

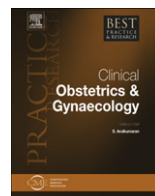


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## Coagulation in pregnancy

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The coagulation system undergoes significant change during pregnancy. The clinician caring for the parturient must understand these changes, particularly when the parturient has a pre-existing haematological condition. Because many haematological conditions are rare, there often is limited information to guide the obstetric and anaesthetic management of these parturients.

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To limit blood loss after trauma it is essential to seal bleeding vessels without affecting blood flow permanently. Haemostasis, defined as the arrest of bleeding, comes from the Greek roots, *haeme* meaning blood and *stasis* meaning causing to stop. The process of haemostasis is a dynamic and delicate equilibrium between coagulation and fibrinolysis (Fig. 1). Coagulation results from an interaction among vessel walls, platelets and coagulation factors.<sup>1</sup> Following endothelial damage, platelets adhere to the subendothelium forming a platelet plug which then becomes permanent with fibrin deposition.<sup>1</sup> Clot formation is limited by antithrombin (AT) and proteins C and S. The fibrinolytic system functions to maintain the fluid state through the breakdown of fibrin by plasmin. Plasmin is generated from plasminogen by the action of tissue plasminogen activator (t-PA).

### Physiological changes to coagulation during pregnancy

Pregnancy is associated with changes in haemostasis, including an increase in the majority of clotting factors, a decrease in the quantity of natural anticoagulants and a reduction in fibrinolytic

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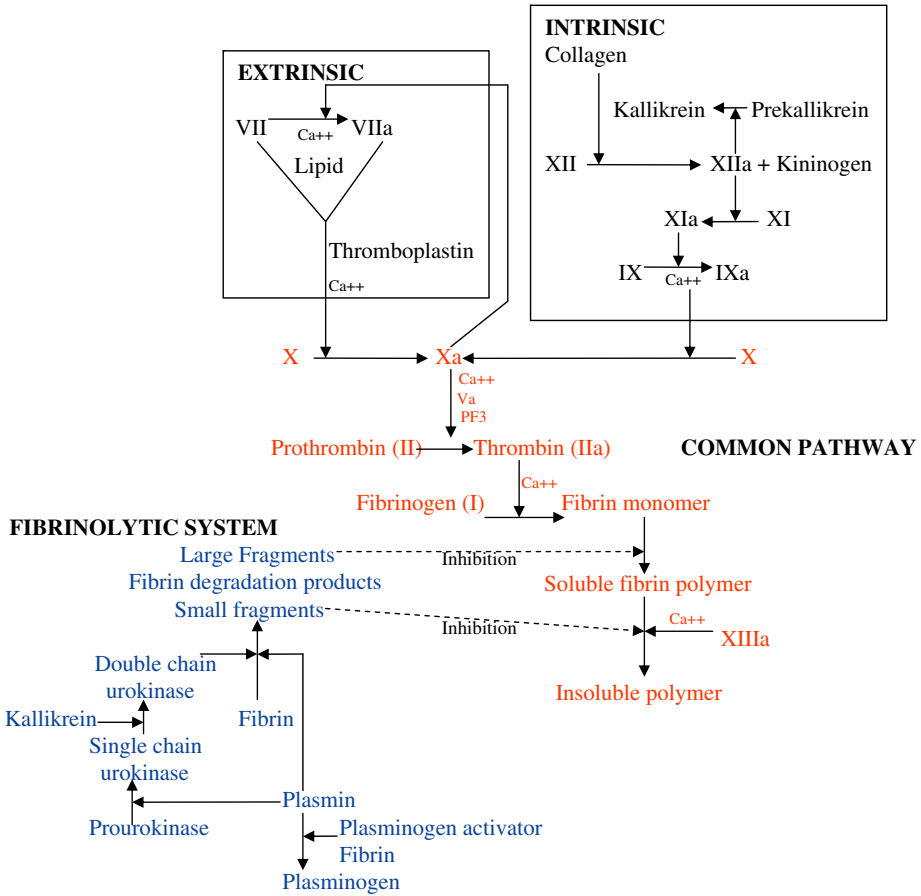


Fig. 1. Normal coagulation pathway.

activity.<sup>2-4</sup> These changes result in a state of hypercoagulability,<sup>2,4</sup> are likely due to hormonal changes<sup>5</sup> and increase the risk of thromboembolism.

The increase in clotting activity is greatest at the time of delivery with placental expulsion, releasing thromboplastic substances.<sup>2</sup> These substances stimulate clot formation to stop maternal blood loss. As placental blood flow is up to 700 ml min<sup>-1</sup>, considerable haemorrhage can occur if clotting fails. Coagulation and fibrinolysis generally return to pre-pregnant levels 3–4 weeks postpartum.<sup>2,3</sup>

a. Platelets

The platelet count decreases in normal pregnancy possibly due to increased destruction and haemodilution with a maximal decrease in the third trimester.<sup>6</sup>

b. Coagulation factors

Factors VIII (FVIII), von Willebrand factor (vWf), ristocetin cofactor (RCoA) and factors X (FX) and XII (FXII) increase during pregnancy.<sup>2,4</sup> Levels of factor VII (FVII) increase gradually during pregnancy and reach very high levels (up to 1000%) by term.<sup>2,7</sup> Fibrinogen also increases during pregnancy with levels at term 200% above pre-pregnant levels.<sup>2</sup>

Other factors either remain at non-pregnant levels or decrease during pregnancy. Factor XIII (FXIII), which is responsible for stabilising fibrin, increases in the first trimester but by term it is 50% of non-pregnant levels.<sup>8</sup> Factor V (FV) concentrations increase in early pregnancy then decrease and stabilize.<sup>2</sup> Factor II (FII, prothrombin) levels may increase or not change in early pregnancy but are normal by term.<sup>2</sup> There is debate about factor XI (FXI) levels with reports indicating increases or decreases.<sup>9,10</sup> Similarly, FIX levels are reported as increasing, decreasing or remaining stable throughout pregnancy. In one study, 50% of carriers of FIX deficiency had FIX levels  $\leq 50$  IU dl<sup>-1</sup> at term.<sup>11</sup>

Protein C levels remain the same or are slightly increased during pregnancy<sup>12</sup> while protein S decreases. AT levels remain normal during pregnancy.<sup>2,4</sup>

### c. Fibrinolysis

Fibrinolysis is reduced in pregnancy due to decreases in t-PA activity, which remains low until 1-h postpartum when activity returns to normal.<sup>4</sup> This reduction is due to the gradual, eventually threefold, increase in plasminogen activator inhibitor-1 (PAI-1) and the increasing levels of plasminogen activator inhibitor-2 (PAI-2).<sup>4</sup> The placenta produces PAI-1 and is the primary source of PAI-2. PAI-2 levels at term are 25 times that of normal plasma.<sup>13</sup> Postpartum, t-PA levels quickly return to normal as PA-1 levels decrease; however, PA-2 levels remain elevated for a few days.

Thrombin-activatable fibrinolysis inhibitor (TAFI) (an antifibrinolytic which cleaves the C-terminal lysine in fibrin to render it resistant to cleavage by plasmin) levels are increased in the third trimester.<sup>14</sup> D-Dimer levels increase in pregnancy<sup>15,16</sup> but are not thought to indicate intravascular coagulation as fibrinolysis is depressed. These D-Dimers may originate from the uterus.<sup>17</sup>

## Tests of coagulation

Obstetric anaesthetists are concerned that providing neuraxial anaesthesia in parturients with coagulation abnormalities may cause bleeding in the epidural or subarachnoid space with neurological impairment (spinal/epidural/neuraxial haematoma). Neuraxial haematomas associated with neuraxial blocks have been reported rarely in parturients.<sup>18</sup> In the non-pregnant population, spinal haematomas associated with neuraxial blocks often occur in patients with an underlying coagulopathy. Ideally, there would be a test that would predict the risk of bleeding in the epidural/spinal space.

### A. Platelet count

Some anaesthetists rely on platelet count as a screening test for coagulation abnormalities in healthy parturients prior to neuraxial block. However, the American Society of Anesthesiologists Practice Guidelines for Obstetric Anesthesia states that a platelet count is not essential prior to neuraxial block in a healthy parturient with no risk factors for bleeding.<sup>19</sup> Although there are some rare conditions that result in abnormal platelet function (e.g., May Hegglin anomaly) a normal platelet count will provide reassurance that coagulation is normal in a healthy parturient. A platelet count at term  $< 70 \times 10^9$  l<sup>-1</sup> may indicate the presence of HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, disseminated intravascular coagulation (DIC), immune thrombocytopenia and other rare conditions co-existing with pregnancy. Questions have been raised about platelet function in pre-eclampsia,<sup>20,21</sup> but as these studies used bleeding time, their results are not considered definitive. However, the concern remains and is not yet resolved.<sup>18</sup>

### B. Prothrombin time

As most coagulation factors increase in normal pregnancy, the prothrombin time (PT) and the activated partial thromboplastin time (APTT) are shortened. The PT and its derived measure, international normalised ratio (INR), test for factors such as FII, FV, FVII, FX and fibrinogen. Some nutritional deficiencies and/or liver disease will decrease these factors prolonging the PT. Furthermore, PT and

APTT may be artificially prolonged due to the presence of an antiphospholipid antibody (APLA), such as lupus anticoagulant. In fact, patients with APLA are prothrombotic.

### C. Activated partial thromboplastin time

The APTT is considered a good screening test for deficiencies of FVIII, FIX, FXI and FXII. The APTT may be prolonged by the presence of an APLA and/or unfractionated/standard heparin (SH). To differentiate between the presence of an APLA and a factor deficiency, the patient's plasma is mixed 50:50 with normal plasma. If the APTT remains abnormal an APLA is present.

### D. Bleeding time

Since its introduction, bleeding time was used to assess platelet function in parturients with thrombocytopenia. A prolonged bleeding time was thought to predict the risk of bleeding, which theoretically could increase the risk of a neuraxial haematoma. However, bleeding time is used rarely now as it has a number of disadvantages: it is invasive, unreliable, highly operator dependent and not suitable to repeated tests. Bleeding time also is insensitive, especially to mild platelet defects, and not a good predictor of bleeding risk.<sup>22,23</sup> Because of these problems, other tests are being studied.

### E. Thrombo-elastography

The thromboelastograph (TEG) provides information about the various stages of coagulation and fibrinolysis. The maximum amplitude (MA) is thought to represent platelet function. TEG is used by some centres to predict the risk of bleeding from coagulation abnormalities; however, the sensitivity and specificity of TEG in pregnancy remain unproven.<sup>24,25</sup> An abnormal test has not been shown to be predictive for development of a neuraxial haematoma, but most anaesthetists will not provide regional anaesthesia if the MA is abnormal.

### F. Platelet function analyser<sup>®</sup> (PFA)

This test measures the speed of formation of a platelet plug *in vitro*, expressed as closure time in seconds. Studies in parturients suggest that it is an effective bedside test of platelet function<sup>26</sup>; however, evidence is lacking to support its routine use.

## Disorders that affect coagulation

### *Thrombocytopenia*

Thrombocytopenia affects 6–10% of all pregnancies.<sup>27</sup> A decrease in platelet count is normal in pregnancy although most platelet counts remain within normal limits ( $\geq 150 \times 10^9 \text{ l}^{-1}$ ).<sup>6,28</sup> A lower than physiological platelet count may occur in pregnancy for many reasons, ranging from the relatively benign, gestational thrombocytopenia to more sinister conditions, such as HELLP syndrome.

Some pre-existing conditions that may cause thrombocytopenia at term include: type 2b von Willebrand disease (vWD), idiopathic thrombocytopenic purpura (ITP), lupus erythematosus and bone marrow disease. Pregnancy-related causes of thrombocytopenia include gestational thrombocytopenia, pre-eclampsia including HELLP syndrome, acute fatty liver of pregnancy, DIC and thrombocytopenic purpura.<sup>27</sup> Severe sepsis, some medications (e.g., SH) and viral infections may coincide with pregnancy producing thrombocytopenia.<sup>27</sup>

#### a. Gestational thrombocytopenia

Gestational thrombocytopenia is a benign condition that occurs during the third trimester with a platelet count that is generally  $\geq 90 \times 10^9 \text{ l}^{-1}$  but may be as low as  $70 \times 10^9 \text{ l}^{-1}$ .<sup>29</sup> In one study, the

incidence of thrombocytopenia was 7.3%, of which 81% were gestational thrombocytopenia.<sup>28</sup> The diagnosis is made by exclusion of other disorders. Parturients with gestational thrombocytopenia are asymptomatic, have a normal platelet count in early pregnancy with no history of previous thrombocytopenia and no evidence of pre-eclampsia. These patients are not at increased risk of haemorrhage, and there is no contraindication to neuraxial anaesthesia.<sup>30</sup>

#### b. Idiopathic thrombocytopenic purpura

ITP may present for the first time in pregnancy and is the most common reason for isolated thrombocytopenia in the first trimester.<sup>27</sup> ITP is an autoimmune disorder which is associated with the production of anti-platelet immunoglobulin (IgG), resulting in platelet destruction in the reticulo-endothelial system. However, anti-platelet IgG is not always present, making the diagnosis problematic.<sup>31</sup>

Laboratory findings include an isolated thrombocytopenia presenting either pre-pregnancy or in early pregnancy with large, well-granulated platelets. Despite low platelet numbers, haemostasis is often normal. The British Committee for Standards in Haematology guidelines recommend a platelet count of  $80 \times 10^9 \text{ l}^{-1}$  for epidural anaesthesia.<sup>32</sup> However, many anaesthetists, such as the authors, would do a neuraxial block (especially spinal anaesthesia) in healthy, asymptomatic ITP patients with platelet counts  $\geq 50 \times 10^9 \text{ l}^{-1}$ . This practice is based on the consideration that a platelet count  $\geq 50 \times 10^9 \text{ l}^{-1}$  is considered sufficient for caesarean delivery.<sup>32</sup>

The key issue in managing an ITP parturient is whether intervention is necessary to prevent haemorrhage. In patients with very severe, symptomatic thrombocytopenia (platelet count  $\leq 10 \times 10^9 \text{ l}^{-1}$ ), treatment is urgently required. One gram per kilogram per day of intravenous gammaglobulin (IVIg), administered over 2 days, will raise the platelet count in approximately 75% of ITP patients<sup>32</sup> and the platelet count will remain elevated for 3–6 weeks. Further IVIg may be required later in pregnancy. Another option is high-dose corticosteroids (e.g., prednisone  $1 \text{ mg kg}^{-1}$  (pre-pregnancy weight) daily).<sup>32</sup> There are no trials comparing IVIg to corticosteroids for effect. Administration of IVIg and/or corticosteroids usually will raise the platelet count to enable neuraxial anaesthesia. Occasionally, a splenectomy is required during pregnancy and this may be done laparoscopically in the second trimester.<sup>33</sup> Platelet transfusion is generally contraindicated, but, in the setting of acute haemorrhage and an extremely low platelet count, it may be life-saving.<sup>32</sup>

### Anaesthetic implications of thrombocytopenia

There is considerable debate about administering neuraxial anaesthesia in parturients with thrombocytopenia. A platelet count from  $70 \times 10^9 \text{ l}^{-1}$  to  $100 \times 10^9 \text{ l}^{-1}$  in an otherwise healthy parturient should not contraindicate regional anaesthesia. Most American anesthesiologists would insert an epidural in a healthy parturient with a platelet count  $\geq 80 \times 10^9 \text{ l}^{-1}$ .<sup>34</sup> A Canadian survey reported that 16.2% of university-based anaesthetists would place an epidural if the platelet count was  $\geq 50 \times 10^9 \text{ l}^{-1}$  in an otherwise healthy parturient.<sup>35</sup>

The situation is more controversial in the setting of pre-eclampsia, including HELLP syndrome. In this situation, most anaesthetists consider the platelet count, the clinical picture (i.e., haemorrhage risk and evidence of coagulopathy) and whether the thrombocytopenia is stable or decreasing. In one report of HELLP syndrome, 12 parturients with a platelet count  $< 50 \times 10^9 \text{ l}^{-1}$  received uneventful epidural anaesthesia.<sup>36</sup> In some cases a platelet transfusion was given immediately prior to neuraxial anaesthesia. In contrast, there is a report of an epidural haematoma in two cases of HELLP syndrome: one after spinal anaesthesia and the other after epidural catheter removal.<sup>37</sup> Both had signs of coagulopathy. Studies using TEG in women with pre-eclampsia suggest that coagulation is normal with a platelet count  $> 75 \times 10^9 \text{ l}^{-1}$ .<sup>38,39</sup>

#### Factor deficiencies

The most common factor deficiencies encountered in pregnancy are von Willebrand disease and haemophilia carrier states.

### a. von Willebrand disease (vWD)

von Willebrand disease is the most frequent inherited bleeding disorder, affecting 1% of the population.<sup>40</sup> vWD is due to quantitative (types 1 and 3) or qualitative (type 2) defects of vWf with autosomal dominant transmission. vWf protects circulating FVIII from proteolysis and is required for normal platelet adhesion to the injury site. In vWD the marked reduction in FVIII activity produces the clinical syndrome.

There are three types of vWD: types 1, 2 and 3 with subtypes in type 2 (2A, 2B, 2M, 2N). Type 1, the most frequent with an incidence of 75%, is usually mild and is characterised by a deficiency of vWf. Type 2 and its subtypes involve abnormalities of binding to glycoproteins and FVIII (qualitative defect). Type 3 is characterised by the complete absence of vWf and is usually severe. Thrombocytopenia occurs with type 2b.

The diagnosis of vWD is made clinically and in the laboratory. The most common symptom of Type 1 vWD in women is menorrhagia,<sup>40</sup> but there may be a history of bruising, epistaxis or other mucosal bleeding, and bleeding after dental extractions or surgery.<sup>41</sup> Laboratory diagnosis involves measuring vWf, RCoA and FVIII levels.

Women with vWD have reasonably good pregnancy outcomes. The increases in fibrinogen, FVII, FVIII, FX and vWf during pregnancy are considered protective. Levels of vWf, RCoA and FVIII should be checked in early pregnancy and in the third trimester to ensure adequate levels for delivery.<sup>40</sup> Pregnant patients with type 3 vWD, type 2 vWD or type 1 vWD with FVIII  $\leq 50$  IU dl<sup>-1</sup>, vWf:RCo  $\leq 50$  IU dl<sup>-1</sup> or a history of severe bleeding should be referred to a centre with appropriate consultants, laboratory and blood bank facilities. Postpartum haemorrhage (PPH) is a common complication in parturients with vWD.<sup>42</sup> Levels of vWf begin decreasing 6 h postpartum, returning to pre-pregnancy levels by 7–20 days.

Desmopressin (DDAVP) is considered safe for parturients with type 1 vWD.<sup>43–45</sup> The normal dose is 0.3  $\mu\text{g kg}^{-1}$ , up to a maximum of 20  $\mu\text{g kg}^{-1}$ . Desmopressin immediately increases vWf and FVIII:RCoA by 200–300%. As hyponatraemia is a complication of repeated doses of DDAVP, some recommend a minimum of 12 hourly intervals and restriction of fluids.<sup>40</sup> Desmopressin is contraindicated or the response is variable in type 2 and ineffective in type 3 vWD.<sup>46</sup>

### Anaesthetic implications of vWD

Based on case reports and retrospective studies, neuraxial anaesthesia appears safe in type 1 vWD parturients with normal third trimester coagulation (FVIII  $\geq 50$  IU dl<sup>-1</sup>).<sup>42,47</sup> In a study of 64 vWD parturients, 15 (17 deliveries) received uneventful, epidural anaesthesia without prophylactic DDAVP or factor concentrate.<sup>47</sup> However, eight had a PPH, coinciding with the postpartum fall in FVIII and vWf levels. Seven of the eight with PPH had type 1 vWD whilst the eighth had type 2A.<sup>47</sup> An epidural catheter should not be removed if coagulation is abnormal.

Most anaesthetists consider neuraxial block contraindicated in types 2 and 3 vWD but there is a report of spinal anaesthesia in a parturient with type-2M vWD whose coagulation was normal except for prolonged platelet adhesion and aggregation.<sup>46</sup>

### b. Factor VIII Deficiency

Also known as haemophilia A, FVIII deficiency is rare in females as it is an X-linked, recessive condition. Rarely, lyonisation of the X chromosome occurs and a woman has low FVIII levels.<sup>11</sup> Haemophilia A is diagnosed when FVIII activity is  $\leq 35\%$ . Recombinant FVIII (rFVIII) is the treatment of choice, if required, in pregnant haemophilia A carriers. Although FVIII levels usually normalise during pregnancy, there are a few case reports of severe FVIII deficiency so check FVIII levels early in pregnancy and in the third trimester.<sup>9,42</sup> In two cases of severe FVIII deficiency, the parturients had successful epidural analgesia for labour after rFVIII.<sup>48,49</sup> One parturient had a spontaneous vaginal delivery<sup>48</sup> and the other a caesarean delivery.<sup>49</sup> The latter parturient had a brachial vein thrombosis 10 days postpartum.<sup>49</sup>

### c. Factor IX deficiency

Similar to haemophilia A, FIX deficiency (haemophilia B, Christmas disease) is X linked, recessive and hence rare in females. As FIX levels may decrease during pregnancy these women may have inadequate coagulation. Known carriers of haemophilia B should have FIX levels checked in the third trimester to ensure adequate coagulation for delivery. Recombinant FIX is the treatment of choice.

### Anaesthetic implications of haemophilia carriers

Neuraxial anaesthesia is not contraindicated provided:

- (i) Factor VIII level is  $\geq 50$  IU dl<sup>-1</sup> at term;
- (ii) PT and APTT are normal;
- (iii) There is no evidence of bleeding or bruising;
- (iv) Replacement therapy has raised the level to  $\geq 50$  IU dl<sup>-1</sup> with normal coagulation in women whose FVIII levels were  $\leq 50$  IU dl<sup>-1</sup>.<sup>9,11,42,48</sup>

In 53 haemophilia A carriers and 12 haemophilia B carriers who had 90 pregnancies, FVIII and FIX levels increased during pregnancy but FVIII levels increased more.<sup>11</sup> In a subset, 8% of haemophilia A carriers and 50% of haemophilia B carriers had FVIII or FIX levels  $\leq 50$  IU dl<sup>-1</sup> at term. Regional anaesthesia was used in 25 deliveries; 20 had normal factor levels ( $\geq 50$  IU dl<sup>-1</sup>) and normal coagulation screens.<sup>11</sup> Five other parturients received regional anaesthesia; one after prophylactic recombinant factor and in the remaining four the carrier status was unknown. There were no complications.

### d. Rarer coagulation disorders and their anaesthetic implications (Table 1)

The rarer coagulation disorders include abnormalities in factors I, II, V, VII, X and XIII.<sup>40,50</sup> In a parturient with a history of coagulopathy, neuraxial block is contraindicated if coagulation is abnormal. As factor levels may drop suddenly postpartum, many anaesthetists are reluctant to provide neuraxial anaesthesia. If neuraxial anaesthesia is administered, close monitoring of coagulation is essential and an epidural catheter should not be removed unless coagulation is normal. If neuraxial block is contraindicated intravenous opioids are appropriate for labour analgesia and general anaesthesia for caesarean delivery.

- i. Factor I (fibrinogen) deficiency<sup>50</sup>
  - Afibrinogenaemia is the total absence of F1.
  - Hypofibrinogenaemia is a decreased level of normal F1.
  - Dysfibrinogenaemia is an abnormality of F1 resulting in altered function.
  - Afibrinogenaemia and hypofibrinogenaemia are associated with recurrent miscarriage and antepartum and postpartum haemorrhage.
  - Dysfibrinogenaemia may have a thrombotic or bleeding phenotype.
  - Management is challenging.
  - Anaesthetic management: Regional anaesthesia is contraindicated in patients with dysfibrinogenaemia. Those with a bleeding phenotype are at risk of a neuraxial haematoma with neuraxial block while those with a thrombotic phenotype are likely on low-molecular-weight heparin (LMWH). Theoretically, patients with hypo- and afibrinogenaemia could be considered for neuraxial block after treatment with fibrinogen concentrate and adequate levels. A full discussion of the risks and benefits of analgesia/anaesthesia should be held with each patient.
- ii. Factor II (prothrombin) deficiency<sup>50</sup>
  - Extremely rare;

**Table 1**  
Rarer factor deficiencies and their implications.<sup>50</sup>

Deficiency	Pregnancy complications	Treatment products	Pregnancy management	Anaesthetic implications
FI	Recurrent miscarriage APH, PPH, Thrombosis	FI conc.; Avoid cryoprecipitate, if possible; Fibrin glue, TXA	AF: FI conc prophylaxis DF: Avoid procedures in nn. Observe unless bleeding; Thromboprophylaxis if history thrombosis	AF: Possibly NA after FI conc & levels >1 g dL <sup>-1</sup> DF: NA contraindicated; FI conc. only if bleeding for CD
FII	PPH	3 or 4 factor PCC; FFP	Reasonable to increase FII level to >25 IU dL <sup>-1</sup>	No reports in pregnancy
FV	Bleeding <sup>51</sup>	FFP	Reasonable to give FFP to raise level >15 IU dL <sup>-1</sup>	GA used for C/D in one case. NA probably CI
FVII	No reports of complications with full-term pregnancies. Haemorrhage with miscarriage	rVIIa; PTCC; FFP; Fibrin glue; TXA	1 case of continuous infusion of rVIIa for elective CD <sup>55</sup>	rFVIIa allowed epidural in severe cases <sup>55</sup>
FX	Bleeding during pregnancy, preterm delivery	TXA; Fibrin glue; FFP; PCC; plasma exchange in one case <sup>57</sup>	FX increases in pregnancy Adverse pregnancy outcome may benefit with replacement – risk thrombosis	NA probably OK if FX levels >20 IU dL <sup>-1</sup>
FXI	PPH	FFP; FXI conc.; rFVIIa; TXA; Fibrin glue	VD: FXI level 15–70 IU dL <sup>-1</sup> + no bleeding history – watch & wait If same level + bleeding history – TXA × 3 days Severe FXI deficiency – FXI conc CD: as for VD	Reports of NA following FXI conc & normal levels <sup>58</sup>
FXIII	Miscarriage, PPH	FXIII conc; FFP; Cryoprecipitate	FXIII conc monthly infusions from diagnosis of pregnancy	NA CI

APH = antepartum haemorrhage; PPH = postpartum haemorrhage; TXA = tranexamic acid; AF = afibrinogenemia; DF = dysfibrinogenemia; conc = concentrate; NA = neuraxial anaesthesia; CI = contraindicated; CD = caesarean delivery; PCC = prothrombin complex concentrate; FFP = fresh frozen plasma; GA = general anaesthesia; VD = vaginal delivery

- Two clinical phenotypes: hypoprothrombinaemia and dysprothrombinaemia;
  - Reports of PPH and foetal loss in early pregnancy;
  - May have prolonged PT and APTT but may also be normal;
  - Prothrombin complex concentrate is treatment of choice (contains FII, FIX and FX);
  - Anaesthetic management: No reports.
- iii. Factor V deficiency<sup>50</sup>
- Rare;
  - Prolonged PT and APTT but with a normal thrombin time;
  - Treatment is fresh frozen plasma (FFP)<sup>51</sup>;
  - If FV levels ≤1 IU dl<sup>-1</sup>, administer FFP (15 ml kg<sup>-1</sup>) when patient is in established labour and continue with close monitoring;
  - If patient has an operative delivery, continue FFP until wound healing<sup>50</sup>;
  - Anaesthetic management: General anaesthesia for caesarean delivery reported in one case.<sup>52</sup> Other reports do not mention anaesthesia.<sup>51,53</sup>
- iv. Factor VII deficiency<sup>50</sup>
- Most common of the ‘rare’ disorders<sup>54</sup>;
  - Prolonged PT corrects with 50:50 mix normal plasma, providing no inhibitor or APLA.
  - Anaesthetic management: There was one report of four pregnancies in three women with a known diagnosis of FVII deficiency.<sup>54</sup> For all four, prophylactic rFVIIa was administered prior

to delivery. Three of the four had a caesarean delivery under uneventful epidural anaesthesia. Two other parturients had uneventful epidural anaesthesia for three pregnancies prior to the diagnosis. There is a report of epidural anaesthesia for caesarean delivery following administration of recombinant FVII (rFVIIa).<sup>55</sup>

- Recombinant Factor VII: Whilst evidence is lacking, rFVIIa is being used for life-threatening PPH, especially when conventional treatment fails. Thrombosis is a known complication of rFVIIa. Published guidelines highlight the importance of attempting all surgical and non-surgical haemostatic procedures to arrest active bleeding prior to administering rFVIIa.<sup>56</sup> These published recommendations are<sup>56</sup>:
  - rFVIIa ( $90 \mu\text{g kg}^{-1}$ ) administered as a single bolus injection;
  - If no response after 20 mins and persistent bleeding, ensure that temperature, acid/base balance, serum calcium, platelets and fibrinogen are optimal before giving a second dose of rFVIIa;
  - If bleeding persists after two doses, consider hysterectomy.
- v. Factor X deficiency<sup>50</sup>
  - Levels usually increase in pregnancy, returning to normal 6 weeks postpartum.
  - Levels  $\geq 10 \text{ IU dl}^{-1}$  do not require replacement, but below that it requires a haematology consultation.
  - Management of severe FX deficiency: FFP, intermediate purity FIX concentrates (prothrombin complex concentrates) and plasma exchange.<sup>57</sup>
  - A multidisciplinary approach is essential.
  - Anaesthetic management: Some women had caesarean delivery but anaesthesia was not specified.
- vi. Factor XI deficiency<sup>50</sup>
  - Also known as haemophilia C, FXI deficiency increases APTT.
  - FXI levels  $\leq 15 \text{ IU dl}^{-1}$  require replacement with FFP for surgery
  - Anaesthetic management: In 13 parturients with FXI deficiency, nine had uneventful neuraxial anaesthesia.<sup>58</sup> Five had prophylactic FFP before neuraxial anaesthesia; those without FFP had mild disease with no bleeding history.
- vii. Factor XII deficiency<sup>59</sup>
  - Homozygous very rare – autosomal recessive;
  - Prolonged APTT, but bleeding not a problem;
  - May be associated with miscarriage;
  - Anaesthetic management: There are no reports.
- viii. Factor XIII deficiency<sup>50</sup>
  - Often miscarry as FXIII is essential for placentation<sup>50</sup>;
  - Up to 50% of severely affected pregnant women require monthly infusion of FXIII concentrate;
  - Monitor FXIII levels as fall during pregnancy. Trough should be  $>3 \text{ IU dl}^{-1}$ ;
  - Anaesthetic management: There are no reports.
- ix. Hereditary combined vitamin K-dependent factor deficiency<sup>50,60</sup>
  - A wide variation in bleeding tendency;
  - Prolonged PT and APTT;
  - Most improve with vitamin K therapy;
  - There is a report of a woman who received oral Vitamin K (15 mg) throughout pregnancy but required FFP for bleeding from an episiotomy.<sup>60</sup>
  - Anaesthetic management: There are no reports.

### Thromboembolic disease

Venous thromboembolism (VTE) is the leading cause of maternal mortality in the developed world.<sup>61,62</sup> The risk of pulmonary embolism and deep vein thrombosis is increased during pregnancy and further increased by an inherited or acquired thrombophilia. VTE occurs in 10 per 100 000 women of childbearing age and affects 100 per 100 000 pregnancies.<sup>63</sup> Pregnancy-related hypercoagulation is maximal immediately postpartum, increasing the risk of VTE at that time.

**Table 2**Risk factors for thromboembolism during pregnancy.<sup>65,68,70</sup>

Risk factor	Risk
History of VTE	1.4–11.1%
Inherited thrombophilia	0–50% depending on condition, e.g. 0–6% with Protein S deficiency, 50% with AT deficiency
Obesity	Increased
Surgery	Risk with CD 20 × >VD
Prolonged immobilization	Increased
APLA syndrome	Increased
Other: age >35, smoking, varicose veins, multiple gestation, pre-eclampsia	Increased

VTE = venous thromboembolism; AT = antithrombin; CD = caesarean delivery; VD = vaginal delivery; APLA = antiphospholipid antibody.

Thromboembolism is 20 times more likely to occur following caesarean delivery than vaginal delivery.<sup>64</sup>

Inherited thrombophilia is present in 30–50% of women with pregnancy-associated VTE. Factor V Leiden (FVL) is the most frequently identified inherited thrombophilia in the Caucasian population.<sup>65</sup> Thrombophilias associated with a high risk of VTE during pregnancy include AT deficiency, protein C or S deficiency, compound heterozygosity for FVL and prothrombin gene mutation (G20210A) or other combinations of thrombophilia, and homozygosity for these conditions.<sup>63,66</sup> Lower-risk thrombophilias include heterozygosity for FVL or the prothrombin gene mutation.<sup>63,66</sup>

There is conflicting evidence about adverse pregnancy outcomes (e.g., pregnancy loss and pre-eclampsia) in women with inherited thrombophilia, even with heparin prophylaxis.<sup>67</sup> However, women with APLA are at high risk for adverse pregnancy outcomes.<sup>67</sup> Although evidence of adverse pregnancy outcome has not been confirmed in women with thrombophilia without APLA (e.g., FVL heterozygotes) many obstetricians recommend heparin prophylaxis during pregnancy.

Guidelines have been developed for antithrombotic therapy during pregnancy.<sup>65,68–70</sup> These recommendations are usually consensus, rather than evidence-based and involve assessing VTE risk. Heparin prophylaxis is recommended for those in higher-risk categories (Table 2). One study of the effectiveness of heparin prophylaxis in pregnancy, based on risk stratification, concluded that the heparin prophylaxis was effective and safe in preventing VTE.<sup>71</sup> As 50% of VTE occurs postpartum, these guidelines recommend heparin or warfarin for 6 weeks postpartum in women with a history of VTE or thrombophilia.<sup>68,70</sup> VTE during pregnancy is treated with therapeutic heparin.

### Anaesthetic implications of thrombophilia

Anaesthetists are commonly asked to provide epidural anaesthesia for labour and/or delivery in women using prophylactic heparin. There is justifiable concern about administering neuraxial anaesthesia in women on heparin due to the risk of a neuraxial haematoma.<sup>72</sup> Neuraxial anaesthesia is contraindicated when a woman is on therapeutic heparin. Consensus-based recommendations regarding neuraxial anaesthesia in patients on antithrombotics have been developed (Table 3).<sup>73,74</sup> Most anaesthetists follow these or similar guidelines when determining whether and when to administer neuraxial anaesthesia in parturients on anticoagulants.

### Summary

The most common factor deficiencies encountered during pregnancy are vWD and haemophilia carrier states. Women with vWD do well in pregnancy as the associated increases in coagulation factors

**Table 3**  
Neuraxial anaesthesia in patients on anticoagulants.<sup>73,74</sup>

Anticoagulant	Coagulation tests	Time to peak effect	Time to normal coagulation after discontinued	Neuraxial anaesthesia	Epidural catheter removal
IV SH	↑ PT ↑↑↑ APTT	Minutes	4–6 h	Must have normal coagulation (check APTT if <4–6 h after last dose, or if additional concerns). Wait 4–6 h after last SH dose; Wait 1 h after procedure before giving heparin dose	4–6 h after last heparin Wait 1 h to give 1st dose after catheter removal
SC heparin (SH)	↑ PT ↑↑↑ APTT	40–50 min	4–6 h	If on 5000–7500 u q12 h no need to measure APTT if elapsed time 4–6 h post-dose in the absence of specific patient concerns NA not contraindicated ↑ risk if also on anti-platelet drugs	4–6 h after last heparin dose or 1 h prior to next dose
LMWH	Anti-Xa activity not recommended as not predictive of risk of bleeding	2–4 h	12+ h	Wait 10–12 h after low dose Wait 24 h after high dose	Low dose: 10–12 h after last dose; High dose: 24 h after last dose Wait ≥2 h to give 1st dose after catheter removal; If traumatic insertion, wait 24 h to give 1st dose. May be safer to wait 24 h for 1st dose.
Warfarin	↑PT; ↑ INR	4–6 days	4–6 days	Normal coagulation (INR) required before NA	Remove catheter if warfarin within 24 h of restart
Aspirin Other NSAIDs	Bleeding time not reliable to predict platelet function	Hours	5–8 days 1–3 days	NA not contraindicated NB: ↑ risk if also on heparin	No ↑ risk

IV = intravenous; SH = standard heparin; PT = prothrombin time; APTT = activated partial thromboplastin time; SC = subcutaneous; u = units; LMWH = low molecular heparin; NA = neuraxial anaesthesia; preop = preoperatively; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drugs.

are considered protective. Haemophilic carriers must be assessed carefully throughout pregnancy and managed appropriately.

In parturients, bleeding associated with neuraxial anaesthesia may rarely occur in the epidural or spinal space. This can produce a neuraxial haematoma, which can cause neurological complications. A neuraxial haematoma is rare in parturients without coagulation abnormalities. Neuraxial anaesthesia is contraindicated in coagulopathic states.

Thromboembolic disease is significantly increased in pregnancy and is further increased in the presence of thrombophilia. There are guidelines for the use of antithrombotic therapy in pregnancy. Similarly, there are guidelines which assist the anaesthetist to determine whether to administer neuraxial anaesthesia in parturients on anticoagulants.

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### Practice points

- Pregnancy is a hypercoagulable state due to the physiological changes of pregnancy.
- The platelet count is decreased at term compared to pre-pregnant states in normal pregnancy.
- Most coagulation factors increase during pregnancy but some do not.
- Parturients with inherited factor deficiencies may require treatment during pregnancy.
- Thromboembolism is the leading cause of maternal mortality and is increased in women with inherited thrombophilia.
- Provision of neuraxial anaesthesia in parturients with coagulation abnormalities is dependent on the condition and the current status of coagulation.

### Research agenda

Due to the rarity of many of the haematological conditions it is impossible to design randomised controlled trials for management of these conditions. Future care of parturients with these conditions will continue to rely on case reports, case series and a greater understanding of the underlying pathophysiology of each condition.

### Conclusion

In summary, pregnancy is associated with major changes in haemostasis including increases in the majority of clotting factors, decreases in the quality of natural anticoagulants and a reduction in fibrinolytic activity. These changes are greatest at the time of delivery. Platelet counts may be lower in pregnancy most commonly due to gestational thrombocytopenia or ITP. Haemostasis is normal in gestational thrombocytopenia and often in ITP despite low platelet numbers.

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