therefore has a 50% chance of hemophilia carriership. Since the probability that a hemophilia carrier will carry a fetus that is a male with hemophilia at each pregnancy is 25%, the absolute probability that the unborn fetus IV.1 will be affected with hemophilia is 12.5%.



**Fig. 16.3** Example pedigree showing estimated probability of hemophilia carriership and transmission in a family with sporadic hemophilia The female proband (II.2-arrowed) already has a son who is affected with hemophilia (III.3) but has no other family history. The mutation responsible for hemophilia in III.1 is most likely to have occurred during spermatogenesis in individual I.3 and so the proband II.2 is likely to be a carrier of hemophilia approximately 90% and so the probability that II.2 is a carrier of hemophilia approximately 90% and so the probability that each subsequent pregnancy will yield a male with hemophilia is approximately 23%.

# Laboratory detection of hemophilia carriership

Determining the probability of hemophilia carriership by pedigree analysis is essential for the genetic counseling process. However, all women who are potential hemophilia carriers should also be offered laboratory carriership detection. Two complementary approaches are available; coagulation factor activity assays and mutation analysis.

### Coagulation factor activity assays

Female carriers of hemophilia usually show reduced activities of coagulation factor VIII or IX (hemophilia A and B, respectively) to levels of 40%–80% that of unaffected individuals.<sup>3</sup> However, there is wide variation in factor activity between carriers and there is significant overlap with women who are not hemophilia carriers. Measurement of coagulation factor activity may therefore guide identification of hemophilia carriers but is insufficient for definitive diagnosis. The ratio of FVIII to Von Willebrand factor (VWF) may be helpful, as these two molecules normally circulate in the plasma with 1:1 stoichiometry. Thus carrier status may be suspected if the ratio falls below 0.7, despite the absolute FVIII level being normal.<sup>4</sup>

#### Genetic detection of carriership

Female hemophilia carriers are heterozygous for mutations in F8 or F9 and demonstration of a hemophilia – associated mutation in these genes is sufficient to diagnose carriership. It is good practice to confirm hemophilia carriership with genetic testing even in women identified as obligate carriers by pedigree analysis. Definitive exclusion of hemophilia carriership in potential carriers requires demonstration that the hemophilia mutation in the family is absent. In this circumstance, prior knowledge of the causative mutation in a male with hemophilia or an obligate female carrier from the family is essential.

Testing the potential for transmission of hemophilia in asymptomatic women raises complex moral issues for the individual and families undergoing testing. The full implications of genetic testing should therefore be discussed during counseling and informed written consent is mandatory. Counseling should include specific discussion about the limitations of F8 and F9 genetic analysis.

#### Mutations associated with hemophilia

Although more than 1800 F8 mutations have now been identified in individuals with hemophilia A, many defects are recurrent and have been recognized in multiple affected families. A major structural rearrangement of the F8 gene resulting from an inversion involving intron 22 accounts for approximately 50% of cases of severe hemophilia A. Other recurrent mutations associated with severe hemophilia A include point mutations, non-sense mutations, deletions, or other major structural changes in F8 that prevent expression of the gene. Mild hemophilia A and hemophilia B are usually associated with point mutations in F8 and F9, respectively, although heterogeneity between affected families means that previously unreported mutations are common.

The mutation databases for hemophilia A (http:// europium.csc.mrc.ac.uk/WebPages/Main/main.htm) and hemophilia B (http://www.kcl.ac.uk/ip/ petergreen/haemBdatabase.html) contain bibliographic references and phenotypic data from previously reported families with hemophilia. These resources are valuable for confirming that a newly identified mutation in a hemophilia family is causative and in predicting the future clinical phenotype of affected males.

# Limitations and hazards of genetic diagnosis of carriership

1. Failure to detect causative mutations.

Approximately 5% of hemophilia mutations are not detected by analysis of the coding sequence of F8 or F9. Similarly, some mutations such as large deletions may be readily detected in males but not in heterozygous female carriers. In these circumstances, detection of carriers currently requires techniques such as linkage analysis. This may not be informative in all families and, because of genetic recombination events, has lower diagnostic accuracy than direct mutation detection by sequencing.

2. False-negative carrier detection because of somatic mosaicism. An individual is a somatic mosaic for hemophilia when a spontaneous hemophilia mutation occurs in a somatic cell during early embryogenesis rather than during gametogenesis in one or other parent. In an affected embryo, the hemophilia mutation is

therefore present in some, but not all, cells including the germ cells. Those germ cells which contain the hemophilia mutation may then go on to form gametes. For women who are somatic mosaics, this population of gametes is then capable of transmitting hemophilia to the subsequent generation.

Somatic mosaicism was identified in a female proband in more than 10% of families with severe hemophilia and, in some cases, the hemophilia mutation was present in up to 25% of maternal cells.<sup>5</sup> In this circumstance, standard genetic testing of DNA obtained from peripheral blood cells may not detect a hemophilia mutation and somatic mosaic mothers may therefore be mis-classified as "not hemophilia carriers." Somatic mosaicism should be considered in all women who have a son with hemophilia but no other family history and who have been classified as "not a hemophilia carrier" by standard genetic testing. For families with sporadic hemophilia B, one study has estimated that women with this background have a risk of hemophilia B in a second fetus of <6%.<sup>6</sup> This very low probability may be similar for all forms of hemophilia and should be discussed during genetic counseling for all potential carrier women.

### Pre-natal diagnosis of hemophilia

Women who have been identified as hemophilia carriers by pedigree analysis and laboratory investigation may be offered several different options for pre-natal diagnosis. Involvement of healthcare professionals with expertise in fetal medicine is essential.

Pre-natal diagnosis in hemophilia may be performed currently for two different reasons:

- to offer a more accurate probability of whether a fetus will be affected with hemophilia by fetal sexing to assist management of delivery;
- to offer early definitive diagnosis of a hemophilia in male fetus by first trimester pre-natal genetic diagnosis to enable the option of termination of an affected pregnancy.

### Pre-natal fetal sexing

• Fetal sexing may be performed by non-invasive (ultrasound or free fetal DNA (ffDNA) analysis) or invasive (chorionic villus sampling (CVS) or amniocentesis) techniques.

- If a female fetus is identified, hemophilia is excluded and hemostatic precautions at delivery are unnecessary.
- Fetal ultrasound allows gender to be identified reliably in most pregnancies from about 18–20 weeks' gestation.
- PCR detection of the fetal SRY locus in ffDNA circulating in maternal plasma is highly specific for a male fetus. This assay requires a maternal venous blood specimen of <20 mL and has >99% diagnostic accuracy at 10–12 weeks' gestation in expert centers.<sup>7</sup> A recent study evaluating the method in 196 women, including hemophilia carriers, showed 100% accuracy as early as 7 weeks' gestation.<sup>8</sup>

#### First trimester pre-natal genetic diagnosis

- First trimester pre-natal genetic diagnosis allows definitive diagnosis of hemophilia in a fetus but requires invasive testing by CVS.
- CVS is an important option for confirmed hemophilia carriers who are considering termination of a male fetus with hemophilia. The uptake of this approach is very low in most reported series of pregnancies in hemophilia carriers.
- CVS for pre-natal genetic diagnosis is performed at 11–14 weeks' gestation and carries a miscarriage rate of approximately 1%. Earlier procedures have resulted in fetal limb reduction defects, particularly if performed before 10 weeks' gestation. Hemophilia carrier mothers with low coagulation factor levels may need treatment to cover the procedure. (See Chapter 15.)
- Placental cells obtained by CVS are first used to determine fetal sex. Detection of the hemophilia mutation present in the family is then performed on male fetuses.
- Advances in very early fetal sexing by ffDNA analysis may enable female fetuses to be identified before 11–14 weeks so that CVS is then unnecessary. Confirmation of gender by fetal ultrasound at 18 weeks' gestation is then recommended.
- Amniocentesis is an alternative technique for pre-natal genetic diagnosis in hemophilia and can safely be performed from 15 weeks' gestation. This technique is therefore less suitable for women contemplating termination of pregnancy.

Amniocentesis is associated with miscarriage rates of 0.5%–1%, but higher miscarriage rates and fetal talipes have been associated with amniocentesis performed before 15 weeks. Cord blood sampling is unsuitable for pre-natal diagnosis of hemophilia because of bleeding risk in an affected fetus.

#### Future techniques for pre-natal diagnosis Third trimester amniocentesis and mutation detection

Amniocentesis performed at around 36 weeks enables genetic diagnosis of hemophilia in male fetuses and carries a risk of preterm labor of approximately 1% in experienced centers. This approach allows hemostatic precautions to be applied only to male fetuses with hemophilia, so that, unaffected male fetuses can be delivered without these constraints. The risk to the fetus of delivery precipitated by the amniocentesis is very small at this late gestation. The potential clinical benefits of this approach in hemophilia are currently under evaluation.

#### **Pre-implantation diagnosis**

Pre-implantation sexing with re-implantation of female or unaffected male embryos requires standard in vitro fertilization techniques, with harvesting of cells from embryos at the 8-cell stage for analysis. Single-cell PCR enables detection of specific mutations in male embryos.<sup>9</sup> These approaches are technically feasible in hemophilia and have now been performed in small numbers of successful pregnancies.

#### Mutation detection using ffDNA or fetal cells in maternal blood

Detection of hemophilia mutations in ffDNA or in fetal cells in maternal blood in pregnancy potentially offers non-invasive pre-natal diagnosis of hemophilia. This approach requires highly efficient purification of fetal material from maternal blood and may only be feasible in the third trimester when ffDNA and fetal cells are most abundant. This approach is currently at early development stage.

# Genetic counseling for other heritable bleeding disorders

Genetic counseling, carrier detection and pre-natal diagnosis should also be considered in families with heritable bleeding disorders other than hemophilia, which may also present bleeding risk to an affected fetus. Most of these rare bleeding disorders show autosomal recessive inheritance (e.g. severe Factor X deficiency, severe Factor V deficiency, Type III VWD) and genetic counseling requires discussion about the transmission of homozygous or compound heterozygous mutations from both parents. Affected fetuses are usually sporadic and arise in families with no bleeding history in heterozygous "carrier" ancestors. For mothers who are known heterozygous "carriers" or who themselves are homozygous or compound heterozygous for a recessive bleeding disorder, accurate prediction of fetal bleeding risk may require partner testing. This is particularly important in consanguineous partnerships where the risk of transmission of homozygous recessive mutations is high.

Genetic counseling for the rare bleeding disorders should reflect that the relationship between plasma coagulation factor activity and bleeding risk in affected individuals is less predictable than in hemophilia and that some disorders show variable penetrance. Since the range of reported mutations in the rare bleeding disorders is less than for hemophilia, detection of previously undescribed mutations in affected families is common. Uncertainty about whether a candidate mutation is the true disease-associated mutation may hamper genetic carrier detection and pre-natal diagnosis in some families.

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# Section 6 Chapter Microangiopathies Pre-eclampsia Eleftheria Lefkou and Beverley Hunt

### Introduction

Pre-eclampsia (PET) is a pregnancy-related multisystem syndrome, that is characterized by newonset of hypertension (blood pressure greater than 140/90 mmHg) after 20 weeks of gestation and proteinuria (greater than 1+, or urinary excretion of protein  $\geq$  300 mg/24 hours) resolving after delivery. PET is also termed toxemia, pregnancy-induced hypertension, and pre-eclamptic toxemia. Symptoms can occur any time after 20 weeks of gestation or even start in the first few days after delivery, and always resolve within a few days to weeks after delivery of the placenta. Early onset PET is when it develops before the 34th week of gestation and late onset PET when it presents after the 34th week of pregnancy. Predisposing factors are shown in Table 17.1. It is not known why some women develop pre-eclampsia, while others with the same risk factors do not.

Eclampsia occurs when PET is complicated by seizures.

**Chronic hypertension** is defined as systolic pressure  $\geq 140 \text{ mmHg}$  and/or diastolic pressure  $\geq 90 \text{ mmHg}$  that antedates pregnancy, that is present before the 20th week of pregnancy, or persists longer than 12 weeks' postpartum.

**PET with chronic hypertension** is diagnosed when a pregnant woman has a history of chronic hypertension and then develops features suggestive of PET after the 20th week of pregnancy.

**Gestational hypertension**, or transient hypertension of pregnancy refers to the situation that is characterized by elevated blood pressure (>140/90 mmHg) after the 20th week of gestation, but without proteinuria, that occurs uniquely during pregnancy and resolves after birth.

The aim of this chapter is to provide a basic understanding of PET and a detailed understanding of hematological complications and their management.

# Epidemiology

Pre-eclampsia (PET), the commonest medical complication of pregnancy, affecting approximately 2%-14% of all pregnancies, remains a major cause of maternal and fetal morbidity and mortality worldwide. It is estimated that 50 000 women die annually worldwide due to PET and eclampsia. In the United States the incidence of PET is approximately 5%-8%, with 75% of cases being mild and 10% of cases due to early onset PET. According to the latest report from the Confidential Enquiry into Maternal and Child Health it remains the second major cause of maternal mortality and morbidity in the UK after venous thromboembolism.<sup>1</sup> The incidence of PET in the UK is reported as 2%-8%, with a fatality rate of 18/ 100 000 pregnancies. Mild PET is under-reported and so the true incidence is potentially much higher.

PET is associated with intrauterine growth restriction (IUGR), in one-third of cases. Premature delivery to prevent the progression of PET is responsible for 15% of all preterm births. Infants of women with PET have a fivefold increase in mortality compared with infants of mothers without the disorder.

The recurrence likelihood for PET is reported as 60% if it had occurred <34 weeks' gestation and 10%–20% if occurred near term. The key to appropriate management is early clinical recognition.

# **Diagnosis of PET**

The diagnosis of PET is based on the maternal history, signs, and symptoms (Table 17.2). The current aim of

Table 17.1 Risk factors for pre-eclampsia (PE
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#### Nulliparity

High body mass index (BMI) (>35 at booking)

Multiple gestation (twins, triplet pregnancies)

Chronic hypertension

Diastolic pressure >89 mmHg at booking

Proteinuria at booking

Previous pregnancy with PET or IUGR child

Family history of PET (in mother or sisters)

Black race

Maternal age under 20 and possibly maternal age over 35 to 40

Diabetes mellitus or insulin resistance

Renal disease

Thrombophilias and hyperviscosity syndromes

Underlying maternal collagen vascular disease

Presence of antiphospholipid syndrome, or antibodies

Increased circulating testosterone

Protein D deficiency in mother during pregnancy

Trisomy 13

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High altitude

Mirror syndrome

Fetal (genetic) factors from donor eggs

Father of Hispanic origin

Parental specific genes

ante-natal care is to monitor for signs of PET at each clinic visit, with assessment of blood pressure, urinalysis and the presence of edema. These visits occur more frequently in the third trimester of pregnancy, especially in women with risk factors. Most women with PET experience only mildly increased blood pressure and small amounts of proteinuria. Edema, especially in the face and hands, is a frequent sign of PET, but is not pathognomonic, for many women without PET also develop edema during pregnancy. Other forms of hypertensive disorders also occur in pregnancy and should be considered in the differential diagnosis of PET.

The maternal manifestations of PET can affect almost every organ, depending on severity. Possible complications of PET in the mother and in the fetus are listed in Table 17.3. Table 17.2 Signs and symptoms of severe pre-eclampsia

Blood pressure greater than 160/110 mm Hg

Impaired kidney function (serum creatinine concentration  $>\!110\,\mu\text{mol/L}$ , urine protein greater than 5 grams in a 24-hour urine collection) or low urine production (less than 500 mL in 24 hours)

Persistent severe headache

Papilledema and/or visual disturbances (blurred vision, diplopia, blind spots, flashes of light, or squiggly lines).

Hyperreflexia, brisk tendon reflexes (3+)

Pulmonary edema, shortness of breath

Nausea, vomiting

Abdominal pain, persistent new epigastric pain or tenderness

Impaired functional liver tests (elevated alanine aminotransferase, aspartate aminotransferase)

Thrombocytopenia (<100×10<sup>9</sup>/L)

Microangiopathic hemolytic anemia

#### Table 17.3 Complications of PET

#### (A) Maternal

- Central nervous system
- Eclampsia
- Cerebral edema
- Cerebral hemorrhage
  Retinal edema
- Retinal blindness
- Cortical blindness
- Liver
- HELLP syndrome
- Acute liver failure
- Hepatic rupture

#### **Renal system**

- Acute renal failure
- Renal cortical necrosis
- Renal tubular necrosis
- Respiratory
- Pulmonary edema
- Laryngeal edema
   Hemostatic system

#### Thrombocytopenia

- DIC
- Microangiopathic hemolytic anemias
- **Cardiovascular system**
- Risk factor for later cardiovascular disease

#### Labor

- Placental infarction
- Placental abruption
- Preterm delivery

#### (B) Fetal–Neonatal

- IUGR
- Prematurity
   Death
- Death
- Neurological complications
- Later cardiovascular disease
# Current concepts on the pathogenesis of PET

Placental dysfunction is the central feature in the development of PET. In 1939 Ernest Page introduced the concept that PET may be due to the reduced perfusion of the placenta.

#### The two stage model of PET

Currently, the development of PET is hypothesized, to be in two stages, according to a theory introduced by the Oxford Group in 1991, and supported and expanded by Roberts.<sup>2</sup> The first stage is reduced placental perfusion and the second the maternal response to this – maternal endothelial cell activation. Failure of endovascular trophoblast invasion is thought to lead to relative under perfusion of the placenta. Under conditions of hypoperfusion, the placenta probably releases factors into the circulation, which then trigger maternal endothelial dysfunction.

Early in normal gestation, cytotrophoblast cells invade the decidua and myometrium. These cells also invade endovascularly, replacing first the endothelium and then the media of the spiral arteries. This creates a system of flaccid, low resistance, large diameter, unresponsive arterioles, that increase placental perfusion. The outcome is an increment in blood flow to the fetus and lack of adrenergic vasomotor control. The endothelial lining is replaced by the cytotrophoblast cells, which adapt to mimick an endothelial pattern of adhesion molecule expression.

In PET, this vascular phenotype is not expressed and the pattern of invasion is much more superficial. There is a restriction of trophoblast invasion into the spiral arteries, particularly those within the myometrium. These decidual vessels may later show atherosis, and superimposed thrombosis augments hypoperfusion. It seems plausible that, consequent to these changes, placental hypoperfusion causes a state of relative hypoxia.

Various factors have been postulated as the substance produced from the placenta that affects blood flow, arterial pressure, and maternal endothelial cell activation (ECA). These factors include oxidative stress, cytokines such as tumor necrosis factor  $\alpha$  (TNFa) and IL-6, insulin-like growth factors, nitric oxide (NO), heparin-binding endothelial growth factor-like growth factor, endothelin-1, arachidonic acid metabolites, angiotensin II type-1 receptor autoantibody (AT1-AA), and angiogenic factors.

Recently, the focus has been on angiogenic factors. It has been proposed that PET could be related to an imbalance between proangiogenic (as vascular endothelial growth factor, VEGF) and antiangiogenic factors as Fms-like tyrosine kinase (sFlt-1) and soluble endoglin (sEng).

sFlt-1 is an endogenous inhibitor of both VEGF and PGF and may regulate placental angiogenesis by preventing the interaction between circulating VEGF and PGF with their proangiogenic receptors. Level of sFlt-1 in the plasma of women with PET are elevated compared with normal pregnancies. When sFlt-1 is exogenously administered via adenovirus mediated gene transfer in pregnant rats and mice, there are increases in arterial blood pressure and proteinuria, as well as decreased levels of VEGF and PIGF, similar to these observed in PET.<sup>3,4</sup> Another observation was that VEGF infusion attenuates the increased blood pressure and renal dysfunction observed in pregnant rats overexpressies sFlt-1.5 Also uteroplacental ischemia has been shown to increase plasma and placental sFlt-1, and to decrease the levels of VEGF and PIGF in late gestation of rats and baboons.<sup>6</sup> Endoglin (Eng) is a component of the transforming growth factor (TGF)-beta receptor complex and a hypoxia inducible protein, and is related to cellular proliferation and NO signaling. Soluble Eng (sEng) has been shown to act as an anti-angiogenic factor, possibly via the inhibition of TGF-beta of binding to cell surface receptors.<sup>7</sup> Recent works showed that sEng inhibits in vitro endothelial cell tube formation and that adenovirus mediated increase of both s-flt-1 and sEng in pregnant rats resulted in IUGR and in a syndrome resembling PET.8 Recently, sEng levels have been proposed as a predictor of PET.9

Whichever factor provokes maternal ECA, when the latter is established, it leads to upregulation of a number of inflammatory molecules, including adhesion molecules. These procedures change the endothelium phenotype from antithrombotic to prothrombotic, with a decrease in the formation of the vasodilator and antiplatelet agents prostacyclin and nitric oxide, the production of endothelin, and finally the downregulation of anticoagulant systems.

Redman's research group in Oxford proposed that the endothelial dysfunction seen in PET is part of a wider inflammatory response and that placental hypoperfusion is not necessarily the sole primary



Fig. 17.1 Summary of current concepts on the pathogenesis of PET. The two stages model of PET.

event. They argue that pregnancy normally elicits an inflammatory response.<sup>10</sup> This is evidenced by changes in granulocytes and monocytes such as increased intracellular production of reactive oxygen species and upregulation of surface molecules such as CD11b and CD64, as well as release of L-selectin, which is related to granulocyte activation. During PET there is increased activation of platelets, neutrophils, and monocytes and an increase in the release of microparticles when compared with normal pregnancy. Perhaps these inflammatory changes are a response to the presence of fetal (or paternal) antigens. If so, then abnormalities of the normal immunomodulation seen at the feto-placental interface could act to trigger PET. HLA-G is important in the prevention of recognition of the placenta as "non-self" and there is a reduction of expression of HLA-G in PET along with abnormal responsiveness of maternal lymphocytes towards fetal cells.

Microparticles are fragments of cell membranes released into the circulation as a result of cellular activation or apoptosis and can have a procoagulant effect. Microparticles in pregnancy are derived from a number of cells, but the predominant population is platelet derived. Vesicles prepared from syncytiotrophoblast microvillous membranes (STBM) have been shown to suppress the proliferation of endothelial cells in vitro. They also affected an in vitro model of endothelial celldependent arterial relaxation. The numbers of STBM detected in the circulation of pre-eclamptic women have been shown to be significantly elevated compared with those with normal pregnancies.

A summary of the currently favored pathogenesis of PET is shown in Fig. 17.1.

# Relation between PET and IUGR/ fetal growth restriction (FGR)

The consequences of placental dysfunction can be twofold – intra-uterine growth restriction and the maternal symptoms and signs of PET. What is not understood is why some women only have FGR, while others have both FGR and PET. It has been suggested that the maternal syndrome of PET may only occur in women with "constitutional factors" (genetics, environmental, dietary, behavior, etc.) that render the mother sensitive to the effects of reduced placental perfusion.

Constitutional factors that have been proposed to act as the inductors of the maternal syndrome of PET, include several dietary factors, metabolic conditions such as diabetes, insulin resistance and uric acid, low melatonin levels, obesity, metabolic syndrome, folic acid and hyperhomocysteinemia, hyperlipidemia with elevated triglycerides, free fatty acids and LDL cholesterol and reduced HDL, maternal vitamin D deficiency, and thrombophilia. The factors that cause ECA may contribute to the development or severity of PET.

# Relation of PET with later cardiovascular risk in women and their babies

Despite PET and FGR occurring only in pregnancy, they have been shown to have long-term consequences. Mothers, who have had PET or have delivered a baby with FGR, experience a 2–8-fold increased risk of atherosclerotic cardiovascular disease (CAD) in later life.<sup>11</sup> It is unclear whether PET causes CAD or whether these two entities share the same causal origin. It has also been shown that the earlier PET presents in pregnancy, the more severe the maternal CAD is. Women with PET before 37 weeks of gestation had eight times more cardiovascular deaths than woman with normal pregnancy 14 years later.

There is a large body of epidemiological studies showing that the long-term consequences of FGR in the baby last well into adulthood. These individuals have a predisposition to develop a metabolic syndrome later in life, manifesting as obesity, hypertension, hypercholesterolemia, cardiovascular disease, and type 2 diabetes, in agreement with the theory of early origin of CAD, also known as "the Barker hypothesis."<sup>12</sup>

A recent study showed positive associations between maternal pre-pregnancy levels of triglycerides, cholesterol, low-density lipoprotein, and baseline systolic blood pressure and subsequent development of PET.<sup>13</sup> The authors concluded that the presence of cardiovascular risk factors prior to pregnancy, are predisposing to PET. The prevalence of chronic hypertension is significantly higher among women with a history of PET (46.7%) as well as those with previous IUGR (8.9%).<sup>14</sup> Women with PET and FGR with chronic hypertension on follow-up had increased carotid intimal-media thickness, suggesting a predisposition to atherosclerosis. Women with previous PET have significantly higher fasting glucose levels, waist circumference, body mass index, and higher prevalence of metabolic syndrome compared to normal women

# New modifications of current theories on the pathogenesis of PET

As long as the initial causative factor for PET remains unrecognized, different theories continue to be generated, some of them challenging the currently accepted origins of PET.

It has been suggested that early (before 34 weeks) and late onset (after 34 weeks) PET are two different clinical entities with different pathogenesis, origins, etiology, severity, and clinical expression. Certainly, FGR is more strongly associated with severe rather than with milder pregnancy-induced hypertension.<sup>15</sup> According to this theory, early PET is associated with reduced perfusion but PET at term may not, suggesting different genetic origins for early and late PET.

Huppetz, in a recent paper, has challenged the placental origins of PET and proposed that PET is a syndrome of early placental formation.<sup>16</sup> He suggested that an insult results in aberrant development and differentiation of the villous syncitiotrophoblast causing impaired maintenance of the placental barrier. This subsequently leads to the release of necrotic and aponecrotic fragments culminating in a systemic inflammatory response of the mother. According to this theory FGR is due, in contrast, to a failure of extravillous trophoblast invasion. This new concept clearly separates the origins of PET and FGR, and proposes alterations in different trophoblast differentiation pathways as origins of both syndromes.

Genome-wide expression analysis in rodents showed that spontaneous differentiation of

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trophoblast stem cells is associated with the acquisition of an endothelial-cell like thromboregulatory gene expression program.<sup>17</sup> This program is developmentally regulated and conserved between mice and humans. They further showed that trophoblast cells sense, via the expression of protease activated receptors, the presence of activated coagulation factors. Engagement of these receptors results in cell-type specific changes. These observations define candidate fetal genes that are potential risk modifiers of PET and suggest that hemostasis can affect trophoblast physiology and thus affect placental function in the absence of frank thrombosis. It is postulated that PET is not only due to a maternal cause, but also that fetal genes could contribute to the development of the disease.

#### Thrombophilia and PET

#### Acquired thrombophilia

Mothers with antiphospholipid antibodies have a predisposition to PET and FGR. Indeed, the development of these conditions before 34 weeks in a woman with antiphospholipid antibodies has now become defining criteria for obstetric antiphospholipid syndrome. This is discussed in more depth in Chapter 11. Other acquired conditions that predispose to thrombosis such as myeloproliferative disease would also be expected to predispose to PET (see Chapter 19).

#### Genetic thrombophilias

An association between PET and inherited thrombophilias was first reported by Dekker et al. in 1995, who proposed that maternal thrombophilia could act as a genetic constitutional factor for the development of PET.<sup>18</sup> Since then, a large number of retrospective and case-controlled studies have examined the association between different types of thrombophilic mutations and PET. The results of published reports have been inconsistent. Meta-analysis of all case-control studies suggests that only FVL mutation is associated with a minor increased risk of PET (odds ratio, 1.18; 95% confidence interval, 1.14 to 2.87). Overall, studies suggest that women with genetic thrombophilia have more severe PET than those without, but thrombophilia itself does not precipitate the condition.

### Prediction of PET

As the exact causative factor that provokes PET is not yet known, at present there is no clear strategy for its prevention and so the clinical and research focus has been on early detection and prediction.

Hyperuricemia is an established marker of severe PET, correlating with the histological severity of renal lesions, and clinically with adverse fetal outcomes, but has a low negative predictive value.

Uterine artery Doppler screening between 20 and 24 weeks identifies mothers at high risk for developing adverse pregnancy outcomes. The correlation between elevated uterine artery resistance and a high risk of PET and/or FGR was first demonstrated at the end of second trimester, probably reflecting the ongoing process of trophoblast invasion into the spinal arteries. Bilateral notching at 20–24 weeks identifies the pregnancies that will have FGR and PET, although there is a high false positive rate.<sup>19</sup>

An algorithm of placental and endothelial markers between 20 and 24 weeks' gestation was developed and showed good prediction of the later development of PET.<sup>20</sup> This study proposed six markers as potential predictive indicators: HDL cholesterol, PAI-1/PAI-2 ratio, leptin, and PIGF. At 20 weeks' of gestation, an algorithm of these markers distinguished PET from the low risk group. At 24 weeks' of gestation the positive predictive value was even better. Increased levels of soluble fms-like tyrosine kinase 1 (sFlt-1) and reduced levels of soluble placental growth factor (PIGF) have been shown to predict the subsequent development of PET, as early as 5 weeks before the onset of PET. Human cancer patients treated with anti-VEGF antibody developed hypertension and proteinuria.

In association with increased levels of sFlt-1, symptoms were dramatically worse, and typical of HELLP syndrome, leading the authors to postulate that increased levels of sFlt-1 were responsible for PET, but the combination of increased sFlt-1 and sEng led to HELLP syndrome. In a longitudinal analysis, the rise in soluble endoglin concentrations occurred earlier and was more marked in pregnancies with subsequent pre-eclampsia.

Soluble endoglin (sEng) is a co-receptor for transforming growth factor  $\beta 1$  and  $\beta 3$ , expressed on trophoblasts. Its levels are increased in preeclampsia<sup>15</sup> and in pregnant rats this has been associated with increased vascular permeability and hypertension. Other serum markers that have been proposed to predict PET as early as the first trimester, are placental protein 13 (PP13), placenta associated plasma protein A (PAPP-A), and long pentraxin 3 (PTX3). All of those markers still need further evaluation in larger multicenter trials.

# Management of pre-eclampsia

At present, the sole effective therapy for pre-eclampsia is delivery and removal of the placenta. Symptoms usually improve within days. Therefore, early diagnosis and timely delivery are imperative for maternal and peri-natal survival.

### Prevention of PET

Several drugs have been tried for the prevention of PET. Despite the first promising publications, it has been shown later that there is a lack of evidence for calcium, vitamin C, and E in PET's prevention. The main drugs that are used for the prevention of PET are antihypertensives and antithrombotics.

#### **Prevention of PET with antihypertensives**

Antihypertensive drugs are used for secondary prevention of PET, in women with mild to moderate hypertension developing or pre-existing to pregnancy. Data from several studies showed that, although there was a reduction in hypertension, it was unlikely that this had a major impact on the progression to PET. Furthermore, it has been argued that the impact to the fetus of lowering maternal blood pressure could provoke FGR. Although there is no big randomized trial, beta-blockers are more likely to have such an impact (eight trials, 810 women; relative risk 1.56, 1.10 to 2.22). The antihypertensive drug methyldopa has often been used in gestational hypertension. Side effects include depression and drowsiness. Other drugs that can be used are labetalol and calcium channel blockers. Atenolol is relatively contraindicated in pregnancy due to possible FGR; absolutely contraindicated are angiotensin converting enzyme inhibitors and angiotensin receptor antagonists due to possible teratogenicity. Diuretics should be avoided in general, and should be kept only for special indications such as renal or cardiac diseases.

#### **Prevention of PET with antithrombotics**

#### Antiplatelet agents

The Collaborative low-dose Aspirin Study in Pregnancy (CLASP study), was a randomized trial of low dose aspirin for the prevention and treatment of PET among 9364 pregnant women.<sup>21</sup> The women were randomly assigned 60 mg aspirin daily or matching placebo. To simulate real obstetric practice, the entry criteria were broad and embraced women thought to be at risk of PET and FGR from 12 to 32 weeks' gestation. Primiparous women, women with pre-existing hypertension or a history of FGR, PET, or stillbirth and women with established PET could all be entered in the study: 74% were entered for prophylaxis of PET, 12% for prophylaxis of FGR, 12% for treatment of PET, and 3% for treatment of FGR. Overall, the use of aspirin was associated with a reduction of only 12% in the incidence of proteinuric PET, which was not significant. Nor was there any significant effect on the incidence of IUGR or of stillbirth and neonatal death. Aspirin did, however, significantly reduce the likelihood of preterm delivery (7% aspirin vs. 2% control); absolute reduction of 5 per 100 women treated. There was a significant trend towards progressively greater reductions in proteinuric pre-eclampsia, the more preterm the delivery. Aspirin was not associated with a significant increase in placental hemorrhage or in bleeding during preparation for epidural anesthesia, but there was a slight increase in use of blood transfusion after delivery. Low dose aspirin appeared safe for the fetus and newborn infant, with no evidence of an increased likelihood of bleeding. The rate of stillbirth, neonatal death, or fetal growth retardation occurring before 32 weeks was 5.3% in the aspirin group as compared with 10.6 % in the placebo group. These findings do not support routine prophylactic or therapeutic administration of aspirin in pregnancy to all women at increased risk of pre-eclampsia or IUGR. Low dose aspirin may be justified in women judged to be especially liable to early-onset PET severe enough to need very preterm delivery. In such women it seems appropriate to start low dose aspirin prophylactically early in the second trimester.

The Cochrane Library Update summarizing data from 37 560 women for 59 trials of aspirin to prevent PET showed that the use of aspirin is associated with a 17% reduction in the risk of pre-eclampsia (46 trials, 32 891 women, relative risk (RR) 0.83, 95% confidence interval (CI) 0.77 to 0.89), an 8% reduction in the relative risk of preterm birth (29 trials, 31 151 women, RR 0.92, 95% CI 0.88 to 0.97); NNT 72 (52 119)), and a 14% reduction in fetal or neonatal deaths (40 trials, 33 098 women, RR 0.86, 95% CI 0.76 to 0.98); NNT 243 (131, 1 666) and a 10% reduction in small-for-gestational age babies (36 trials, 23 638 women, RR 0.90, 95% CI0.83 to 0.98). The authors concluded that antiplatelet agents, largely low dose aspirin, have moderate benefits when used for prevention of PE and its consequences.<sup>22</sup>

The Perinatal Antiplatelet Review of International Studies (PARIS) Collaborative Group published a meta-analysis, included 31 randomized trials of PET primary prevention enrolling a total of 32.217 women and their 32.819 infants.<sup>23</sup> According to their results antiplatelet agents, particularly aspirin, moderately reduce the relative risk for PET, preterm births before 34 weeks' gestation, and serious adverse pregnancy outcomes. For women randomized to receive antiplatelet agents, the relative risk of developing PET, compared with women in control groups, was 0.90 (95% confidence interval (CI) 084-0.97). The risk of delivering before 34 weeks' gestation was 0.90 (95% CI, 0.83-0.98) and of having a pregnancy with a serious adverse outcome was 0.90 (95% CI, 0.85-0.96). Use of antiplatelet agents was not associated with any significant effect on the risk for death of the fetus or newborn, risk of having an infant born small for gestational age, or risk for bleeding events for either the women or their babies. No subgroups of women who were substantially more or less likely to benefit from antiplatelet agents than any other were identified.<sup>23</sup> Despite these two large meta-analyses, further studies are required to assess which women are most likely to benefit, when treatment is best started, and at what dose.

#### Heparin and antithrombin concentrates

Heparin as monotherapy or in combination with aspirin has also been suggested for the prevention of PET in women with high risk pregnancies, but data are not yet sufficient for a final conclusion. For example, a recent study investigated the effect of low molecular weight heparin (LMWH) on pregnancy outcome, on the maternal blood pressure values, and on uteroplacental flow in angiotensin-converting enzyme (ACE) non-thrombophilic women, with insertion/deletion (I/D) polymorphism, with history of PET.<sup>24</sup> The study included 80 women, 41 treated with dalteparin 5000 IU/day, and 39 untreated (control group). This study suggests that LMWH may reduce the recurrence of PET, of negative outcomes, and the resistance of uteroplacental flow, and also prevents maternal blood pressure increase in ACE DD homozygote women with a previous history of PET.

Antithrombin (AT) levels are reduced in PET. Previous randomized controlled trials of AT therapy in PET between 24–35 weeks' gestation have shown significantly improved maternal symptoms and birth weight.<sup>25</sup> A further trial examined AT therapy in severe PET in women presenting before 32 weeks' gestation. 42 patients were enrolled and each received 3000 IU per day for 7 days compared to albumin 582 mg/day for 7 days. An equal number of women discontinued the intervention in the AT and placebo (albumin) groups. AT treatment improved or at least preserved fetal biophysical status. It prolonged the pregnancy to reach 34 weeks and fetal growth rate was preserved. However, AT treatment of PET is still largely confined to research settings.

#### Planning for the optimal timing of delivery

One can justify PET, of any severity, presenting after 34 weeks as an indication for delivery. If earlier than 34 weeks, the balance of expectant management is set against risk to the mother, but potentially benefits the child in terms of risks of prematurity. Generally, hemodynamic instability, fetal distress, and rapid disease progression are indications for delivery. There is no evidence base to support these decisions, as only small trials of expectant management prior to 34 weeks vs. delivery have been carried out.

If an induced pre-term delivery is contemplated, it may be necessary to give prostaglandins to ripen the cervix. Steroid therapy to improve fetal lung maturity should also be considered, in discussion with the pediatric team. In general, a vaginal delivery is considered safer than Cesarean section for those with complications of PET. For both forms of delivery, a platelet count of greater than  $50 \times 10^9$ /l is recommended, and platelet transfusions may be necessary to achieve this.

Regional anesthesia is also generally preferred, but depends on the platelet count, and guidelines recommend a count of greater than  $80 \times 10^9$ /L, in the setting of normal platelet function. Coagulation parameters should also be checked prior to delivery because of the risk of DIC in PET.

It should be emphasized that the disease does not abate immediately post-delivery and that seizures can occur up to a week later. Hence, seizure prophylaxis, anti-hypertensive therapy, and frequent monitoring should be continued for an appropriate period, e.g. 12– 48 hours for seizure prophylaxis and close monitoring, up to 12–16 weeks or indefinitely for anti-hypertensive therapy.

# Other pharmaceutical management of PET

#### Anti-hypertensive drugs for the management of PET

The most used anti-hypertensive drugs in the management of PET are methyldopa, labetalol, and nifedipine.<sup>25,26</sup> Labetalol is quite safe and effective, decreasing heart rate and having fewer side effects than other drugs (lack of reflex tachycardia, hypotension, or increased intracranial pressure).<sup>25</sup> Best avoided drugs are high dose diazoxide, due to increased risk for hypotension and Cesarean section, and the serotonin receptor antagonist kentaserin.<sup>25</sup>

In general, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor-blocking drugs (ARB), and diuretics should be avoided. Nifedipine should be given orally and not sublingually.

Concern has been about hydralazine as first-line treatment (due to the potential unpredictable hypotension) and the combination of nifedipine and magnesium sulfate.

#### **Magnesium sulfate**

Magnesium sulfate is the drug of choice for the prevention and treatment of pre-eclampsia. The epidemiological and basic science evidence suggesting that magnesium sulphate when given to early pregnancy in women considered at risk of preterm birth may be neuroprotective for the fetus, has now being confirmed by a recent Cochrane systematic review.<sup>26</sup> It acts by causing cerebral vasodilation, thereby reversing the ischemia produced by cerebral vasospasm during an eclamptic episode. Data suggest that women receiving magnesium sulfate therapy have a 58% lower risk of eclampsia than placebo and that also reduces the risk for maternal death.<sup>26</sup> A possible side effect is flushing, which occurs in one-quarter of women.

# Suggesting guidelines for the management of established PET

- Close in or outpatient monitoring of vital signs, deep tendon reflexes, neurological examination.
- Bed rest and relaxation.
- Fetal monitoring: external fetal monitor, oxcytocin challenge test, biophysical profile.
- Give steroids to accelerate fetal lung maturation when < 34 weeks of gestation; betamethasone

12 mg IM/day for 2 doses, or dexame thas one 6 mg IM/ 12 hours  $\times$  4 doses.

- Careful fluid restriction to reduce the risk of fluid overload. Total fluid intake should be limited to 80 mL/h (max 150 mL/h), or 1 mL/kg/h, urine output can be tolerated as low as 10 mL/h.
- Give supplemental oxygen.
- Maintain diastolic blood pressure < 110 mmHg/ and systolic < 160 mmHg with anti-hypertensive drugs.
- Give prophylactic intravenous magnesium sulfate for the prevention of eclampsia during labor and the postpartum.
- Laboratory monitoring; complete blood count, platelets count; coagulation studies in severe PET (PT, PTT, fibrinogen, FDP) urea, serum creatinine, uric acid, serum electrolytes, liver functional tests, lactate dehydrogenase.

# Suggesting guidelines for the management of eclampsia

- Close monitoring.
- Give oxygen.
- Fluid restriction is advisable to reduce the risk of fluid overload. Total fluid should be limited to 80 mL/h, or 1 mL/kg/h.
- Give magnesium sulfate. Alternative drugs include diazepam, phenytoin.
- Give steroids if <34 weeks' gestation.
- Urgent delivery.

# Hematological complications of PET

All the changes taking place during PET due to endothelial cell activation can produce hematological complications.

Frequent (at least every 8 hours) full blood count and coagulation screen should be performed in case of severe PET, or where there is suspicion of subsequent development of hematological complications.

# Thrombocytopenia

The most common hematological complication of PET is thrombocytopenia, occurring in 18% of preeclamptic women. This is probably due to platelet and endothelial activation generating thrombin and causing platelet consumption. In general, the severity of thrombocytopenia is related to the severity of PET.

If the platelet count is greater than  $40\,000 \times 10^9/L$ , the risk of bleeding is small. In the majority of cases thrombocytopenia resolves after delivery, but rarely may continue to fall after birth. Severe thrombocytopenia persisting after delivery could be a possible indicator of developing microangiopathic hemolytic anemia.

#### Management of thrombocytopenia in PET

Platelet counts of  $> 50 \times 10^9$ /L in patients with otherwise normal coagulation are regarded as safe for normal vaginal delivery and Cesarean section. Concerns over the risk of hematoma formation and neurological damage have led to the use of regional anesthesia not being recommended unless the platelet count is  $< 75 \times 10^9$ /L with a normal coagulation screen. This recommendation is based on consensus rather than on evidence.

If platelet count  $<50 \times 10^9$ /L and there is no bleeding, then no treatment is necessary unless there is active bleeding, when it is appropriate to transfuse platelets.

# Disseminated intravascular coagulation (DIC)

DIC is a clinicopathological syndrome characterized by a systemic activation of coagulation leading to microvascular deposition of fibrin, and thus to consumption of coagulation factors, platelets and physiological anticoagulants. This produces a reduction in platelet count, a fall in fibrinogen, and a prolongation of the activated partial thromboplastin time (APTT) and international normalized ratio (INR).

Prolongation of PT and APTT with severe thrombocytopenia and low fibrinogen levels (<1.0 g/L) are signs of a developing DIC-like state and hence frequent estimation of platelet count, fibrinogen (using Clauss method), prothrombin time (PT), and APTT is strongly recommended. Laboratory evidence of a consumptive coagulopathy should be sought before microvascular bleeding becomes evident, so that appropriate and aggressive action can be taken to address the underlying cause.

DIC occurs in about 10%–12% of all cases of PET and in 7% of severe PET. The etiology of DIC in

pre-eclampsia is not well understood, but is probably a consequence of endothelial cell activation. In only 10%–15% of DIC cases in PET, it can become more systematic and even lethal. In PET there is a low grade fibrin deposition in the renal and placental microcirculation.

DIC in obstetric patients could be a complication of other obstetric conditions or of none related directly with pregnancy. The most common causes of DIC in obstetrics, besides PET, are abruption placentae and amniotic-fluid embolism (occurring in more than 50% of obstetric cases), and retained dead fetus, sepsis, and septic abortion.

#### Management of DIC

Management of DIC involves (1) treating the cause and (2) replacement of missing hemostatic components with blood products. Rarely, chronic DIC requires low dose anticoagulation to "switch off" the stimulus to DIC.

Hematological treatment consists of platelets, FFP, and cryoprecipitate (see Table 17.3, Chapter 13c), but avoiding circulatory overload. Novel therapeutic strategies are based on current insights into the pathogenesis of DIC, and include anticoagulant strategies (e.g. directed at switching off coagulation stimulus) and strategies to restore physiological anticoagulant pathways (such as activated protein C concentrate). These have not been evaluated adequately in the management of DIC in pregnancy and postpartum.

#### **HELLP** syndrome

#### Definition

HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) occurs in the second and third trimester of pregnancy and presents occasionally postpartum. There are no clear definition criteria for HELLP.

#### **Epidemiology of HELLP**

This disorder complicates between 0.5% and 1% of pregnancies and is associated with a maternal morbidity ranging between 1% and 4%. HELLP syndrome is reported in PET with an incidence ranging between 2% and 50% (5% and 15%), depending on the population studied and the diagnostic criteria used: 70% of cases occur ante-natally and 30% occur within the first 48 hours' to 7 days' postpartum. 20% of women who develop HELLP post-labor had no evidence of PET before delivery. The incidence of HELLP is Table 17.4 Differential diagnosis of HELLP syndrome

Acute fatty liver of pregnancy
Gal bladder disease
Gastroenteritis
Appendicitis
Diabetes insipidus
Hemolytic uremic syndrome
Thrombotic thrombocytopenic purpura
Idiopathic thrombocytopenic purpura
Acute renal failure
Pyelonephritis
Glomerulonephritis
Peptic ulcer
Flair of systemic lupus erythematosus
Viral hepatitis

significantly increased among white middle-class and older multiparous women. DIC is founded in approximately 20%–30% of women with HELLP. Recurrence rates in subsequent pregnancies is 3% for HELLP, 10%–14% for IUGR and 18%–20% for PET.

#### **Clinical presentation of HELLP**

The clinical presentation is with fatigue and malaise for a few days, followed by nausea, vomiting, shoulder, neck, epigastric or right upper quadrant pain, headache, and visual disturbances. Right upperquadrant or epigastric pain is thought to be due to obstruction of blood flow in the hepatic sinusoids, which are blocked by intravascular fibrin deposits. Usually, the patients present with significant weight gain, due to the associated generalized edema, and with proteinuria greater than 1+ (in 90% of cases). Severe hypertension is not a constant or a frequent finding in HELLP syndrome. That is why it can usually be misdiagnosed as having another disease (listed in Table 17.4).

#### Pathophysiology of HELLP syndrome

The pathophysiology is not clear, but it is helpful to consider that it represents PET confined to the liver, which may result in necrosis of areas of the liver. According to one theory, pre-eclamptic patients are already prone to spontaneous hemorrhages. The liver is thought to be particularly prone because fibrin split products can deposit in the reticuloendothelial system of the liver. Multiple previous subclinical spontaneous hemorrhages within the small hepatic sinusoids and arterioles may go unnoticed symptomatically and leave the liver in a fragile state. Fibrin thrombi may be left uncleared in the liver. Occasionally, a trigger (such as DIC) may cause extreme hypoperfusion of the liver, leading to infarction.

As the liver is the primary site of plasma protein production and pregnancy is a hypermetabolic condition, a specific plasma protein profile was noted in women with HELLP syndrome compared with normal control cases. The primary candidate identified was serum amyloid A (SAA), which was significantly different between the HELLP cases and controls. However, further work is needed to determine if this is truly a predictive marker for the development of HELLP or merely a surrogate of liver impairment.

#### **Complications of HELLP**

Possible complications of HELLP syndrome include subcapsular hematoma of the liver, liver rupture, excessive bleeding, DIC, pulmonary edema, acute renal failure, abruptio placentae, peri-natal asphyxia, fetal death, and maternal death.

#### **Diagnosis of HELLP syndrome**

The diagnosis is made by the findings of fragmentation on the blood film, low platelets and abnormal liver function tests, and with abdominal ultrasound. The patient may or may not have signs of PET.

#### Management of HELLP syndrome

Stabilization of hypertension, if present, and other manifestations of HELLP, such as seizures or DIC are required as well as fetal monitoring. The only certain therapeutic measure is prompt delivery, and in the majority of cases women have complete recovery within 24-48 hours after labor, although some women may continue to have symptoms for up to 14 days. In the majority of patients, normalization of platelet count and resolution of HELLP occurs 5 days postpartum. If these signs of disease persist beyond 5 days postpartum (and indeed if they don't begin to improve within 48 hours of delivery), the diagnosis of HELLP should be reconsidered. Ideally, all women with HELLP should be referred to a tertiary hospital. Anti-hypertensive drugs, steroids, and plasma exchange/plasmapheresis have also been used with variable results.

A Cochrane review summarized the evidence on the effects of corticosteroids on maternal and neonatal

mortality and morbidity in women with HELLP syndrome.<sup>28</sup> From the five studies reviewed (n = 170), three were conducted antepartum and two postpartum. Four of the studies randomized participants to standard therapy, or to the administration of dexamethasone. One study compared dexamethasone with betamethasone. The conclusions were that there is insufficient evidence to determine whether steroid use in HELLP decreases the major maternal and peri-natal morbidity and the maternal and peri-natal mortality.

#### Platelet transfusions and HELLP syndrome

A randomized trial of women with class 1 HELLP syndrome received either dexamethasone (n = 26) or dexamethasone and platelet transfusions (n = 20). Liver function tests were significantly higher in the steroid plus platelets group. Platelet count normalized significantly faster in the dexamethasone only group, and the postpartum stay was more prolonged in the dexamethasone and platelet group. The group that received platelets reported complications such as wound dehiscence, wound infection and pulmonary edema.<sup>11</sup> A previous report of intrapartum use of platelets when platelet count was  $<40 \times 10^9$ /L did not find a significantly lower incidence of hemorrhagic complications. As a result, platelet transfusion is not often used in the management of HELLP.

# Massive bleeding secondary to placental abruption

Placental abruption is defined as the premature separation of a normally located placenta. Patients with defective placentation and abnormal placental vasculature, such as in PET, are predisposed to ischemia and rupture of these placental vessels, which is thought to lead to placental abruption. Other risk factors include smoking and cocaine use. Presenting features include mild vaginal bleeding, signs of hypovolemia, fetal compromise, uterine contractions or hypertonicity, DIC, and renal failure. Ultrasonography may be useful to confirm the position of the placenta, or the presence of a large hemorrhage, but is insensitive.

The management of placental abruption, whether expectant or with delivery depends on the extent of the abruption, the gestational age of the fetus, and the presence of fetal or maternal compromise. A full review is beyond the scope of this chapter and is covered in other sources. In general terms, however, delivery may be vaginal (usually due to the stimulation of rapid labor in response to the abruption), or by Cesarean section. The latter scenario may occur in the case of failed progression of labor or in maternal or fetal instability. Expectant management with or without the use of tocolytics may be possible if the presentation of bleeding is less acute and earlier in the pregnancy.

DIC often occurs in association with abruption, particularly with a complete abruption, and may follow within hours. The specific management of DIC has already been mentioned. The hemostatic management of massive bleeding is presented in Chapter 13c.

The maternal complications of placental abruption include massive hemorrhage, DIC, renal failure, and amniotic fluid embolism. Fetal complications relate primarily to premature delivery, i.e. stillbirth (adjusted relative risk of 8.9), growth restriction (adjusted relative risk of 2.0), and complications of prematurity.

### Differential diagnosis of PET and HELLP by microangiopathic hemolytic anemias (MAHA)

The differential diagnosis of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) from PET and HELLP may be difficult (see Chapter 18). TTP is diagnosed during pregnancy or postpartum, with 75% of episodes occurring around the time of delivery.

Postpartum HUS is a rare syndrome of unknown cause, not related to *E. coli* (D-). The prognosis is poor for both the mother and the fetus. It is recognized that HUS recurs in subsequent pregnancies, although the reason for that is not known. Many pregnant women who survive after HUS develop chronic hypertension and chronic renal failure later in life. Plasma exchange (PE) has low response rates.

### Acute fatty liver of pregnancy (AFLP)

HELLP syndrome should be distinguished from AFLP, a rare condition, also associated also thrombocytopenia, but without microangiopathic hemolytic anemia. Clinical presentation is similar with HELLP, occurring almost always in the third trimester. DIC accompanies AFLP in 90% of cases. Maternal mortality is approximately 15% and fetal mortality <5%.

### Summary

- Pre-eclampsia (PET), the new onset of hypertension after 20 weeks' of gestation and proteinuria, resolving after delivery, affects approximately 2%–14% of all pregnancies and remains a major cause of maternal and fetal morbidity and mortality worldwide.
- Placental dysfunction is considered to be the central feature in the development of PET.
- Current hypothesis is that PET is a two-stage disease: the first stage is reduced placental perfusion and the second stage is the maternal response to this with endothelial cell activation.
- Proposed placental factors produced from the placenta that affect blood flow, arterial pressure and maternal endothelial cell activation (ECA) include oxidative stress, cytokines (TNF-a,IL-6), and angiogenic factors (VEGF, s-FLT-1, sEng).
- Maternal constitutional factors that have been proposed to act as inductors of the maternal syndrome of PET, include several dietary factors, metabolic conditions (diabetes, insulin resistance, and uric acid), obesity, metabolic syndrome, folic

acid and hyperhomocysteinemia, hyperlipidemia, maternal vitamin D deficiency, and thrombophilia.

- PET is associated with fetal growth restriction (FGR), in one-third of cases.
- Despite PET and FGR occurring only in pregnancy, they have been shown to have long-term consequences for both mother and fetus. Mothers who have had PET or who have delivered a baby with FGR, experience a 2–8-fold increased risk of atherosclerotic cardiovascular disease (CAD) in later life.
- The key to good management is early detection and secondary prevention with anti-hypertensive and antithrombotic drugs (aspirin, heparin).
- Hematological complications of PET include thrombocytopenia, disseminated intravascular coagulation (DIC), HELLP syndrome, and massive bleeding after placental abruption.
- Differential diagnosis includes microangiopathic hemolytic anemias: (thrombotic thrombocytopenic purpura, TTP, hemolytic uremic syndrome, HUS), and acute fatty liver of pregnancy.

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**Microangiopathies** 



# Thrombotic thrombocytopenic purpura and other microangiopathies

Marie Scully and Pat O'Brien

# Introduction

Thrombotic microangiopathies (TMAs) describe the clinical and pathohistological effects of thrombosis in small vessels. There is usually thrombocytopenia and anemia and review of the blood film confirms the microangiopathic process, with evidence of red cell fragmentation and often polychromasia. One of the earliest diagnoses was by Moschowitz in 1924, who described a young woman with anemia and thrombocytopenia, neurological and renal symptoms, and signs with fever. This described the typical pentad of features of acute thrombotic thrombocytopenic purpura (TTP). However, in pregnancy, the differential diagnosis may be very difficult and often clinical suspicion in conjunction with laboratory parameters requires differentiation from other TMAs, which are specific to this period. The diagnostic challenge is the differentiation from acute fatty liver of pregnancy (AFLP), preeclampsia (PET) or eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets), antiphospholipid syndrome (APS), systemic lupus erythematosus (SLE), hemolytic uremic syndrome (HUS), and disseminated intravascular coagulation (DIC) (See Table 18.1).

# Moderate to severe thrombocytopenia presenting during pregnancy

Thrombocytopenia is defined by a platelet count  $<150 \times 10^9$ /L. It results from increased destruction and/or decreased production and can affect 10% of pregnancies. The most common is gestational thrombocytopenia, accounting for 75% of all cases. Rarely, the count is below 70  $\times$  10<sup>9</sup>/L, typically in the third trimester and it returns to normal within 12 weeks postpartum. It is thought to result from a hemo-dilutional effect in pregnancy and placental platelet

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destruction. There is very little risk of hemorrhage to the mother or the fetus.

ITP (immune thrombocytopenic purpura) occurs in 5% of pregnancies with thrombocytopenia and is a result of immunological peripheral platelet destruction. Maternal treatment and precautions during delivery may be required, but rarely does it have an effect on the fetus (Chapter 4).

PET and HELLP account for 21% of all cases of thrombocytopenia in pregnancy; the platelet count (and other pathological features) usually return to normal within 3–5 days after delivery.

# Placental profiles in high risk pregnancies

Abnormal uterine artery blood flow in the second trimester is indicative of an increased risk of placental pathology later in the pregnancy, including intrauterine growth restriction (IUGR) and PET. Uterine artery Doppler examination is often carried out at around 24 weeks' gestation in women considered to be at increased risk of these disorders. Increased resistance in the uterine arteries (indicated by increased pulsatility index or "notched" waveforms) are associated with a sixfold increased risk of thrombotic placental injury, leading to IUGR and/or PET, compared with normal uterine artery Dopplers. However, the sensitivity of this test is poor, so its use is usually restricted to high risk women. In early pregnancy, increased levels of biochemical markers such as alpha fetoprotein (AFP), beta-human chorionic gonadotrophin (β-HCG), and decreased levels of placental protein 13 (PP-13), in the absence of Down syndrome and spina bifida, are associated with an increased risk of PET, IUGR, placental abruption, and intra-uterine fetal death. These biochemical markers can improve the

Table 18.1	Typical features in	pregnancy	' associated	microanc	giopathies
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	МАНА	Thrombocytopenia	Coagulopathy	HBP	Abdominal symptoms	Renal impairment	Neurological symptoms
PET	+	+	±	+ + +	±	±	++
HELLP	+	+	±	+	+ + +	+	±
TTP	++	+++	_	±	+	++	+ + +
HUS	+	++	±	++	+	+ + +	±
AFLP	±	+	++	+	++	+	±
SLE	+	+	±	+	±	++	+
APS	+	++	±	++	_	++	++

MAHA: microangiopathic hemolytic anemia, HBP: High blood pressure.

PET: pre-eclampsia, HELLP: hemolysis, elevated liver enzymes and low platelets, TTP: thrombotic thrombocytopenia HUS: hemolytic uremic syndrome AFLP: acute fatty liver of pregnancy SLE: systemic lupus erythematosis APS:

 $\pm$ : possibly occurs.

+++: definitive feature.

predictive value of uterine artery Doppler imaging for the prediction of the smaller subset of women with a high risk of later developing serious problems related to placental disease.

# Thrombotic thrombocytopenic purpura (TTP)

TTP is an acute life-threatening disorder associated with thrombocytopenia, microangiopathic hemolytic anemia, and symptoms related to microvascular thrombosis. Clinically, in addition to a low platelet count (below  $150 \times 10^9$ /L, but more usually  $<50 \times 10^9$ /L), patients are anemic secondary to fragmentation hemolysis with an associated acute consumption of folate. Corresponding blood film changes include polychromasia, anemia, reduced platelets, and fragmented red blood cells. Bilirubin is often raised, but the direct antiglobulin test is negative and the clotting screen is normal. Lactate dehydrogenase (LDH) is increased, often out of proportion to the degree of hemolysis, due to associated tissue ischemia.

Von Willebrand factor (VWF), a plasma glycoprotein synthesized by megakaryocytes and endothelial cells, normally circulates as multimers of 500–20 000 kDa. Ultra-large VWF multimers (ULVWFM), which have a molecular weight greater than 20 000 kDa, and are not normally detected in plasma, were initially detected in patients with chronic relapsing TTP. Subsequently, a deficiency of VWF-cleaving protease in patients with TTP, was defined in 2001 as "a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13" or ADAMTS 13.<sup>1</sup> This enzyme is required to break down ULVWFMs. Failure to do so, due to an inherited deficiency or acquired reduction of ADAMTS 13, or due to antibodies to ADAMTS 13, for example, leads to platelet adhesion and aggregation of UL VWFMs and resulting microvascular thrombosis. Hence, platelet transfusions are relatively contraindicated in TTP, as infusions potentiate the effects of platelet aggregation on UL VWFMs.

Pregnancy is a precipitating cause of acute TTP, accounting for approximately 10%–25% of all cases of TTP in women. From the Oklahoma registry, 19 of the 61 women of child-bearing age presented with TTP during pregnancy or postpartum.<sup>2</sup> TTP is more common in women (3:2), and 45% of all cases of TTP occur in women of child-bearing age. There is also a risk of relapse of TTP during subsequent pregnancies in women diagnosed with TTP.

Other pregnancy-related thrombotic microangiopathies, such as pre-eclampsia / HELLP and hemolytic-uremic syndrome may further complicate the diagnosis of TTP. Gestational thrombocytopenia, which occurs in around 7% of pregnancies and is a diagnosis of exclusion, may explain a reduction in platelet counts, when all other laboratory parameters are normal. Management approaches differ for these conditions, although differentiation may be clinically challenging.

# Hemostatic changes of normal pregnancy-Factor VIII, Von Willebrand Factor (VWF), and ADAMTS 13

Normal pregnancy is associated with marked changes in hemostasis, which are hormonally mediated and protect against severe hemorrhage at the time of delivery, but ultimately result in a hypercoagulable state. Factor VIII and VWF increase in parallel in the first half of pregnancy; thereafter, the increase in VWF is greater throughout the remainder of pregnancy, returning to normal levels over the 6 weeks' postpartum. Reciprocal changes of VWF and ADAMTS 13 have been documented. Therefore, with the increased VWF in pregnancy, ADAMTS 13 would be expected to decrease. A review of ADAMTS 13 in normal women with no history of TTP documented a reduction in ADAMTS 13 activity in the second and third trimesters of pregnancy. A further study in healthy women confirmed a reduction in ADAMTS 13 activity after the first trimester (weeks 12-16) up until the end of the post-natal period when the levels normalized to pre-pregnancy levels. ADAMTS 13 activity was lower in non-pregnant nulliparous women (mean 65%) compared with parous women (mean 83%). In pregnancy and post-delivery, mean ADAMTS 13 activity was slightly, but non-significantly, lower in primigravidae than in multigravidae (68% vs. 74%). ADAMTS 13 was unaffected by platelet count, but was higher in smokers than in non-smokers during pregnancy (mean 79% vs. 70%, respectively). There was a significant correlation between higher VWF:Ag levels and lower ADAMTS 13 activity.<sup>3</sup> The reason for the decrease in ADAMTS 13 during pregnancy may be twofold. First, enzyme levels decrease with excess substrate, VWF. Second, a hormonal influence, possibly estrogen, may lower ADAMTS13 levels. A role for the effect of estrogen on parity, and ADAMTS 13 levels, are in line with estrodiol levels in the pregnant and non-pregnant state.

# Women presenting with acute TTP during pregnancy

Women presenting with TTP during pregnancy appear to fall into two groups: those with congenital TTP and those with acquired, antibody mediated TTP. Congenital TTP may first present during pregnancy and these women are more likely to relapse in subsequent pregnancies. Diagnosis is confirmed with ADAMTS 13 activity <5%, no evidence of an inhibitor, and confirmation by mutational analysis of the ADAMTS 13 gene, revealing a homozygous or compound heterozygous abnormality. To date, the published literature includes 14 patients, eight of whom received plasma during pregnancy. In women who present with acquired TTP related to pregnancy, the literature presents varying outcomes. Successful pregnancy outcome can be achieved in women with an initial episode of TTP.<sup>4</sup> In the Oklahoma registry,<sup>5</sup> there were 11 women who had a total of 17 pregnancies subsequent to a diagnosis of acute TTP in pregnancy. Two of these pregnancies were associated with TTP recurrence and neither infant survived. In women with no TTP in a subsequent pregnancy (15/17), infant survival was 80%. However, it appears from the remaining published literature, with the proviso that these are small case series and there is likely to be some reporting bias, that the risk of recurrence in subsequent pregnancies is approximately 50%, and infant survival rates are around 67%.

### Risk associated with pregnancy in women with previous acquired idiopathic (non-pregnancy associated) TTP

A particular concern in women who have had acute TTP unrelated to pregnancy is the risk of relapse from TTP during a subsequent pregnancy. From the Oklahoma Registry,<sup>5</sup> of 7 women with idiopathic TTP, 3 had recurrent relapsing TTP. In the 12 subsequent pregnancies following a diagnosis of TTP, 3 developed TTP in pregnancy and infant survival was 67%. Interestingly, in women who did not relapse from TTP during pregnancy (9/12 pregnancies, 75%), infant survival was only 33% (3/9). From the literature to date, including 20 women who had a total of 26 pregnancies following the diagnosis of acute TTP, 17/26 had a relapse of TTP during pregnancy and infant survival was 15/26. In those patients in whom ADAMTS 13 testing was available, normal levels prepregnancy/onset of pregnancy were associated with a lower likelihood of relapse. Another important feature of women reported in the literature is the number of complications documented associated with thrombotic microangiopathies, such as pre-eclampsia and HELLP syndrome, as well as reduced fetal survival (see Table 18.2). It could be hypothesized that women with TTP are at increased risk of prothrombotic complications and increased risk of placental infarction, despite normal routine TTP-based laboratory parameters.

Thrombotic microangiopathies during pregnancy may be clinically indistinguishable and very difficult to treat. With the normal reduction in ADAMTS 13

Reference	Number of pregnancies	In utero fetal death	Maternal death	Pre-eclampsia/ HELLP	Other
10	16	4		1	
11	6	1	-	-	-
5	29*	8	-	11/2	11x first trimester spontaneous abortions
12	4	3 (set of twins)	1	1	-
13	10	2	1	-	1x fetal distress, 1x placental abruption
4	5	2	-	-	1x Hypertension, 1x first trimester spontaneous abortion

**Table 18.2** Complications in pregnancy in women with a history of TTP

\*: Includes patients with HUS, but excludes those presenting with bloody diarrhea, therefore 29 pregnancies in 18 women. HELLP: hemolysis with elevated liver enzymes and low platelets.

Table 18.3 Thrombotic Thrombocytopenic Purpura Presenting During Pregnancy

<u> </u>	Number of women	Trimester					
References	during pregnancy	First	Second	Third/postpartum			
14	25	4	6	15			
15	9	0	0	9			
16	4	0	0	4			
17	9	2	1	6			
10	5	3	1	1			
5	19	1	3	15			
11	3	1	1	1			
12	4	1	1	2			
13	9	1	3	5			
4	3	1	2	0			
Total	90	14	18	58			

from the onset of the second trimester, it had originally been proposed that this was the time of increased presentation of acute TTP. However, it now appears that the greatest risk is in the third trimester or postpartum (see Table 18.3).

### Treatment of TTP in pregnancy

The combination of thrombocytopenia and MAHA encompasses a number of diagnoses in pregnancy and it is often difficult to differentiate TTP from these. The primary decision is whether delivery will be associated with remission of the TMA (as in PET or HELLP) or whether plasma exchange should be instigated, as recovery following delivery is unlikely and there is a risk of multi-organ dysfunction/ death. A further complicating issue is the development of HELLP/PET following delivery, which may occur in 20%–30% of cases of TTP in pregnancy.

If TTP develops in the first trimester, plasma exchange (PEX) may allow continuation of pregnancy with delivery of a live infant. However, as HELLP/preeclampsia or TTP can present in the post-natal period or there may be progression of symptoms despite delivery, PEX is the most appropriate option. With the availability of ADAMTS 13 activity measurement and detection of inhibitors to ADAMTS 13 (or more specifically IgG antibodies), it may be possible to distinguish TTP from other pregnancy associated TMAs, specifically if ADAMTS 13 activity is <5% and/or if IgG antibodies are present. In HELLP syndrome, ADAMTS 13 activity is reduced (median 31%, range 12%–43%) but with no inhibitor/antibodies to ADAMTS 13 and higher VWF levels. Steroids may be useful in HELLP syndrome and in TTP, but for different reasons. They have been used empirically in TTP because of the underlying autoimmune basis of the disorder, and in HELLP may accelerate recovery from delivery.

However, women presenting with thrombocytopenia, MAHA, neurological features (such as stroke/TIAs, seizures, encephalopathy), and renal impairment, should be treated with PEX until the diagnosis of TTP is excluded. In women with congenital TTP, the risk of relapse in a subsequent pregnancy is such that elective plasma therapy during pregnancy is warranted. Plasma infusions may be satisfactory; however, to deliver sufficient volumes, PEX may be required. The optimal frequency of plasma replacement is unknown; the half-life of ADAMTS 13 is 2–3 days and plasma therapy every 2 weeks appears satisfactory.<sup>4</sup>

In women with acquired TTP, it is not as easy to predict who are likely to relapse and the literature is sparse in this area. The previous history of TTP and the ADAMTS 13 activity at the onset of pregnancy may be helpful in differentiating patients most likely to relapse. A normal ADAMTS 13 at the onset of pregnancy appears to predict women at reduced risk of subsequent relapse.<sup>4</sup> However, if there is low ADAMTS 13 activity (<5%) at the onset of pregnancy, consideration should be given to elective therapy to prevent relapse. In contrast, women with normal ADAMTS 13 activity at the onset of pregnancy, who maintain normal routine laboratory parameters, ADAMTS 13 activity, and antibody/inhibitor levels throughout pregnancy, do not usually require intervention for TTP. A reduction in ADAMTS 13 activity (<10%) may be the trigger for elective therapy to prevent microvascular thrombosis during pregnancy.

Supportive therapy during pregnancy has not been addressed in the literature; specifically, low dose aspirin (LDA) and/or prophylactic low molecular weight heparin (LMWH). All patients in our cohort are maintained on LDA throughout pregnancy and women with a documented thrombophilia or a past history of venous thromboembolism (VTE) associated with TTP are started on prophylactic LMWH. The aim is to optimize implantation and preserve placental function as abnormalities of the utero-placental circulation, resulting in insufficiency are established in the first trimester. LDA/LMWH may be beneficial in other thrombophilic disorders during pregnancy, reducing the risk of placental abnormalities secondary to infarcTable 18.4 Physiological changes during normal pregnancy

Test	Change in pregnancy
Bilirubin	Unchanged
Aminotransferases	Unchanged
Alkaline phosphatase	Increase two to fourfold
Cholesterol	Increase twofold
Prothrombin time	Unchanged
Fibrinogen	50% increase
Hemoglobin	Decrease in later pregnancy
White cells	Increase

tion. However, this therapy has not been formally evaluated in pregnancy associated TTP. There are no data on the microvascular effects of "subacute" TTP before presentation with thrombocytopenia. Therefore, women with a previous pregnancy loss due to TTP or low ADAMTS 13 activity at the onset of pregnancy can be assumed to be at increased risk of further episodes of placental disorders in subsequent pregnancies. Interestingly, especially as reported in the Oklahoma registry data, there were a large number of first trimester losses in such women. This may be due to the underlying TTP risk, but there is no conclusive histological confirmation.

Therefore, women with congenital TTP require therapy with plasma, either as infusions or as PEX. In women with acquired, previous acute TTP episodes, the baseline ADAMTS 13 activity, and inhibitor/antibody status at the onset of pregnancy may be useful in the identification of those most likely to relapse. Monitoring of enzyme activity in those with normal early pregnancy levels may be useful, but in women with low (<5%) ADAMTS 13 activity and/or raised IgG antibody levels, which appear to be at increased risk of relapse, elective PEX may be useful. Adjunctive therapy with LDA in all women +/- prophylactic LMWH, should be added to help prevent complications related to placental thrombosis.

#### Liver disease in pregnancy

There are some changes in liver function in normal pregnancy (see Table 18.4), but clinically abnormal liver function can be detected in 3%–5% of all pregnancies. The cause may be coincidental to pregnancy or pre-existing chronic liver disease may be documented. However, in the majority of cases, pregnancy itself is the precipitant. Hyperemesis gravidarum

typically occurs in the first trimester and intrahepatic cholestasis of pregnancy (ICP) in the second or third trimesters. PET, HELLP and acute fatty liver of pregnancy (AFLP) are also associated with abnormal liver function.

# Intrahepatic cholestasis of pregnancy (ICP)

ICP has been associated with impaired sulphation and abnormalities of progesterone metabolism. Clinically, initially there is pruritus, which in 10%-25% progresses to jaundice associated with 10-20-fold increases in aminotransferases, but a less marked rise in bilirubin. The diagnosis is helped by measuring bile acid levels. Treatment is supportive and ursodeoxycholic acid (UDCA) is used. Steroids, although useful for fetal lung maturation pre-delivery have not been shown to be beneficial compared with UDCA therapy. The main risk of raised bile acid levels is to the fetus; there is an increased risk of placental insufficiency but more importantly an association with sudden intrauterine fetal death, the precise cause of which is not clear. Resolution of the condition occurs with delivery. However, recurrence occurs in 45%-70% of subsequent pregnancies or with use of the combined oral contraceptive pill, the progesterone only pill (mini-pill) appears not to increase the risk of recurrence.

# Acute fatty liver of pregnancy (AFLP)

This is a rare disorder (incidence estimated at 1/13 000 deliveries), but is an acute life-threatening illness associated with significant maternal and peri-natal mortality.<sup>6</sup> Typically, it presents in the third trimester, between the 30th and 38th weeks of pregnancy, although it has been rarely described in the first and second trimesters. It usually affects primigravid women, although reports of recurrence in subsequent pregnancies have been documented.

*Clinically*, presentation is non-specific with headache, fatigue, nausea, vomiting (70%), and right upper quadrant or epigastic pain (50%). Progression of the illness is often rapid and, early in the presentation, there may be gastrointestinal hemorrhage, coagulation abnormalities, acute renal failure, infection, pancreatitis, and hypoglycemia. Later in the disease process, liver failure and encephalopathy may occur. Early delivery is imperative and improvement

occurs over 1–4 weeks' postpartum, although an improvement in liver function is usually seen within a few days of delivery.

*Diagnosis* is suggested by the clinical features and may be confirmed by liver biopsy. Histologically, there is characteristic microvesicular steatosis and with Oil Red O staining, cytoplasmic vesiculation as a result of microvesicular fat. However, because of the acute presentation and laboratory features including coagulopathy, it is usually not possible to undertake liver biopsy, and the diagnosis is made by a combination of clinical and biochemical features.

In routine laboratory tests, there may be a raised white cell count and thrombocytopenia with normoblasts on the blood film. There is DIC (with prolonged PT, APPT, and reduced fibrinogen). Urea, creatinine, and uric acid levels are raised, there are elevated ammonia levels and hypoglycemia. Serum aminotransferases are markedly raised and alkaline phosphatase are three to four times the normal level (although this is raised in normal pregnancy because of placental production).

The primary *differential diagnoses* are acute fulminant hepatitis and severe HELLP, although the latter are less likely to be associated with hypoglycemia and prolonged PT. The histological features of liver biopsy are described above.

Pathogenesis: with advances in molecular biology, it has become evident that AFLP may result from mitochondrial dysfunction. There is a strong association between AFLP and a deficiency of the enzyme long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) in the fetus, a disorder of mitochondrial fatty acid beta-oxidation.  $\beta$ -oxidation of fatty acids is a major source of energy for skeletal muscle and the heart, while the liver oxidizes fatty acids under conditions of prolonged fasting, during illness, and at periods of increased muscular activity. Mitochondrial βoxidation of fatty acids is a complex process. LCHAD is part of an enzyme complex, the mitochondrial trifunctional protein (MTP), associated with the inner mitochondrial membrane. MTP contains four  $\alpha$  and four  $\beta$  subunits. A hydratase enzyme is located in the amino-terminal domain and LCHAD is located in the carboxy-terminal region of the  $\alpha$  subunit. The  $\beta$  subunit contains thiolase enzymatic activity. Defects in the MTP complex are recessively inherited and are due to an isolated LCHAD deficiency, specifically associated with G1548C mutation, with relatively normal hydratase and thiolase activities. In complete MTP

deficiency, there is a marked reduction in all three enzymes. A few hours after birth, children with these disorders, which are primarily LCHAD, present with non-ketotic hypoglycemia and hepatic encephalopathy, progressing to coma or death if untreated.

Studies suggest an association between fetal MTP defects and AFLP. In one study, in every pregnancy in which the fetus had an LCHAD deficiency, the mother developed AFLP or HELLP syndrome. Subsequent work in pregnancies without a LCHAD deficient fetus found that the pregnancy progressed normally, with no liver dysfunction. In another study of prospectively screened mothers who developed AFLP (27 pregnancies) or HELLP (81 pregnancies), 5 fetuses in the AFLP group, but none in the HELLP group, had an MTP mutation.

The precise mechanism by which a LCHADdeficient fetus causes AFLP in a heterozygote mother remains unclear. However, there are several hypotheses. The mother who is heterozygote for an MTP defect has reduced capacity to oxidize long chain fatty acids. The stress of pregnancy associated with altered metabolism, increased lipolysis, and decreased  $\beta$  oxidation, and the hepatotoxic LCHAD produced by the fetus or placenta may accumulate in the maternal circulation. Therefore, approximately one in five women who develop AFLP may carry an LCHAD-deficient fetus. Screening of newborn infants at birth for this disorder of fatty acid oxidation can be lifesaving and allows for genetic counseling in subsequent pregnancies.

# Hemolysis, elevated liver enzymes and low platelets (HELLP)

This is a microangiopathy associated with endothelial cell injury, fibrin deposition, platelet activation and consumption, and areas of hepatic hemorrhage and necrosis. The underlying precipitating cause is unknown but it occurs only in pregnancy and the incidence is between 0.17% and 0.85% of all live births. Maternal mortality is 3%–4%, with fetal mortality reaching approximately 25%, mainly due to prematurity. Diagnostically, there is considerable overlap with other TMAs especially PET, and they may represent different points on a single pathological spectrum (see Chapter 17). There are no obvious precipitating factors associated with development of HELLP and it typically presents between the second and third trimesters, although approximately a quarter of all cases are postpartum.<sup>7</sup> Typical presenting symptoms include upper abdominal pain and tenderness, nausea, vomiting, malaise, headache, and rarely jaundice.

There are no clinical or laboratory factors that are diagnostic, but bilirubin is not usually raised. Aminotransferases can be marginally increased or up to 20-fold. HELLP syndrome may be classified according to the degree of thrombocytopenia: HELLP 1 ( $\leq 50 \times 10^9$ /L), HELLP 2 (between 50 × 10<sup>9</sup> and 100 × 10<sup>9</sup>/L) and HELLP 3 (between 100 × 10<sup>9</sup> and 150 × 10<sup>9</sup>/L).

Serious maternal complications include DIC, placental abruption, acute renal failure, pulmonary edema, and hepatic failure, occasionally requiring liver transplantation. Hepatic rupture is a further rare, acute, life-threatening complication.

### Pre-eclampsia (PET)

This is classically defined as the triad of hypertension, proteinuria, and edema, but is best thought of as a multisystem disorder resulting from endothelial damage. It is a leading cause of maternal and neonatal morbidity and mortality, affecting 5%-10% of all pregnancies. It is more common in primigravid women. It rarely occurs before 24 weeks of gestation and the incidence rises as pregnancy advances, being most common in the third trimester. Liver involvement is common although rarely severe and is the most common cause of hepatic tenderness and liver dysfunction in pregnancy. It is an indicator for delivery because of the increased risk of severe eclampsia, hepatic rupture, DIC, and necrosis. The high peri-natal morbidity and mortality are partly due to the association with placental insufficiency and IUGR, but partly due to premature delivery for maternal indications. Severe PET is complicated in 2%-12% of cases by HELLP syndrome, consistent with the idea that they lie on a spectrum of a single disorder. Renal impairment, eclampsia (convulsions), and abnormalities of the coagulation system are further complications.

### Hemolytic uremic syndrome (HUS)

D+ (diarrhea positive) HUS is typically preceded by an illness with a verotoxin-producing bacteria, usually *E.coli* 0157:H7. Atypical, D– (diarrhea negative) HUS, is rare, with an incidence of 1/25000 pregnancies, and in nearly all documented cases associated with pregnancy, occurs postpartum. Atypical HUS (aHUS) may be familial and has a poorer prognosis, with a mortality of 25% acutely and 50% requiring chronic renal therapy. Like all TMAs, it is a disease of microvascular endothelial activation, cell injury, and thrombosis, but associated with complement deregulation, leading to an increase in activity in the alternative pathway. Mutations within the complement regulatory proteins and activating components are found.

Typically, the presentation in HUS is of MAHA, thrombocytopenia, and renal impairment. The primary pathology is in the renal arterioles and interlobular arteries, with widespread endothelial cell swelling, leading to exposure of the underlying basement membrane. The vessel lumens are occluded by red cells and platelet fibrin thrombi. The pre-glomerular pathology distinguishes it from D+HUS and TTP. There is consequently excess complement activation particularly along glomeruli, arteriolar endothelium, and basement membranes. More than 50% of cases result from mutations in complement genes controlling the alternative complement pathway. Mutations may affect complement regulatory genes, such as Factor H, I or MCP, or complement activating genes, Factor B (CBF), or C3 (C3). Single nucleotide polymorphisms and antibodies, such as to Factor H, have also been found to play a role. Factor H mutations, mostly heterozygote, account for 15%-30% of all cases of aHUS.8 MCP mutations account for 10%-13% of aHUS patients, the majority being heterozygote, with approximately 25% homozygous/compound heterozygote.

# Treatment

This is primarily supportive, including red cell transfusion, blood pressure control, and renal dialysis. The role of plasma therapy remains undetermined, but has been successful in some cases.

# Exacerbation of systemic lupus erythematosis (SLE)

SLE is an autoimmune disease, the active phase of which may be associated with thrombocytopenia, hemolytic anemia, pancytopenia, and an increase in double-stranded DNA. The disorder is multisystem and, typically, there are associated skin and joint symptoms. Serum complement levels may be normal or decreased. An acute exarcerbation occurs in 25%–30% of women during pregnancy, but it may occur for the first time during pregnancy<sup>9</sup> or in the postpartum period. An acute episode of lupus nephritis, associated with hypertension and proteinuria, may be difficult to differentiate from HELLP or pre-eclampsia.

Antiphospholipid antibodies (aPL) may be present in 30%–49% of women with lupus and further increase the risk of thrombotic events, the risk of tissue ischemia and TMA. Thrombocytopenia is present in a minority.

# Disseminated intravascular coagulation (DIC)

In pregnancy, DIC must not be forgotten as a cause of MAHA with an abnormal clotting screen. Usually, there is an underlying precipitating cause that must be treated and it can be a complication of any of the above TMAs in severe cases. Treatment of DIC requires platelet transfusions to maintain a count  $>50 \times 10^9$ /L, fresh frozen plasma, and cryoprecipitate, depending on the level of abnormality of the coagulation parameters.

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# Malignant conditions

# **Myeloproliferative disorders**

Claire Harrison and Susan E. Robinson

# Introduction

The myeloproliferative disorders (MPDs) encompass chronic myelogenous leukemia (CML), polycythemia vera (PV), myelofibrosis (PMF), primary thrombocythemia (PT also known as essential thrombocythemia or ET), rarer entities such as chronic neutrophilic leukemia, chronic eosinophilic leukemia, chronic myeloproliferative disease unclassifiable, and the mast cell diseases. This chapter will concentrate upon the management of the more common classical Philadelphia negative MPDs; PT, PV, and PMF in pregnancy.

# Epidemiology

The incidence of the classical Philadelphia negative MPDs combined is approximately 6/100 000– 9/100 000, with a peak in frequency between 50 and 70 years of age; they are less frequent in women of reproductive age.

Thrombosis and hemorrhage are a major cause of morbidity in MPD patients; progression to myelofibrosis or an acute leukemia occur less frequently. Historical case reports of pregnancy in MPDs have suggested significant maternal morbidity and poor fetal outcome. An increase in awareness of MPDs, advanced maternal age, and automation of blood counts to include a platelet count has led to an increase in the diagnoses of MPDs in women of a reproductive age. Hence issues concerning the management of these disorders in pregnancy are a real clinical challenge to hematologists and obstetricians that is compounded by a lack of clinical data and evidence-based guidance. This chapter provides a summary of the epidemiology, pathogenesis, and diagnosis of the MPDs in pregnancy and a management strategy developed from current experience attained in a tertiary referral center.

# Previous reports of MPD in pregnancy

A recent meta-analysis reported the outcome of 461 pregnancies in women diagnosed with PT.<sup>1</sup> The mean age was 29 years and the mean platelet count at the beginning of pregnancy was  $1000 \times 10^9$ /L declining to  $599 \times 10^9$ /L in the second trimester. The live birth rate was 50%-70%, first trimester loss occurred in 25%–40%, and late pregnancy losses in 10%. Rates of placental abruption (3.6%) and intrauterine growth restriction (IUGR) (4.5%) were higher than in the general population. Postpartum thrombotic episodes were reported in 5.2% of pregnancies and pre/postpartum hemorrhage in 5.2%. A summary of 208 historical cases of PT collated from case series that included greater than six pregnancies produced comparable data (presented in Table 19.1). The literature for pregnancies affected by PV is sparse; pregnancy outcome in a case series of 18 pregnancies in PV combined with 20 historical reports was concordant with the pregnancy outcomes in PT (and is summarized in Table 19.2).<sup>2</sup> In PV first trimester loss was the most frequent complication (21%), followed by late pregnancy loss (18%), IUGR (15%) and premature delivery (13%), which included three neonatal deaths resulting in a 50% survival rate. Maternal morbidity was also significant including three thromboses, one large postpartum hemorrhage, four cases of pre-eclampsia and one maternal death associated with evidence of a deep vein thrombosis, pulmonary emboli, sagittal sinus thrombosis and disseminated intravascular coagulation. Lastly, PMF is the least prevalent MPD in women of child-bearing age. A report of four pregnancies in PMF combined with four historical cases suggested a 50% risk of fetal loss; however, no maternal complications of thrombosis or disease progression were noted but the numbers are probably too small to draw any firm conclusions (summarized in Table 19.3).<sup>3</sup>

*The Obstetric Hematology Manual*, ed. Sue Pavord and Beverley Hunt. Published by Cambridge University Press. © Cambridge University Press 2010.

Reference	Number of pts	Number of Pregnancies	Previous thrombosis	Previous hemorrhage	Maternal outcome	Live birth total	Pregnancy loss total	Loss <12/40	Loss >12/40	IUGR	Placental abruption	Live birth premature delivery <37/40	Live birth FTD
6	ω	11	Detail not available	Detail not available	Detail not available	4	7	9	-	Detail not available	-	2	2
10	Q	6	0	0	1 Phlebitis 1 Leg ulcer 1 PPH	00	<del></del>		0	0	0	<del>.                                    </del>	7
11	Ø	10	Detail not available	Detail not available	Detail not available	7	e	0	m	Detail not available	0	0	7
12	6	15 (1 TOP)	1 VTE 2 TIA	0	2 VTE 2TIA 1 Hemorrhage	0	Q	m	7	2	0	4	S
13	13	16	1 VTE	0	3VTE	13	£	e	0	0	0	e	10
14	12	30 (1 Ectopic)	Detail not available	Detail not available	1 PE	17	13	4	Ø	2	2	2	12
15	6	17	1 CVA 1 VTE	1 Epistaxis	1 TIA 2 Acquired vWD 3 Vaginal bleeds 2 Epistaxis	11	Q	9	0	0	0	m	Ø
16	20	43 (2 TOP, 1 Ectopic)	Detail not available	Detail not available	Detail not available	22	21	16	2	Detail not available	<del></del>	<del></del>	21
17	12	17	0	0	3 Vaginal bleeds	7	10	80	2	0	0	0	7
18	16	40	Detail not available	Detail not available	1 Eclampsia 2 Pre-eclampsia 1 Vaginal bleed	26 (1 Twin)	15	13	2	-	0	7	23
Total	108	208				124 (60%)	85 (41%)	60 (29%)	20 (10%)	5 (2%)	7 (3%)	22 (11%)	102 (49%)
FTD: full term Adapted fron	i delivery; IU 1 refs. 4 and	IGR: intrauterine <u>c</u> 5.	growth restrictior	η; TOP: elective ter.	mination of pregnancy								

Table 19.1 Summary of reported pregnancies affected by PT

Live birth premature Live birth Placental delivery birth station) IUGR abruption <37/40 FTD	0 0 0	0 0 0 0 1 2 2 PET	5/40) PET 1 0 0 1	4/40 and 2 0 1 (32/40) 0 t0)***	+ 7 0 0 1 (7 months, 0 ths) PET 0 PET), 1 (8 months)	0 0 0 2	0 0 0	0 0	3 0 1 (34/40, 9 IUGR), 1 (36/40), 1 26/40) (NND)	6 0 6 17
Stil M (ge	0 dC	00	1 (3	2 (2 <sup>,</sup> 28/4	2 (5 mor	0	0	0	7	~
ey FTr	1 TC	0 0	0	0	0	0	-	0	4	00
Pregnand loss total	-	0 0	<del>-</del>	2	2	0	<del>-</del>	0	7	16 s
Live birth total	0	- 0	-	-	5	2	-	<del></del>	1	22 3 NND
Maternal outcome	Death*	Alive Alive PET	Alive PET	Alive PE postpartum	Alive PET	Alive PPH	Alive, PE 24/7 postpartum	Alive	Alive PET in 1	1 death 4 PET 2 PE 1 PPH
High risk	No	o o Z Z	No	0 N	Yes	No	No	No	°Z	1 yes
Treatment during pregnancy	Aspirin + dipyrimadole	N NI	None	Aspirin, heparin** venesection	Nil	Nil	Heparin 3/52 postpartum	Hydroxyurea 9/40 then nil	Varied: Venesection, Aspirin, Interferon LMWH, vitamin C+E	
Previous hemorrhage	No	0 O N	No	No	No	No	No	No	OZ	None
Previous thrombosis	No	0 N N	Superficial thrombo phlebitis	Q	Yes, CVA	No	No	No	Yes (1 patient)	1 CVA 1 thrombo phlebitis
No. of Pregnancies	-	3	2	m	4	2	2	-	18 (1 twin)	38
Number or of Pts	-		-	-	-	2	-	<del>.</del>	$\infty$	38
Auth	19	20	21	22	23	24	25	26	27	Total

\*\* postpartum heparin after 2<sup>nd</sup> pregnancy, LMWH throughout third pregnancy, aspirin throughout both pregnancies \*\*\*multiple placental infarcts in first and abnormal uterine artery Doppler waveforms and Severe IUGR in third pregnancy Adapted from ref. 2.

irth iture iks	ve on at 36			/e / at 34 e to 2000 g						
Live bi prema delive <37 w	1 Electiv inductio wks	0	0	1 Electi delivery wks due IUGR bi weight	1 FTND	1 FTND	0	0	4	
'lacental bruptior										
GR a P	0	0	0	0	0	0	0	0	0	
⊇ €	0	al 0	al 0	<del></del>	0	0	ac 0 on	0	-	
Stillbirth (gestatio	0	30 (placent infarctions)	27 (placent infarctions)	0	0	0	24/40 cardi malformati	0	e	
First trimester miscarriage	0	0	0	0	0	0	0	<del></del>	0	
Maternal outcome	No complications	No complications	No complications	No complications	Disseminated TB	Postpartum hemorrhage	No complications	No complications		
Treatment during pregnancy	Supportive	None	None	Interferon $\alpha$	Aspirin	Aspirin, LMWH	Aspirin, LMWH	Aspirin, LMWH	S	
Treatment Pre pregnancy	Supportive	None	None	Interferon α	Aspirin	Aspirin	Aspirin	Aspirin	ſ	
Previous hemorrhage	N	No	No	°N N	No	No	No	No	0	n normal delivery.
Previous thrombosis	N	No	Placental infarctions	Placental infarctions	0 N	Digital ischemia	Digital ischemia	Digital ischemia	m	in, FTND: full terr
Pregnancy	-	-	2	m	3 (nb. 2 preceeding PMF diagnoses)	, , ,	2	ŝ	00	rowth restrictio
Patient	-	_			∢	8	8	Ω	4	om ref. 3 uterine g
hor I		·				-		-	7	pted fro 3: Intrau
Aut					30				Tota	Ada IUGf

Table 19.3 Summary of literature regarding PMF in pregnancy

Historical reports of pregnancy in MPD are likely to be subject to selection bias, favoring cases associated with a poor outcome; prospective surveillance of pregnancies in MPDs and the development of structured evidence-based guidance would be of benefit in this field.

### Pathogenesis

MPDs result from the transformation of a hematopoietic progenitor cell and are characterized by overproduction of mature blood cells. The proliferation of one single cell type predominates, resulting in increased numbers of granulocytes (CML), erythrocytes (PV), platelets (PT), or fibroblasts (PMF). A single, acquired point mutation in the Janus kinase 2 (JAK2) gene occurring in the majority of patients with PV and almost half of those with ET and PMF was discovered in 2005. The mutation is a guanine to thymidine substitution that substitutes phenylalanine for valine at position 617 (V617F) of the JAK2 protein. This residue is located within the JH2 pseudokinase domain, which negatively regulates the JH1 catalytically active kinase domain. The wild-type JAK 2 protein binds to multiple cytokine receptors including the erythropoietin, thrombopoietin, and granulocytecolony stimulating factor receptors that are essential for hemopoietic stem cell biology and differentiation. The JAK2 protein with the V617F mutation enables constitutive, cytokine independent activation of the JAK-STAT, PI3K, and MAPK signal transduction pathways at various stages of development and in various lineages of hemopoietic cells (Fig. 19.1). Four further mutations affecting the JAK2 exon 12 that were recently identified define a distinctive myeloproliferative syndrome that affects patients who previously received a diagnosis of PV or idiopathic erythrocytosis. Finally, two further mutations in the thrombopoietin receptor MPL W515L/K have been described in patients with PMF(5%) and PT(1%). The reported mutations have been shown to produce an MPD-like phenotype in various murine models.

# Pathogenesis of placental infarction and thrombosis

Thrombosis is consistently identified as the leading cause of maternal mortality in apparently healthy normal pregnancies. Thrombotic occlusion of the placental circulation may be a late manifestation of placental dysfunction or an independent mechanism of pregnancy morbidity. In women with PT, placental thrombosis was reported in pregnancies which resulted in late fetal loss, pre-term delivery, and IUGR. IUGR, which is associated with utero-placental dysfunction, is known to occur in other acquired and inherited causes of thrombophilia.

Multiple factors are likely to contribute to the pathogenesis of thrombosis in MPDs, including the degree of thrombocytosis, leukocytosis, raised hematocrit, activation of platelets and leukocytes, the formation of platelet leukocyte aggregates, circulating prothrombotic and endothelial factors, and their interactions.<sup>6</sup> It is of interest to our understanding of how the MPD phenotype contributes to placental dysfunction that independently, studies of MPDs and preeclampsia both report increased platelet activation, platelet monocyte aggregate formation, and microparticle formation. It is currently unclear whether the presence of the JAK2 V617F and MPL W515L/K mutations increase the risk of thrombosis in MPDs and, if so, by what mechanism. However, recently a study of 103 pregnancies in 62 women with PT, identified the JAK2 V617F mutation as an independent predictor of pregnancy complications (P = 0.01). A total of 17 (71%) of 24 women carrying the JAK2 mutation had complications at first pregnancy. The study concluded that women with PT with the JAK2 V617F mutation had a twofold higher risk of developing complications than those without the mutation. A recent matched case control study of unexplained first pregnancy loss involving 32683 patients is in support of these findings. In 3496 pairs of women the JAK2 V617F mutation occurred more frequently in patients with pregnancy loss (1.06%) than in control subjects (0.20%).

# Diagnosis

The diagnosis of MPDs in pregnancy requires an increased awareness of these disorders occurring in pregnant women. Suspicion may be secondary to an abnormal full blood count, a thrombotic, or hemorrhagic event and should prompt referral to a hematologist. In view of pregnancy morbidities and the likelihood of improved outcome with intervention, these women benefit from a diagnosis being made pre-conceptually, during pregnancy or the postpartum period. The following section details local policy including adaptation for diagnostic investigations in pregnancy.



#### Fig. 19.1 Jak-Stat pathways.

#### Primary thrombocythemia

There is no diagnostic hallmark for this condition. The diagnosis is made by excluding other MPDs and a reactive or secondary cause of a thrombocytosis. Causes of a reactive thrombocytosis include iron deficiency anemia, chronic inflammation (e.g. rheumatoid arthritis, or inflammatory bowel disease), splenectomy, acute hemorrhage, and malignant disease. Where conditions co-exist that may cause a reactive thrombocytosis, this may make the diagnosis more difficult. In pregnancy the platelet count may fall especially during the second and third trimesters, thereby masking the diagnosis.

Historically, the diagnostic criteria for PT were those of the polycythemia vera study group; 40 years on, continual development of the diagnostic criteria for MPDs set the stage for the World Health Organization diagnostic criteria 2001, modified in 2007. The revised WHO criteria require characteristic bone marrow morphology (this is a controversial aspect not universally accepted), a platelet threshold of  $450 \times 10^9$ /L and molecular analysis for the JAK 2 V617F mutation and other clonal markers. Investigations should include a blood count, blood film, hematinics, renal, and liver profile, CRP, ANA and RhF, genetic screen for the JAK2 V617F, MPL W515L/K, and *bcr/abl* mutation and abdominal ultrasound scan.

#### Polycythemia vera

An erythrocytosis requiring investigation is defined as a packed cell volume (PCV) greater than 0.48 in non-pregnant women; in pregnancy this threshold has not formally been defined. To determine whether there is an absolute increase in PCV or an erythrocytosis or an apparent increase due to reduced plasma volume has traditionally required a red cell mass study, which would be contraindicated in pregnancy. Red cell mass scans have been largely superseded by testing for the presence of the JAK2 V617F mutation, which indicates the presence of the majority of PV cases. The JAK2 V617F mutation negative erythrocytosis cases may still be PV without a genetic marker or with a JAK2 exon 12 mutation; alternatives include a pseudo/apparent, primary congenital, secondary congenital or acquired, or an idiopathic erythrocytosis, all of which require definition.

The current British Committee for Standards in Haematology guideline for investigation and management of erythrocytosis<sup>7</sup> suggest a staged approach to investigation as the differential diagnosis is broad and secondary causes must be excluded. This is followed by investigations to confirm or refute a diagnosis of a JAK2 V617F positive PV. The majority of patients (excluding borderline erythrocytosis) and all ex- and current smokers will require a chest X-ray. This should be avoided in pregnancy unless there is a strong suspicion of a causative lung pathology, in which case appropriate screening should be used. Urinalysis is a simple effective screen for renal disease, which should be performed in all patients at the initial visit. Patients may present with co-morbidity, thus regardless of a diagnosis of PV a review of secondary causes is pertinent. Additional investigation of possible secondary causes will vary according to symptoms or signs present.

# Myelofibrosis

Myelofibrosis is very rare indeed in women of childbearing age. To achieve this diagnosis it is necessary to exclude other MPDs (PV, PT and CML) as well as disorders in which marrow fibrosis can develop as a secondary feature such as metastatic carcinoma, lymphoma, irradiation, TB, and leishmaniasis. The following features are generally necessary to confirm a diagnosis of MF: splenomegaly, increased bone marrow fibrosis (coarse reticulin fibers arranged in parallel in trephine biopsy), a leukoerythroblastic blood film (immature red cells and myeloid precursors with tear drop-shaped red cells) and the exclusion of secondary causes of myelofibrosis (see above). In all suspected cases of MF a bone marrow aspirate and trephine are required.

### **Treatment options**

Women of reproductive age with a diagnosis of MPD should receive information and assurance regarding management and outcome of future pregnancies. If fertility issues arise, optimal disease management may need to be re-addressed prior to a timely referral for standard fertility investigation. A risk assessment according to disease status, concomitant illnesses, and prior obstetric history forms the basis for a discussion of the risks and benefits of therapeutic options in pregnancy. According to perceived risk, the therapeutic options include aspirin, heparin, venesection, cytoreductive agents, and thromboembolic deterrent stockings. From pre-conceptual planning to the postpartum period, access to joint care from an obstetrician with experience of high risk pregnancies and a hematologist in a multidisciplinary setting is paramount.

The pre-conception to postpartum management plan should include:

- informed multidisciplinary care and education;
- risk assessment and discussion of therapeutic options and implementation of an appropriate management plan;
- additional monitoring during pregnancy;
- further optimization of disease control, if fertility is an issue, prior to timely referral for standard investigation;
- A comprehensive delivery and postpartum plan.

This approach enables optimal disease control with the aim of increasing the possibility of conception, implantation, and maintenance of placental function. Thus reducing complications secondary to placental dysfunction, such as IUGR and pregnancy losses. An emphasis upon the prevention of thrombosis and hemorrhage and management of events pre- and postpartum is also required.

Two key treatment aims, in high risk non-pregnant patients with MPDs, are to attain a platelet count less than  $400 \times 10^9$ /L and a PCV less than 0.45 and possibly less than 0.42 in women who remain symptomatic. In pregnancy an increase in the plasma volume reduces both the platelet count and PCV, which is likely to further alter blood cell rheology. Interestingly, it has been suggested that the decrease in platelet count is greater than that expected in a normal pregnancy. One theory is whether the placenta produces an interferonlike substance. An understanding of this physiological dilutional effect and the brisk return to pre-pregnancy levels in the postpartum period in MPD pregnancies, are important when considering optimal monitoring intervals and suitable treatment targets. The target PCV and platelet count in pregnant women with MPDs are ongoing debates, but appropriate targets are probably a platelet count of less than  $400 \times 10^9$ /L and a hematocrit certainly less than 0.45 and probably in the mid gestation appropriate range.

#### Aspirin

Low dose aspirin is considered safe in pregnancy in accordance with the Collaborative Low dose Aspirin Study in Pregnancy (CLASP), although its use for thromboprophylaxis in MPDs has never been assessed by a controlled trial. The European Collaborative Lowdose Aspirin in Polycythaemia Vera (ECLAP) study supports the use of low dose aspirin in non-pregnant patients with PV. Aspirin has been the most widely used therapy (in at least half of published pregnancies) for pregnancies affected by PT. Although the evidence is both retrospective and based on small numbers, the use of low dose aspirin in pregnancy in myeloproliferative disorders seems advantageous, and a low risk strategy for the pregnancy. A recent update of the largest case series of pregnant women with PT to date provided analysis of pregnancy outcomes treated with aspirin vs. those managed by observation alone. There was no evidence that therapy with aspirin positively influenced pregnancy outcome in women with PT; however, interpretation should be cautious as with all retrospective reports.

#### Low molecular weight heparin

A study of women with the Factor V Leiden, prothrombin gene mutation or protein S deficiency, and one fetal loss demonstrated aspirin to be inferior to low molecular weight heparin (LMWH) in terms of live birth rate and birth weight. The successful use of LMWH in other pregnancies at high risk of thrombosis and in reducing fetal morbidity has drawn attention to the possibility of its use, in addition to aspirin, during pregnancy in women with MPDs with a previous thrombosis or pregnancy-related events.

Our regime for LMWH use, if necessary, in pregnant patients with MPDs is:

- ante-natal dose of LMWH, e.g. 40 mg enoxaparin daily or 5000 IU dalteparin daily, increasing to 12 hourly from 16 weeks onwards;
- at low body weight (e.g. < 50 kg), lower doses of LMWH may be required, e.g. 20 mg enoxaparin daily or 2500 IU dalteparin daily;
- In obese patients (e.g. BMI > 30 in early pregnancy), higher doses of LMWH may be required, e.g. 40 mg enoxaparin 12 hourly or 5000 IU dalteparin 12 hourly;
- postpartum dose of LMWH, e.g. 40 mg enoxaparin daily or 5000 IU dalteparin daily for 6 weeks;
- if uterine artery Dopplers are repeatedly abnormal, increase to a therapeutic dose of LMWH.

In women with previous arterial thrombotic events or in those with recurrent thrombosis on warfarin prior to pregnancy, therapeutic doses of subcutaneous LMWH may be required. Some patients may require monitoring of anti-Xa levels.

# Graduated elastic compression stockings (GECS)

GECS may be used ante-natally and during the postpartum period. There are no trials to support such practice, but the British Society for Haematology (BSH) guidelines suggest that all women with previous venous thrombosis or a thrombophilia should be encouraged to wear GECS throughout their pregnancy and for 6–12 weeks after delivery.

#### Cytoreductive therapy

Cytoreduction is used where necessary to reduce the platelet count or a raised PCV that is resistant to venesection, but these agents should preferably be avoided in pregnancy, particularly in the first trimester. None of the cytoreductive drugs mentioned in this chapter have a product licence for use in pregnancy. The expected natural fall of the platelet count and hematocrit during pregnancy may reduce the need for cytoreduction or venesection. However, in high risk situations where cytoreduction is deemed necessary (see below), interferon  $\alpha$  (IFN- $\alpha$ ) is the drug of choice. There are no reports of teratogenic effects in animals or adverse effects in the admittedly small numbers of pregnancies exposed to this drug. However, some evidence suggests that IFN- $\alpha$  may decrease fertility and

 Table 19.4
 95% ranges for hematological variables during pregnancy

Gestation	First trimester	Second trimester	Third trimester
Hb (g/dL)	11-14.3	10-13.7	9.8–13.7
PCV (I/L)	0.31-0.41	0.30-0.38	0.28–0.39
Platelet count (10 <sup>9</sup> /L)	174-391	171-409	155-429
Adapted from ref. 8.			

so it is best avoided in women with difficulty conceiving. In relation to hydroxyurea, the outcomes of small numbers of pregnancies have been published and these are mainly without fetal complications, although one stillbirth and one malformed infant have been reported after exposure to hydroxyurea. Teratogenicity in animals has also been reported. Thus the use of hydroxyurea is probably contraindicated at the time of conception and during pregnancy. The use of anagrelide in pregnancy is similarly not recommended because of insufficient documentation of its use in this situation and because of the possibility of thrombocytopenia in the fetus.

### Venesection

Although the natural fall in the hematocrit or PCV in pregnancy may obviate the need for venesection, it is an option in resistant cases. If venesection fails to control the PCV, then cytoreduction should be considered. The target PCV for a pregnant woman has yet to be determined. A reasonable target PCV would be the middle of the gestation appropriate range (Table 19.4). There is currently no evidence for maintaining it lower than this in pregnancy, although this has been an area of controversy.

# Recommendations for management of MPDs in pregnancy

An overview of the small groups of MPD patients and individual cases described in the literature does not enable confident management guidelines to be drawn up. The following are recommendations based on current knowledge of this and other thrombophilic states and upon personal experience in a tertiary referral unit. Good communication between consultant obstetrician and hematologist is essential. Table 19.5 High risk MPD pregnancy criteria

- Previous venous or arterial thrombosis in mother (whether pregnant or not)
- Previous hemorrhage attributed to MPD (whether pregnant or not)\*
- Previous pregnancy complication that may have been caused by a MPD:
  - Three pregnancy losses < 10 weeks</li>
  - One or more pregnancy losses >24 weeks
  - Intra-uterine growth restriction or other evidence of placental dysfunction
  - Intra-uterine death or stillbirth (with no obvious other cause)
  - A significant ante- or postpartum hemorrhage (requiring red cell transfusion)
  - Severe pre-eclampsia (necessitating preterm delivery < 37 weeks)</li>
- Platelet count rising to >1500 × 10<sup>9</sup>/L prior to pregnancy or during pregnancy\*
- Diabetes mellitus or hypertension requiring treatment
- JAK2 V6127F mutation, the status of this as a risk marker is currently unclear

Note \* these criteria would be an indication for cytoreductive treatment but  $\textit{not}\,\text{LMWH}.$ 

### Pre-conceptual meeting

The patient should ideally have a pre-conceptual meeting with both an obstetrician and a hematologist to discuss a plan of management for a future pregnancy, including the necessity for cytoreductive therapy. Ideally, this should be written out and copied to the patient.

# Control of platelet count and haematocrit

If a patient is already taking hydroxyurea or anagrelide, this should be gradually withdrawn before conception, followed ideally by a wash-out period of 3 months for hydroxyurea following the last dose. The platelet count and PCV must be closely monitored thereafter. Careful venesection should be commenced if the hematocrit rises above the gestational appropriate range. Cytoreduction with IFN- $\alpha$  may be necessary in cases with a raised PCV resistant to venesection or persistent thrombocytosis. Most patients with a clear indication for cytoreductive therapy pre-pregnancy will require cytoreduction during pregnancy.

Cytoreduction with IFN- $\alpha$  may also be necessary if any of the factors are present, or if they develop in the index pregnancy, which in our experience defines a high risk MPD pregnancy (Table 19.5). Treatment should be guided by monitoring the full blood count and by maintaining the platelet count less than 400  $\times$  10<sup>9</sup>/L and the PCV in the appropriate gestational range.

#### Management of thrombotic risk

#### Assessment of need for antithrombotic medication

The assessment of the need for antithrombotic medication should preferably be done in the pre-conceptual meeting, but on-going individual risk assessment should occur and may warrant commencing or increasing thromboprophylaxis.

#### Aspirin

In the absence of clear contraindications, i.e. asthma, history of peptic ulceration, or current hemorrhage, all patients should be on aspirin (initially 75 mg once daily) throughout the pregnancy and for at least 6 weeks after delivery. In the event of a platelet count in excess of  $1000 \times 10^9$ /L, acquired von Willebrand disease should be excluded prior to commencing aspirin.

#### Low molecular weight heparin

Consider the use of subcutaneous LMWH during pregnancy in addition to cytoreduction in patients with any of the high risk MPD pregnancy factors listed in Table 19.5 with the exception of hemorrhage and extreme thrombocytosis. LMWH is an option to be introduced in patients with persistently abnormal uterine artery Dopplers. Once adequate hemostasis has been achieved postpartum, all women should be offered 6 weeks of LMWH thromboprophylaxis in the absence of a prior history of a significant hemorrhage. Caution should be applied to cases where women have a previous history of a significant hemorrhage with a platelet count <1000 × 10<sup>9</sup>/L and no other obvious cause except for platelet dysfunction secondary to a MPD.

#### Graduated elastic compression stockings

Consider the use of GECS as a supplementary therapy throughout pregnancy and for 6–12 weeks after delivery in accordance with current BSH guidelines.

#### Maternal and fetal monitoring

#### Maternal monitoring

Full blood count monitoring, blood pressure, and urine testing should be performed 4 weekly until 24 weeks and thereafter at 2-weekly intervals.

#### Fetal monitoring

The local protocol for fetal monitoring includes scans at 12 and 20 weeks. If the uterine artery Doppler ultrasound at 20 weeks is abnormal, it should be repeated at 24 weeks; if abnormal then, consideration should be given to increasing or escalating therapy. Regular growth scans should also be performed.

Uterine artery doppler scanning at 20 and 24 weeks will reveal whether the woman has bilateral notching. The persistence of bilateral notching indicates increased resistance to flow and possible placental dysfunction. The presence of persistent bilateral notching at 24 weeks should prompt commencing or increasing LMWH to 40 mg s/c twice daily, and further treatment escalation including interferon  $\alpha$  and the possibility of an early delivery may need to be considered.

#### Delivery

Prior to labor or Cesarean section, it is important to discuss the implications of the use of thromboprophylaxis for epidural or spinal anesthesia with the woman and obstetric anesthetist following locally agreed protocols. If a woman develops a hemorrhagic problem while on LMWH, the treatment should be stopped and hematological advice sought; a platelet transfusion may be useful in patients with MPDs. It should be remembered that excess blood loss and blood transfusion are risk factors for VTE, so thromboprophylaxis should be begun or reinstituted as soon as the immediate risk of hemorrhage is reduced. The third stage of labor should be managed actively.

#### Postpartum thromboprophylaxis

The time of greatest risk for VTE associated with pregnancy is the immediate puerperium period. The prothrombotic pregnancy phenotype does not revert back to normal until 6 weeks after delivery. All MPD patients should receive 6 weeks of postpartum LMWH thromboprophylaxis unless contraindicated. Aspirin should also be continued for at least 6 weeks. As discussed above, where women have a history of hemorrhage, the addition of postpartum heparin should be cautious and considered on an individual case basis.

#### Postpartum assessment

The platelet count and PCV may rise dramatically postpartum, but can usually be controlled with cytoreductive therapy or venesection. Cytoreductive therapy suitable immediately post-delivery if required include hydroxyurea, IFN- $\alpha$  and anagrelide, the choice and dose depending on previous experience in that patient. Hydroxyurea, IFN- $\alpha$ , and possibly anagrelide are excreted in breast milk, so breast feeding is then contraindicated. In the current literature there is no evidence that pregnancy predisposes MPD patients to acceleration of their disease to PMF or acute leukemia, nor would this be anticipated. The most significant risk is of thrombosis in the mother and adverse fetal outcome. A frequent question asked by these patients is what is the chance of their children being affected by MPD. Until recently, it was believed that familial MPD was relatively rare and, whilst this is true for large kindreds with many affected individuals, it has become apparent that up to 8% of MPD patients may have an affected relative, usually a cousin, aunt, uncle, etc. Parent:child combinations are extremely uncommon and routine testing of children is not recommended.

### Dilemmas

The following section includes a series of challenging cases, which enable discussion of management options accordingly in these women with complex pregnancies.

#### Case 1

A 37-year-old lady with a diagnosis of PT is referred for a tertiary opinion regarding conception and pregnancy management. The referral to a hematologist and initial diagnosis of PT followed a full blood count screen by her GP. The obstetric history includes one full-term spontaneous vaginal delivery 12 years previously. Following remarriage 3 years ago, she has undergone two spontaneous miscarriages <10 weeks. The current platelet count is  $1700 \times 10^9$ /L, current medication includes aspirin 75 mg daily.

In an attempt to establish when the patient developed PT prior to the official diagnosis, any previous full blood counts could be reviewed. However, this is unlikely to change the management in this case. The diagnosis of PT and obstetric history are suggestive of poor pregnancy outcome secondary to PT. The platelet count enables us to stratify the patient as being at high risk of a vaso-occlusive event and outside of pregnancy would suggest benefit from commencing cytoreductive therapy. With the stated aim to conceive in the near future, the appropriate cytoreductive agent would be interferon  $\alpha$  as this could be continued throughout pregnancy. A screen for an acquired von Willebrand's disease should be completed prior to continuation of aspirin. The woman should be monitored in her local clinic and the dose of interferon adjusted to maintain a platelet count  $<400 \times 10^9$ /L. If a pregnancy is confirmed, monitoring according to the treatment algorhythm should commence and follow-up could be shared between the local hospital and tertiary referral unit. The patient does not currently meet the criteria to commence LMWH ante-natally, although may benefit from heparin and aspirin for 6 weeks postpartum. However, a discussion within the multidisciplinary pre-conceptual meeting in view of patients age and prior obstetric history may conclude the addition of LMWH from conception as suitable on an individual basis regardless that the history is of two not three miscarriages <10 weeks. Clearly, these complex cases need to be managed upon an individual basis and management plans may need to encompass aspects which are outside of general guidance. Close collaboration between the local hematology and obstetric unit and the tertiary center may enable delivery outside of the tertiary center dependent upon the progress of the individual pregnancy.

#### Case 2

A pregnant 26-year-old woman diagnosed with PV following investigation of menorrhagia and epistaxis 4 years previously is referred for an opinion at 9 weeks' gestation. There is no prior obstetric history, and the current management is low dose aspirin and venesection. Her current blood count reveals Hb 15 g/dL, HCT 0.47, plt  $567 \times 10^9$ /L.

The history of hemorrhage and or epistaxis may be attributed to MPD in this case and, if so, the woman would meet the criteria to consider interferon in this pregnancy, but this is a relatively soft indication and the authors would not use this treatment in this setting. However, this history should be examined carefully as hemorrhage is rare in these conditions and, even though the platelet count is not markedly abnormal, it would be wise to screen for von Willebrand's disease. With no history of thrombotic events or pregnancy complications, there is no indication for ante-natal heparin prophylaxis unless uterine artery dopplers subsequently suggest impaired placental function; heparin should be given for 6 weeks postpartum. Aspirin should be continued throughout pregnancy. The current PCV is outside the appropriate range for the first trimester and venesection should be considered if tolerated.

#### Case 3

A 32-year-old woman diagnosed with PMF 3 years ago following a recent hepatic vein thrombosis attends clinic to discuss treatment options regarding future pregnancies. She has one healthy daughter of 5 years delivered by Cesarean section following a trial of labor which failed to progress. Current medication includes aspirin, warfarin, and hydroxyurea. The question of future cord blood stem cell storage is also raised. Her current blood count in Hb 11 g/dL, PCV 0.35, plt 147, Wbc 7.6  $\times$  10<sup>9</sup>/L.

In the pre-conception planning, a management plan regarding anticoagulation, cytoreductive therapy, and review of concomitant liver disease is required. The issues of stem cell storage needs to be addressed regarding reasoning and practicalities. Clearly, the woman may have a personal interest in cord stem cell storage and this needs to be addressed preconceptually. This complex case would benefit from follow-up and delivery in a tertiary referral center.

The aspirin should be continued throughout pregnancy; testing should be performed in the fortnight following a possible conception in order to stop the warfarin as early as possible and commence LMWH. In view of the history of a hepatic vein thrombosis, a therapeutic dose of LMWH should be used and switched back to warfarin postpartum. Three months prior to conception the hydroxyurea needs to be stopped and interferon commenced. Optimization of any concomitant liver pathology and portal hypertension secondary to the previous hepatic vein thrombosis is important. The obstetric history needs to be reviewed in light of whether portal hypertension and varices are present. The presence of varices may require banding and additional medication, which should be instigated and followed up by the gastroenterology team. The planned mode of delivery according to concomitant pathology needs to be addressed in a multidisciplinary meeting.

#### Case 4

A pregnant 31-year-old female with diabetes is referred at 10/40 with a platelet count of 759  $\times$  10<sup>9</sup>/L from the combined endocrine obstetric clinic and is subsequently diagnosed with PT.

Although there is no previous obstetric history, a diagnosis of diabetes suggests a high risk pregnancy. Outside of pregnancy, the patient would be in the high risk of vaso-occlusive event group secondary to the diagnosis of diabetes. Low dose aspirin should be commenced and continued postpartum. A prophylactic dose of LMWH once daily increased to twice daily at 16 weeks followed by 6 weeks' postpartum prophylactic once daily LMWH should be considered. Interferon would also be considered in this case.

#### Case 5

A 29-year-old pregnant woman with a diagnosis of PT with no prior obstetric history or thrombotic events attends clinic at 15/40. Hb 12 g/dL, HCT 0.34, Plt 580  $\times$  10<sup>9</sup>/L.

Low dose aspirin throughout pregnancy continued indefinitely postpartum, combined with 6 weeks postpartum heparin prophylaxis would be appropriate in this case. Additional treatment will depend upon how the pregnancy progresses.
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Malignant conditions

# Effects of chemoradiotherapy for hematological malignancy on fertility and pregnancy

Seonaid Pye and Nina Salooja

# Introduction

Section 7 Chapter

Advances in treatment for hematological malignancies over the last two decades have led to marked improvements in survival, and for many patients this translates to cure. Consideration of the long-term sequelae of treatments administered are therefore becoming increasingly relevant to the overall management strategies of these disorders and, since many of the potentially treatable hematological cancers occur in children and young adults, this includes concerns about future fertility. The chemotherapy agents and radiotherapy used to treat leukemias and lymphomas can affect reproductive potential in a variety of ways. In this chapter we will consider:

- the general effects of chemoradiotherapy on female fertility;
- the incidence of infertility following radiation and chemotherapy;
- the likely outcome of pregnancy in a patient treated for hematological malignancy;
- the strategies available for the preservation of fertility in patients who require potentially sterilizing treatment.

# General effects of chemoradiotherapy on fertility

Normal reproduction requires interplay between the gonads and the hypothalamic-pituitary-endocrine axis. In addition, the uterus must be receptive to implantation and capable of effecting appropriate growth in pregnancy. Damage to hormone producing cells in the hypothalamus, pituitary, or gonads can lead to infertility as well as more direct damage to the germ cells, reproductive tracts, or sexual organs.

In females the production of germ cells (oocytes) ceases before birth. Thereafter, the number of oocytes decrease throughout life, either by a mechanism of preprogrammed cell death (physiological apoptosis) or else post-menarche, in menstruation. When the number of oocytes falls below a critical number, ovulation and ovarian function cease. A female's fertility potential is therefore related to the number of oocytes, which are present in the ovary. Chemotherapy and radiotherapy both lead to an additional irreversible reduction in oocyte numbers by mechanisms which involve activation of apoptotic pathways.

The chance of retaining ovarian function following such external insults to germ cell numbers depends on the starting number of oocytes and this is related to the age of the patient. Thus young women who start with high numbers of oocytes are more likely to recover menses and fertility following chemoradiotherapy, although they remain at risk of premature ovarian failure. Older women with relatively low numbers of oocytes remaining in the ovary pre-treatment, frequently experience immediate and irreversible cessation of ovarian function. Clinically, this may be accompanied by severe vasomotor symptoms and biochemically it is associated with low serum levels of estradiol with significantly elevated levels of FSH and LH.

# The incidence of infertility following radiation

The clinical effects of radiotherapy on fertility depend on the dose and radiation field in addition to patient age as discussed above. Animal studies have shown that increasing doses of ovarian radiation lead to loss of primordial follicles in a dose-dependent manner. The dose at which 50% of human oocytes are lost (LD50) has been estimated to be <2Gy.<sup>1</sup> Considering

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Site of irradiation	Tissues relevant to fertility potential
Irradiation to the cranium, for example: (a) total body irradiation (b) craniospinal irradiation (c) direct cranial irradiation	Hypothalamic–pituitary axis
Irradiation to the abdomen or pelvis, for example: (a) total body irradiation (b) total lymphoid irradiation (c) craniospinal irradiation (d) direct irradiation to the pelvis or abdomen	Ovaries Uterus Reproductive tract

the radiation fields, treatment impinging on either the cranium or reproductive tract can lead to impairment of fertility (Table 20.1).

### Direct cranial irradiation

Irradiation of the hypothalamic–pituitary axis leads to a classical pattern of hormone loss, with growth hormone being the most sensitive and first to be affected followed by the gonadotrophins. In patients with intracranial disease associated with acute leukemia, direct cranial radiation may be administered. Doses in the range 18–24 Gy may result in isolated growth hormone (GH) deficiency. In addition, subtle disturbances in the menstrual cycle may occur, although their relevance to future reproductive potential is unclear. Delayed puberty has been described in young girls who receive doses above 24 Gy.

Patients with pituitary and primary brain tumors can be given higher doses of radiation exceeding 50 Gy. Such doses can damage pituitary function directly, but features of hypopituitarism in patients who have received doses less than 50 Gy are more likely to be secondary to hypothalamic dysfunction.

### Direct abdomino-pelvic radiation

As discussed above, radiation to the ovaries leads to damage which is dose related. Abdomino-pelvic irradiation also damages the uterus with adverse effects documented on the endometrium, myometrium, and vasculature. In a study which investigated length and blood flow of the uterus in ten women aged 15–31 following 20–30 Gy abdominal radiotherapy, there were significant reductions in uterine length and blood flow compared with women whose treatment had not included abdominal radiation.<sup>2</sup>

Radiation induced damage might also be expected to impair implantation and/or growth and development of a fetus and there is data to support this. In a study where 38 patients were given 20–26.5 Gy abdominal radiotherapy in childhood, there were four documented conceptions but no live births, all miscarrying in the second trimester.<sup>3</sup>

## Total body irradiation

This affects all of the radiation sites relevant to fertility potential. It is usually given together with chemotherapy, as conditioning prior to stem cell transplantation(SCT) and serves two separate functions:

- suppression of the host immune system to allow donor engraftment;
- eradication of hemopoiesis in the host bone marrow.

Doses of 8–15 Gy are administered either as a single dose or in fractions. At these doses, the effects on the hypothalamic–pituitary axis are usually minimal, but both ovarian function and uterine function are compromised. The incidence of ovarian failure is high. In a single center study, which included 144 women who had received total body irradiation (TBI) as conditioning for SCT, all became amenorrheic immediately post-transplant and only 9 of the 144 recovered menses at a median of 4 years following treatment.<sup>4</sup> All who regained ovarian function were aged less than 25 at the time of SCT.

Uterine function following TBI has been less extensively studied, but in a study which included 12 women who had received TBI in childhood, there was a reduction in uterine volume to 40% of adult size despite the use of sex steroid replacement therapy.<sup>5</sup> These patients had received either unfractionated TBI at a midline dose of 8.5–10 Gy (n = 4) or a total midline dose of 10.9–11.7 Gy in three fractions (n = 8). These data suggest that the adverse effects of radiation may be more marked if given pre-pubertally, before optimum growth of the uterus has been achieved.

# The incidence of infertility following chemotherapy

The likelihood of infertility following chemotherapy depends on

- the drug(s) administered;
- the doses to which the patient is exposed;

- the underlying disease;
- patient age.

Chemotherapy agents can be divided into classes based upon their mechanism of action (Table 20.2).

Meirow<sup>6</sup> provides an elegant analysis of sterilizing effects of different classes of chemotherapeutic agents (Fig. 20.1). Data on 168 patients treated with combination chemotherapy were evaluated and the odds ratio for ovarian failure calculated for exposed versus

Table 20.2 Classes of chemotherapeutic agents and their action

Drug class/subclasses	Examples	Mechanism of action
Alkylating agents Nitrogen mustards Nitrosureas Alkyl sulfonates Triazines Ethylenimines Platinum drugs*	Cyclophosphamide, chlorambucil, melphalan BCNU (carmustine), Lomustine Busulfan Dacarbazine Thiotepa, altretamine Cisplatin, carboplatin	DNA damage
Antimetabolites	Methotrexate, 5-fluorouracil, 6-mercaptopurine, gemcitabine, cytarabine (Ara-C), fludarabine	Interfere with nucleic acid or nucleotide synthesis
Antibiotics Anthracyclines	Daunorubicin, doxorubicin, epirubicin, idarubicin	Various mechanisms, e.g. interference with enzymes involved in DNA synthesis
Other	Bleomycin, mitomycin-C. mitoxantrone**	
<b>Topoisomerase Inhibitors</b> Topoisomerase I Topoisomerase II	Topotecan Etoposide (VP-16), Mitoxantrone**	
<b>Mitotic inhibitors</b> Taxanes Vinca alkaloids Epothilones	Paclitaxel, docetaxel Vinblastine, vincristine Ixabepilone (ixempra)	
Tyrosine kinase inhibitors	Imatinib, dasatinib	
Miscellaneous	Bortezomib (Velcade), L-asparaginase	
* platinum drugs are grouped	here with alkylating agents because they have a simil	ar mechanism of action.

\*\* similar to doxorubicin but also acts as topoisomerase II inhibitor,

Fig. 20.1 In 168 cancer patients treated by combination chemotherapy, the overall ovarian failure rate was 34%, representing an odds ratio of 1.0. Medications were in five drug categories (alkylating agents, platinum derivatives, antibiotics, anti-metabolites, and plant alkaloids) and analysis was performed on these groups. The fraction contributed by each of the chemotherapeutic classes was analyzed by the odds ratio of exposed versus non-exposed patients. The results were adjusted for age. (Figure reproduced with permission from Preservation of Fertility, Tulandi and Gosden 2004, page 31.)



Age	Number of patients	Number developing amenorrhea	Average cumulative dose at onset of amenorrhea	
>40	13	13	5.2 g (range 1.4–8.4 g)	
30–40	5	4 (2 subsequently resumed menses)	9.3 g (7–11 g)	
20-30*	5	3	20.4 g (14–24.5 g)	
From Ref. 7. * these patients received other treatment modalities in addition to CY.				

Table 20.3 Relationship between dose of cyclophosphamide and age

unexposed patients. Results were then adjusted for age by logistic regression analysis. These data show that alkyating agents and platinum derivatives are associated with the highest risks of ovarian failure with odds ratios of 3.98 and 1.7, respectively.

For many individual drugs, however, the true age-related, dose-related incidence of infertility is unknown because there are insufficient longitudinal data using them as single agents. A notable exception to this is cyclophosphamide for which there are extensive published data. This is because the drug is useful in the treatment of a variety of diseases that affect women of child-bearing age: these include breast cancer, autoimmune disorders such as SLE, and hematological malignancies. Cyclophosphamide also plays an important part in conditioning treatment given prior to allogeneic stem cell transplantation where it can be used as:

- a high dose single agent (for example, in patients transplanted for severe aplastic anemia, SAA);
- in combination with busulfan (for example, pediatric and adult transplantation for leukemia);
- together with total body irradiation (for example, in adults transplanted for leukemia).

The relationship between ovarian failure and age in women administered cyclophosphamide was clearly demonstrated by a study in which premenopausal women with breast cancer were treated with cyclophosphamide (CY) at a dose of 100 mg/day.<sup>7</sup> The data are illustrated in Table 20.3 and show that a total cumulative dose in excess of 11 g will lead to cessation of menstruation in most women over the age of 30 but not younger women.

Although the cumulative dose administered is important as illustrated above, data from transplant centers where cyclophosphamide is administered in a single high dose as pre-transplant conditioning suggest that this may be a particularly gonadotoxic approach. Follow-up of 43 women with SAA who received CY in doses of 200 mg/kg as pre-transplant conditioning demonstrated acute cessation of menstruation in all 27 of these patients who were less than 26 years of age at the time of transplant subsequently recovered ovarian function in comparison with only 5 of the 16 women aged  $>26.^4$ 

More limited data are available on other chemotherapeutic drugs used as single agents. An association of busulfan with ovarian failure has been noted as far back as the 1950s with cumulative doses of 150–400 mg associated with acute amenorrhea. More recent data from transplant patients in which high doses of busulfan (BU) are incorporated into pre-transplant conditioning regimens further highlights the gonado-toxicity of this agent. In a large European multicenter evaluating pregnancy following SCT, the combination of BUCY as pre-transplant conditioning appeared more gonado-toxic than CY/TBI as there were no pregnancies in patients with malignant disease who had received BUCY in standard doses for pre-transplant conditioning.<sup>8</sup>

There are fewer protocols involving use of chlorambucil as a single agent in young females. In a small study of 10 pre-pubertal girls exposed to cumulative doses of chlorambucil ranging from 9–28 mg/kg for autoimmune disease, all had normal pubertal development including normal age at onset of menarche.<sup>9</sup> Larger cumulative doses of 535–750 mg/m<sup>2</sup> administered to women with breast cancer, however, are associated with ovarian failure.<sup>10</sup>

Data on drug combinations will now be discussed in the context of the underlying disease.

### Acute leukemias

Conventional treatments for acute myeloid leukemia (AML) and acute lymphocytic leukemia (ALL) are generally less gonado-toxic than those used to treat lymphomas. Typical induction regimens for AML involve drugs such as cytarabine, daunorubicin, and etoposide followed by consolidation treatment, which may incorporate amsacrine or mitoxantrone. The incidence of persistent gonadal damage following treatment with anthracycline-based regimens during childhood or adulthood has been reported as <10%. AML survivors had a 6% incidence of acute ovarian failure in the Childhood Cancer Survivors Study published in 2006.<sup>11</sup>

Acute lymphoblastic leukemia is the commonest childhood cancer, although it also affects adults. In addition to induction and consolidation phases, treatment of ALL also incorporates a maintenance phase and CNS-directed therapy. The latter is generally administered as intrathecal chemotherapy with cranial or craniospinal irradiation reserved for those at high risk (5%-20%) of CNS relapse. The drugs commonly used in the treatment of ALL are glucocorticoids, vincristine, anthracycline, and asparaginase. High dose methotrexate may be administered to those with high risk disease and a tyrosine kinase inhibitor, imatinib, is used for patients who have Philadelphia positive ALL. The incidence of persistent gonadal damage in females following treatment of childhood ALL with standard UKALL protocols is less than 20%. Those who received craniospinal irradiation or cyclophosphamide as part of their treatment are at greatest risk. Data from the Childhood Cancer Survivors Study demonstrated an acute ovarian failure rate in ALL survivors of 14%.<sup>11</sup>

### Chronic leukemias

Chronic lymphocytic leukemia is predominantly a disorder of the elderly and so will not be discussed further. Chronic myeloid leukemia (CML) is typically a disorder of middle-aged adults, but a significant number of cases occur in women of child-bearing age (15-49). In the past, the mainstay of treatment for chronic myeloid leukemia (CML) has been treatment with hydroxycarbamide (formerly known as hydroxyurea) followed by stem cell transplantation. In the last 10 years, however, there has been considerable success in managing CML with tyrosine kinase inhibitors such as imatinib: the first example of a molecularly targeted therapy. Imatinib was first administered to patients with CML in 1998 and has now been used to treat more than 60 000 patients worldwide. It is given orally and is generally well tolerated. To date, there are limited data available on the effects of imatinib on fertility. Reproductive studies in animals have shown imatinib is terato
 Table 20.4
 Treatment regimens for Hodgkin's disease and likelihood of gonadal failure

Risk of gonadal failure	Combination chemotherapy regimens for Hodgkin's lymphoma
High risk (>80%)	MVPP MOPP ChIVPP/EVA COPP
Intermediate risk	BEAM (BCNU, etoposide, cytarabine and melphalan) VEBEP Alternating ABVD/MOPP or COPP CHOP
Low risk (<20%)	VAPEC-B BEACOPP VEEP ABVD

genic in rats, so patients are advised to avoid pregnancy while taking it. Nonetheless, 180 pregnancies have been reported in patients who were taking imatinib.<sup>12</sup> Dosage data were not available in every case, but many were receiving standard doses of 300–400 mg. Recent data, however, suggest that higher doses of imatinib may be associated with premature ovarian failure.<sup>13</sup>

### Lymphomas

Hodgkin's and non-Hodgkin's lymphoma (HL and NHL) together account for approximately 10% of pediatric cancers (4% HL, 6% NHL). With modern treatments for HL in excess of 90% of children and adolescents can expect to be cured. Alkylating agents have played a major role in many of the combination chemotherapy protocols proposed for the treatment of HL and many of these have therefore been associated with infertility (Table 20.4). In the 1970s, treatment regimens containing nitrogen mustard such as MOPP (nitrogen mustard, vincristine, procarbazine, and prednisolone) and MVPP (nitrogen mustard, vinblastine, procarbazine, and prednisolone) were used and were associated with oligo- or amenorrhea in approximately 20%-40% of women. In the mid 1970s, however, it was discovered that a new regimen combining doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was as efficacious a treatment as MOPP or MVPP, but lacked the gonado-toxicity. ABVD has become the modern gold standard of treatment and the risk of sterilization in women under the age of 25 is almost zero.<sup>14</sup> Women treated with inverted Y-irradiation, in addition to alkylating agents, have

been shown to have a significantly higher risk of premature menopause, however.

Non-Hodgkin's lymphomas (NHL) can be broadly subdivided into low grade and high grade lymphomas. Low dose oral chemotherapy such as chlorambucil is appropriate for many patients with low grade disease and it has been discussed above. The gold standard treatment for high grade NHL is a combination of the following drugs: cyclophosphamide  $(750 \text{ mg/m}^2)$ , doxorubicin, vincristine, and prednisolone (CHOP). Pre-menopausal women treated using this regimen are likely to develop amenorrhea during chemotherapy, but the majority (95%) will resume menstruation shortly after completion of treatment. The risk of permanent ovarian failure is highest in those aged 40 or more at the time of treatment. Even when higher doses of cyclophosphamide are used as in "mega-CHOP," in which  $2-3 \text{ g/m}^2$  cyclophosphamide are administered, it appears that the risk of persistent ovarian failure may be low with 92% (12/13) of women regaining ovarian function in one study.<sup>15</sup> Women in this latter study who were aged <40 years were offered GnRH analogs in parallel with their chemotherapy in an attempt to preserve fertility. A second study which combined data on various chemotherapy regimens for NHL in premenopausal women found a higher incidence of ovarian failure of 44%,16 but the patient characteristics and details of chemotherapy regimens used were not reported and this is likely to underlie the discrepancy. Childhood NHL is treated with similar protocols to childhood ALL and the risks of infertility and delayed puberty are low. In a recent prospective study of survivors of childhood NHL or ALL, all 40 females treated with chemotherapy alone or chemotherapy plus cranial irradiation underwent spontaneous menarche. Whether these patients will subsequently undergo premature ovarian failure is not known, however.17

# The likely outcome of pregnancy in a patient treated for hematological malignancy

There are several reasons why pregnancy outcome might be adversely affected by prior treatment with chemoradiotherapy. Irradiation to the uterus may affect implantation, potentially predisposing to miscarriage or intra-uterine growth retardation. Chemotherapy agents such as cyclophosphamide can cause gene mutations, chromosomal breaks, and rearrangements raising the possibility of an increased risk of congenital malformations.

Although the focus of this chapter is on the relationship between chemoradiotherapy and fertility potential, effects on other maternal organs may cause complications for pregnancy and delivery. Cardiac and pulmonary toxicities, for example, are well described following some regimens. Patients at risk of such complications should have a cardiorespiratory review early in pregnancy, including an echocardiogram and pulmonary function tests and may require assessment by an anesthetist prior to delivery. Similarly, patients with renal impairment will require expert review and monitoring throughout pregnancy.

There are some data to support concerns of an adverse pregnancy outcome resulting from pelvic irradiation. A retrospective multicenter study identified 139 pregnancies in 111 female patients who had received SCT.8 Of these 111 women, 39 had received autologous stem cells and 74 had received allogeneic stem cells. Of the latter group, 21 had been conditioned with TBI-containing regimens. In this study, the majority of pregnancies were uncomplicated; however, 20% of female allograft recipients had pre-term singleton deliveries (normal incidence approximately 6%) and 23% had low birth weight singleton babies (normal incidence approximately 6%). These complications were confined to women who had received total body irradiation. The incidence of Cesarean section was significantly higher amongst allografted women at 42% compared with approximately 16% in the normal population, but the incidence of congenital anomalies amongst offspring was not increased.

A further report from the Childhood Cancer Survivor Study looked at pregnancy outcome for 4029 pregnancies in 1915 women previously treated for cancers in childhood. The pregnancy outcome of the sibling closest in age to the patient was used for control data. Their results showed that women treated with pelvic irradiation tended to have smaller babies than the controls and delivered earlier, at an average of 37.23 weeks vs. 38.47 weeks for controls. Use of daunorubicin or doxorubicin was also linked adversely to birth weight but there was no clear dose–response relation-ship.<sup>18</sup>

Despite the theoretical concern of congenital abnormalities arising in offspring of survivors of cancer treatment, available data do not demonstrate a substantial increase in risk in patients where conventional chemotherapy has been used prior to conception. It may be, however, that existing studies do not have sufficient power to detect a small difference.

# Effects of chemotherapy during pregnancy

The risks of teratogenicity are significant if chemotherapy is administered *during* pregnancy, particularly in the first trimester. Management of hematological malignancy in pregnancy will therefore depend on the stage of pregnancy when a diagnosis is made and the balance of risk between delaying treatment and teratogenicity. In patients who require curative chemotherapy in the first trimester, then therapeutic termination should be discussed. This would include patients with acute leukemia and also some patients with aggressive or extensive/bulky lymphomas. In some cases it may be possible to delay treatment to later in pregnancy or even until after delivery. In patients with CML, for example, leukapheresis can be used to temporarily control the white cell and platelet counts. There have been reports of certain chemotherapy agents being administered in the second and third trimester without complication, for example, adriamycin, CHOP, and rituximab; however, data is limited. Some highly teratogenic drugs, such as methotrexate and dacarbazine, should be avoided at all stages of pregnancy.

Recent data also highlight concerns about the potential teratogenic effects of imatinib. As discussed above, this tyrosine kinase inhibitor is used in the management of both CML and Philadelphia positive ALL. In rats imatinib leads to exencephaly, encephaloceles, and deformities of the skull bones. Female rats administered doses >45 mg/kg (which equates to approximately half the maximum human dose of 800 mg/day, based on body surface area) experienced significant post-implantation loss with increased fetal resorption, stillbirths, non-viable pups, and early pup mortality. In a study which included data on pregnancy outcomes for 125 women exposed to imatinib at conception and during part or all of the first trimester there were 12 offspring identified with abnormalities, 3 of which were terminated electively. Of the offspring with identifiable anomalies, 3 had strikingly similar complex malformations, which were unlikely to have occurred by chance.<sup>12</sup> Imatinib does not appear to damage chromosomes, but it is capable of interacting with several target proteins of relevance to embryonic development, such as cKIT and PDGFR.

# Strategies for fertility preservation

Some women who require treatment for cancer have more than one therapeutic option. In such cases, women who hope to commence a family after treatment may be able to avoid potentially sterilizing treatment. In women who require pelvic irradiation, it may be possible to laparoscopically transpose the ovaries outside the field of radiation, leaving the ovarian blood supply intact. This is not always successful, however; not only can the ovaries migrate back into the field of radiation, but complications can occur as a result of the procedure such as chronic pain or formation of ovarian cysts. Alternatively, modified field radiation can sometimes be planned to omit/reduce radiation to the ovaries. Scatter radiation can nonetheless contribute to ovarian failure and follow-up remains important.

In women whose treatment is highly likely to result in infertility, cryopreservation of embryos prior to treatment offers the best hope for parenthood postchemoradiotherapy. This technique requires ovarian stimulation over a 2-week period, following which mature oocytes in their second metaphase are collected. These oocytes are fertilized in vitro before freezing. This option is not open to all patients with cancer, however. Ovarian stimulation takes 2 weeks, but it has to be timed in relation to the menstrual cycle. Treatment delays can therefore extend to 6 weeks and this is prohibitive for many patients with cancer. Additional complexity arises if the patient lacks a male partner to provide sperm. The option of donor sperm can be considered, but this requires careful counseling in relation to future implications (see below).

In healthy women who attempt pregnancy with transfer of thawed embryos, the pregnancy rate is 20%–30%. There are several reasons why the outcome of artificial reproductive techniques (ART) may be lower in women with cancer, however. Firstly, women with cancer do not always respond well to stimulation regimens and the quality and number of oocytes may be lower than expected. Secondly, many patients will have compromised endometrial function in addition to ovarian failure as a result of their treatment. This could potentially impede implantation or fetal growth and development. There are some data to support this from a European multicenter study which included 9 women who conceived using ART

following TBI.<sup>8</sup> Among the pregnancies to these women, the incidence of preterm delivery and low birth weight offspring was high, and median birth weights were lower than expected for gestational age. Although there are a number of case reports of successful pregnancies using cryopreserved embryos following systemic cancer therapy, it is difficult to quote accurate success rates for these patients and some will elect to use a surrogate if available to carry their embryos.

# Experimental approaches to restoring fertility

#### Freezing unfertilized oocytes

Although this is a promising option for women requiring sterilizing treatment who lack a partner to provide sperm, live birth rates following this procedure are currently low at about 2%.<sup>19</sup> This is too low to justify routine use of this technique in clinical practice. Low pregnancy rates partly reflect the susceptibility of the mature unfertilized oocyte to thermal and osmotic injury, which exceeds that of the preimplantation embryo. Furthermore, it is probable that poorer quality embryos are generated following oocyte cryopreservation. Vitrification, which involves ultrarapid cooling, has improved post-thaw oocyte survival and pregnancy rates in small studies, but further information is required on the efficiency and safety of this technique. Nonetheless, in recent years there have been reports of successful pregnancies in women treated for cancer using this technique. Yang and colleagues<sup>20</sup> report a patient with Hodgkin's disease who had frozen oocytes thawed and fertilized by ICSI after cryopreservation for 6 years. During the time that the oocytes were frozen, the patient had multiple relapses and was treated with combination chemotherapy (ABVD followed by COPP followed by fludarabine) and total body irradiation (200 cGy) in the context of a nonmyeloablative SCT. Nine embryos were obtained from her frozen oocytes and all of these were implanted over the course of three separate cycles. A surrogate was used because of concerns of radiation damage to the patient's uterus, and a successful pregnancy occurred after the final cycle of implantation.

#### Freezing ovarian tissue

This is currently the only option open to pre-pubertal patients or to those women whose disease will not tolerate a significant delay in treatment. Cortical fragments containing primordial follicles with immature oocytes can be obtained by laparoscopy and frozen. Ideally, ovarian tissue should be obtained before the patient has been exposed to chemotherapy, but this is not always possible and is not an absolute requirement. Attempts to restore ovarian function and fertility have involved reimplanting the ovarian tissue, either orthotopically adjacent to the ovary or heterotopically, for example, into the anterior abdominal wall. A major concern with this technique is the possibility of reintroducing cancer cells, and a thorough histological assessment of the tissue should be made before re-transplantation. In 2005 Meirow et al. described a successful pregnancy in a patient with non-Hodgkin's lymphoma using cryopreserved ovarian tissue in conjunction with IVF and additional pregnancies have been reported since.<sup>21</sup> However, it is likely that ovarian tissue transplanted in this way will have a limited lifespan and transplantation of ovarian tissue should probably be reserved for assisting the restoration of fertility rather than for restoring hormone production.

The use of assisted reproductive techniques in cancer patients raises a range of ethical concerns, including several issues relating to consent. Consent takes place when two or more people agree upon a course of action and it implies that agreement occurred:

- without coercion;
- based on the provision of information; and
- that the participants have the ability to understand the facts and implications of the action ("competence").

In the UK, consent for long-term cryopreservation of gametes is governed by the Human Fertilization & Embryology Authority (HFEA) and they have constructed guidance and consent forms, which are available at www.hfea.gov.uk. The consent of both partners is required when embryos are cryopreserved and also when the embryos are replaced. If either partner withdraws consent, the embryos cannot be used. In the UK, young people aged 16-18 can consent to treatment under the Family Law Reform Act 1969 ("competent minors"). The position in younger patients was established in the case of Gillick v West Norfolk Area Health Authority (1985). As a result of this case, children who are of sufficient understanding and capable of expressing their own wishes (Gillick competent) can also make informed decisions. Under HFEA

regulations, parents or guardians cannot give consent on behalf of a child for the storage or use of gametes. Immature germ cells obtained from gonadal tissue of pre-pubertal children do not come under this remit, however. The tissue can therefore be recovered with parental consent if it is considered to be in the best interest of the child.

# Conclusions

Treatment of hematology cancers is constantly evolving to produce improved survival data and incorporate better tolerated agents. As a result of this, an increasing number of young patients diagnosed with hematological malignancies can now hope to lead relatively normal adult lives and for many this includes the expectation of parenthood. Management of possible infertility should start before cancer treatment is administered and, ideally, should include a full discussion of: (1) treatment options and the likelihood of infertility associated with each option; (2) strategies for preserving fertility if the chance of sterilization as a result of treatment is high. Full data are not always available, however, particularly where new drugs are used or when experimental methods for preserving fertility are considered. Long-term follow-up studies of patients treated for cancer remains a central priority to provide the core information required for such pre-treatment counseling.

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