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Disorders of coagulation in pregnancy

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Abstract

The process of haemostasis is complex and is further complicated in the parturient because of the physiological changes of pregnancy. Understanding these changes and the impact that they have on the safety profile of the anaesthetic options for labour and delivery is crucial to any anaesthetist caring for the parturient. This article analyses current theories on coagulation and reviews the physiological changes to coagulation that occur during pregnancy and the best methods with which to evaluate coagulation. Finally, we examine some of the more common disorders of coagulation that occur during pregnancy, including von Willebrand disease, common factor deficiencies, platelet disorders, the parturient on anticoagulants, and the more rare acute fatty liver of pregnancy, with a focus on their implications for neuraxial anaesthesia.

Key words: blood coagulation disorders; epidural anaesthesia; pregnancy; spinal anaesthesia

Editor's key points

- Obstetric patients undergo many physiological changes that impact haemostasis, in addition to congenital and acquired disorders of coagulation.
- Major issues include von Willebrand disease, factor deficiencies, anticoagulant therapy, and massive haemorrhage.
- Careful assessment and planning facilitate safe delivery and neuraxial anaesthesia to minimize risks of peripartum haemorrhage and epidural haematoma.

The mechanisms of haemostasis are complex. While one can evaluate traditional models of coagulation, in reality the process of clot formation occurs on multiple levels with intricate feedback systems that are not well represented in the typical coagulation cascade.[1] This process is even more complex in the parturient, where changes such as physiological anaemia and fluctuating coagulation factor concentrations alter the balance between bleeding and clot formation in preparation for peripartum blood loss.[2] Although thrombosis is certainly of concern in the otherwise healthy parturient, those who also have a coagulation disorder can be difficult to classify on the spectrum between thrombotic and haemorrhagic risk. It is crucial that anaesthetists who care for pregnant patients have an understanding of these changes in coagulation; not only to ensure the safety of neuraxial anaesthesia, the mainstay anaesthetic for both labour and Caesarean delivery, but also for the management of haemorrhage, which is common in the parturient.[3] The overall estimated risk of epidural or spinal haematoma after neuraxial anaesthesia in the obstetric population is 1:168 000.[4] Vandermeulen and colleagues[5] reviewed 61 instances of anaesthesia-related spinal haematoma in pregnant and non-pregnant patients and found that it most often occurred in patients with coagulopathies (68%). As such, the goals of this article are as follows: to analyse current theories on coagulation and how it changes during pregnancy; to examine how we currently evaluate coagulation; and to review some disorders of coagulation unique to the parturient and their implications for neuraxial anaesthesia.

Coagulation systems and changes in the parturient

As stated at the outset, the classical coagulation cascade represented by the intrinsic and extrinsic system meeting at the common pathway does not accurately represent how coagulation

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occurs *in vivo*.[1] Current theories have transitioned to a cell-based model in which both systems work together to form thrombin either on the surface of the site of vascular injury (extrinsic system) or on the surface of platelets (intrinsic system).[6] The formation of thrombin is broken down into initiation and propagation phases, in which tissue factor is the main initiator of coagulation (Fig. 1).[7 8] Once initiation occurs, the cascade is amplified through the activation of platelets, which is mediated by the release of thrombin and circulating von Willebrand Factor (VWF), in addition to platelet receptors and vessel wall components.[1 6] The activated factors form on the surface of platelets, making the tenase complex (IXa, VIIIa, and the substrate X), which in turn provides materials for the prothrombinase complex (Xa and Va), generating thrombin burst, ultimately forming fibrin from fibrinogen.[6] This system is balanced both by the anticoagulant system, including tissue pathway factor inhibitor, protein C, and protein S, and by the fibrinolytic process, which is activated as the clot is being formed.

Multiple changes occur to the coagulation system as pregnancy progresses, with the largest changes being seen at term gestation.[9 10] While plasma volume itself increases up to 40%, red blood cell volume increases by only 25%, leading to a decrease in hemoglobin concentration known as the physiological anaemia of pregnancy.[11] Platelet counts often decrease, both from dilutional effects and because of consumption by the uteroplacental unit.[12] This decrease is rarely great enough to impact bleeding.[2]

Coagulation factor concentrations change dramatically throughout pregnancy. A comprehensive review is beyond the scope of this paper and can be found in other works.[12–19] A summary of the changes is presented in Table 1. The sum of all these changes leads to approximately double the coagulation activity seen when compared with the non-pregnant state, and pregnancy is therefore known as a hypercoagulable state.[19] Despite the significant changes that occur to the coagulation system, standard coagulation tests, such as prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT), do not change during pregnancy or are very slightly decreased.[17]

Assessment of coagulation

Although a thorough bleeding history is likely to be the best screening tool for global coagulation function, laboratory assessment is often sought to confirm or diagnose potential disorders. Currently, routine screening for coagulation deficits is not recommended in the face of a negative bleeding history.[20] Many institutions use 'standard' coagulation tests as listed in the previous section to assess coagulation in patients with potential bleeding disorders; however, these tests were not designed for this purpose and have several drawbacks. First, the standard PT, INR, and aPTT were not designed to be tests to assess the body's ability to form clot, because they focus almost exclusively on plasma factors.[1] Specifically, PT and INR testing is used to monitor vitamin K-dependent factors II, V, VII, and X and is most commonly used for patients on warfarin. Testing of aPTT was designed to assess factors VIII, IX, and XI for patients either with factor deficiency or on heparin therapy.[21] As such, they are poor tests to assess clinical coagulopathy, especially in the bleeding patient.[22 23] Additionally, traditional coagulation tests take a long time to perform, typically with up to an hour turnaround time.[24 25] Whole-blood point-of-care tests have been developed to overcome some of the disadvantages of traditional tests. For example, thromboelastography (TEG®) and thromboelastometry (ROTEM®) are two viscoelastic tests that can be run on whole or citrated blood and can measure clot kinetics and strength from formation to fibrinolysis.[1 26]

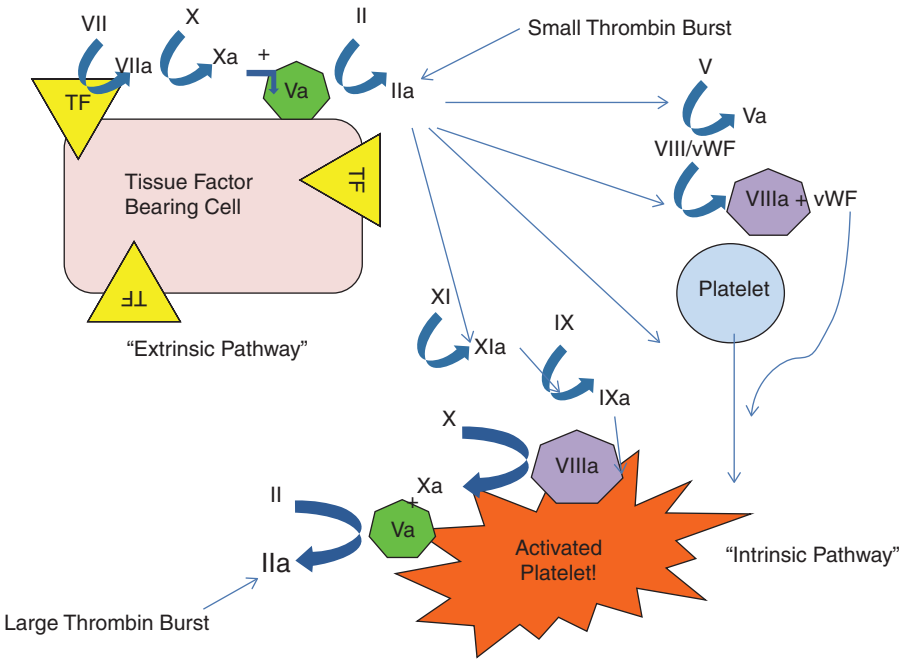

Fig 1 Cell-based model of coagulation showing the small thrombin burst generated by tissue factor-presenting cells (traditional extrinsic system) and its interaction with the formation of the large thrombin burst from the surface of activated platelets (traditional intrinsic system). The initial formation of the factor Va is of debated origin.[8] TF, tissue factor; vWF, von Willebrand factor.

Table 1 Haemostatic changes in pregnancy[9–19]

Haemostatic parameter	Change at term pregnancy (% change)
Factors II and V	No change
Fibrinogen	Increases more than 100%
Factor VII	Up to 1000% increase
Factors VIII, IX, X, XII and VWF	Increase more than 100%
Factor XI	Variable
Factor XIII	Up to 50% decrease
Protein C	No change
Protein S	Up to 50% decrease
D-dimer	Up to 400% increase
Platelet count	Up to 20% decrease

Thromboelastography was first introduced by Hartert in 1948,[27] but was not used clinically until 1985.[1] After the specimen is placed in a cup, a plastic pin with a torsion wire is lowered, and the cup begins to rotate. Although not required, a coagulation activator such as kaolin can be used to speed processing and standardize results.[28] As clot forms between the wall of the cup and the pin, the torque on the wire is translated into an electrical signal that is traced as a curve relative to time (Fig. 2). Five parameters are measured, each of which is correlated with a different portion of clot formation and breakdown.[29] Common measurements and their corresponding coagulation implications are seen in Table 2. Although the entire test takes 30 min to complete, the results are often available as they unfold in real time, giving the clinician access to clot dynamics from start to finish, with initial values (R, K, α-angle, and MA; see Table 2 for definitions) available in a few minutes.[30] Although the test can be run on whole blood, it is

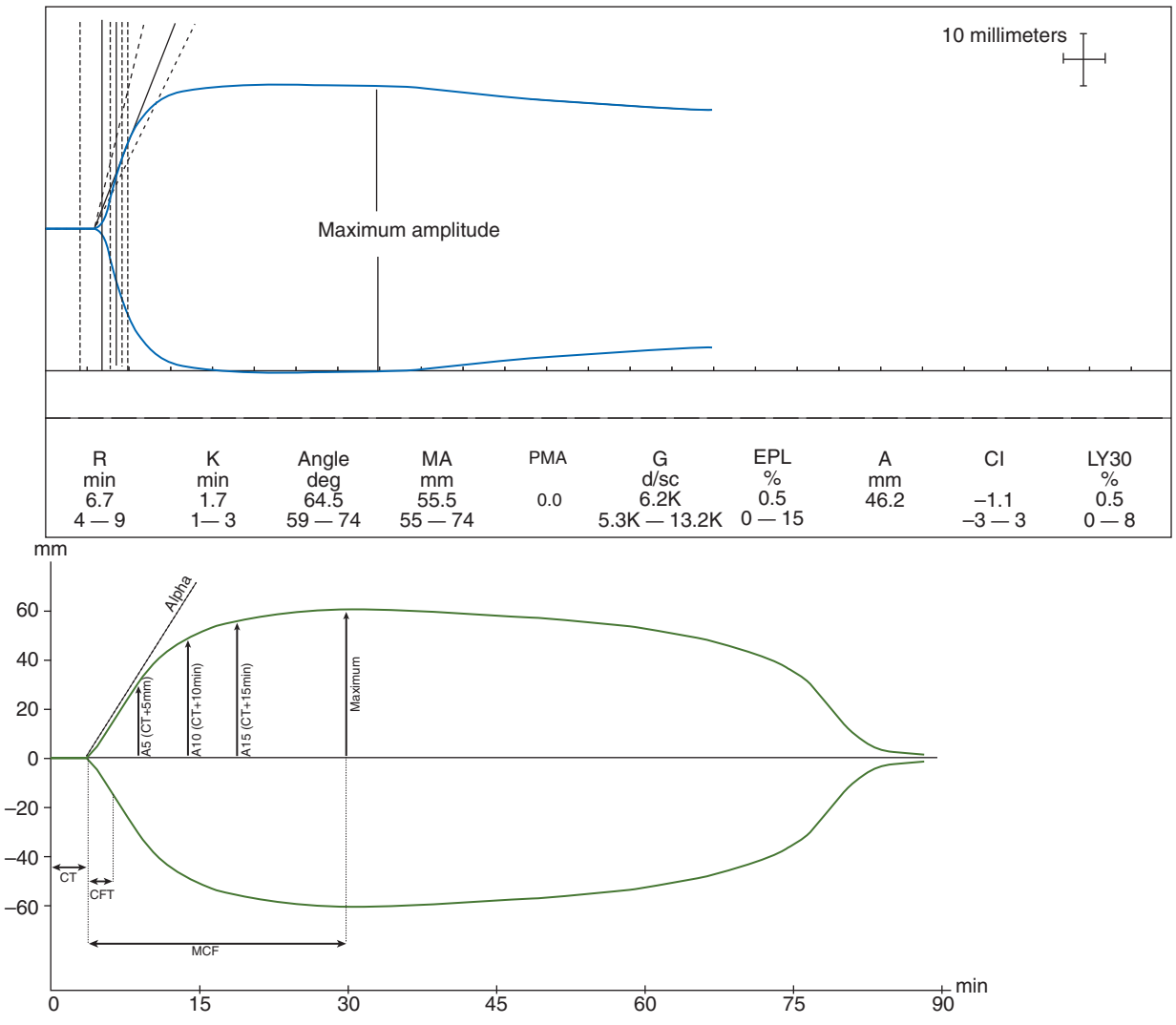

Fig 2 A typical thromboelastogram (TEG®) and thromboelastogram (ROTEM®) curve from a patient without coagulopathy with normal indices. A, current amplitude; Alpha, α-angle; A5, A10, and A15, amplitude at specific minute interval; CFT, clot formation time; CI, coagulation index; CT, clotting time; Deg, degree; EPL, estimated per cent lysis; G, clot strength; K, kinetics time; LY30, lysis 30 min after MA; MA, maximal amplitude; MCF, maximum clot firmness; PMA, projected maximal amplitude; R, reaction time.

Table 2 Commonly used thromboelastography (TEG®) and thromboelastometry (ROTEM®) parameters. A, amplitude; CFT, clot formation time; CT, clotting time; K, kinetics time; LI30, lysis 30 min after CT; LY30, lysis 30 min after MA; MA, maximal amplitude; MCF, maximal clot firmness; R, reaction time

TEG®	ROTEM®	Definition	Representative coagulation process
R	CT	Time to amplitude of 2 mm	Clotting factor activation
K	CFT	Time from amplitude 2 to 20 mm	Factor amplification and fibrin cross-linkage
α-Angle	α-Angle	Angle between line in middle of graph and tangential line of the body of graph	Factor amplification and fibrin cross-linkage
A (A10, A15)	A (A10, A15)	Amplitude at a specific time	Clot strength (fibrinogen, platelets, factor XIII)
MA	MCF	Maximal amplitude of graph	Maximal clot strength (fibrinogen, platelets, factor XIII)
LY30	LI30	Percentage of lysis 30 min after MA/CT	Fibrinolysis

Table 3 Viscoelastic test values in term pregnancy *vs* control subjects.[38–43] A, amplitude; CFT, clot formation time; CLI30, clot lysis index at 30 min after CT; CT, clotting time; K, kinetics time; LY30, lysis 30 min after MA; MA, maximal amplitude; MCF, maximal clot firmness; R, reaction time. TEG values are listed as means with [2SD]. ROTEM values listed as medians with [interquartile ranges]. (–), data not reported

Viscoelastic test TEG®	R-Time (min)	K-Time (min)	α-Angle (deg)	MA (mm)	LY30 (%)
Controls	6.7 [3.8–9.8]	2.0 [0.7–3.4]	62.3 [47.8–77.7]	60.6 [49.7–72.7]	1.2 [−2.3–5.77]
Term pregnancy	7.0 [1–13]	2.0 [0.2–3.8]	64.8 [47.6–82.0]	75.4 [64.6–86.2]	1.6 [0–8.80]
ROTEM®	**CT (s)**	**CFT (s)**	**MCF (mm)**	**CLI30 (%)**	
Controls					
INTEM	159 [138–189]	78 [65–98]	58 [54–62]	98 [98–100]	
EXTEM	51 [45–55]	101 [88–121]	59 [57–62]	99 [99–100]	
FIBTEM	51 [44–53]	(–)	13 [11–16]	(–)	
APTEM	63 [56–67]	96 [78–116]	58 [56-62]	99 [98–100]	
Term pregnancy					
INTEM	155 [132–186]	66 [58–78]	66 [63–69]	100 [99–100]	
EXTEM	53 [47–62]	74 [66–89]	67 [64–71]	100 [99–100]	
FIBTEM	52 [46–65]	(–)	19 [17–23]	(–)	
APTEM	57 [52–75]	74 [64–96]	67 [64–70]	100 [99–100]	

not uncommon to use additives, such as heparinase, arachidonic acid, or Glycoprotein IIb/IIIa inhibitors, for clarity in certain clinical scenarios or to isolate specific portions of the clotting process.[29] The current machine has multiple channels, allowing more than one specimen to be run at a time so that results can be compared. For example, one can run a standard TEG with kaolin next to a Functional Fibrinogen TEG (platelet inhibitor added) to focus in on the effects of fibrinogen.[31] While the quality control of the current machine can be considered labour intensive, new cartridge-based machines with a more favourable quality-control process are in development.

ROTEM® is based on the same principles as TEG. Whereas with TEG the cup rotates and the pin remains still, with ROTEM the pin rotates and the cup remains still.[32] The optical graph looks similar to TEG and reports on five similar parameters (Fig. 2 and Table 2). The interpretation of the graph is similar to that of the TEG.[33] Additives can be used to enhance ROTEM testing. The INTEM and EXTEM use additives from their prospective cascades [phospholipid and ellagic acid for the intrinsic (INTEM) pathway and tissue factor for the extrinsic (EXTEM) pathway], respectively, to differentiate between abnormalities from the different pathways.[1] For a more clear picture on the need for fibrinogen one can use the FIBTEM assay, in which a platelet inhibitor is added to differentiate between platelet and fibrinogen dysfunction.[34] This test can be used as a surrogate marker for Clauss fibrinogen testing with rapid turnaround (10 min), which is useful when managing obstetric haemorrhage.[35–37] Lastly, APTEM analysis uses aprotinin with tissue factor added to confirm or rule out hyperfibrinolysis.[1]

Both TEG and ROTEM have been examined in pregnancy to compare with non-pregnant populations; caution should be used when interpreting both tests on pregnant patients with regard to 'normal values'. Reference ranges for the parturient during different stages in pregnancy for both TEG and ROTEM have been reported and confirm earlier evidence of the hypercoagulable state of pregnancy.[38 39] A summary comparing changes in test parameters is shown in Table 3.[38–43] Although there is a growing body of literature demonstrating reference ranges for parturients, the values are not congruent from study to study, which might be because of differences in patient populations or different reagents being used for standardization. Specific ranges for non-pregnant values should be calibrated for each institution. For example, de Lange and colleagues[38] report maximal lysis percentages with a range as high as 41%, which is much higher than values reported in non-pregnant patients.[40] Additionally, changes to coagulation occur as pregnancy progresses, which means that 'normal values' can change with time. Karlsson and colleagues[39] trended the changes in TEG at different points during pregnancy and postpartum to account for changes that occur during pregnancy.

Applications of viscoelastic tests in the obstetric population have been studied particularly in the arena of postpartum

Table 4 Relationship between FIBTEM A5 and Clauss fibrinogen assay (r=0.6).[2] A5, amplitude at 5 min

FIBTEM A5 (mm)	Clauss fibrinogen (mg dl^{-1})
15	300
10	200
6	100

haemorrhage (PPH) but less to determine the safety of neuraxial anaesthesia.[37 42 44] Huissoud and colleagues[35] compared 51 patients with PPH and found greatly decreased FIBTEM values by ROTEM in those who had significant bleeding. In this same study, clot amplitude (CA) values at 5 and 15 min were 100% sensitive and 85–88% specific to detect low fibrinogen levels (<1.5 g litre^{-1}) and can therefore be used to direct therapy with fibrinogen concentrate or cryoprecipitate.[35] While it is important to note that FIBTEM assays are not exact fibrinogen measurements, they measure similar parameters of the ability to form clot.[36] Collis and Collins[2] recommend a rough guide for comparing FIBTEM results with Clauss fibrinogen (Table 4). Karlsson and colleagues[45] examined TEG profiles in patients with severe PPH (>2 litres) and demonstrated rapid clot initiation but reduced clot strength, when compared with patients who had normal deliveries, further highlighting the role of fibrinogen in PPH. Although current guidelines[46] support the use of point-of-care coagulation testing, no specific thresholds for viscoelastic tests are recommended.[47–49] In their review, Collis and Collins[2] provide a sample algorithm for using FIBTEM in a transfusion algorithm, and although viscoelastic-based algorithms exist in other areas, such as cardiac[50] and liver surgery,[51] they might not be applicable to the obstetric population.

In addition to the management of PPH, viscoelastic tests have been studied to ascertain whether they can be used to guide the use of neuraxial anaesthesia. Orlikowski and colleagues[52] measured platelet counts, TEG parameters, standard coagulation panels, and bleeding time in healthy pregnant women and in those with pre-eclampsia. They found that the maximal amplitude (MA) remained normal (53 mm) until platelet count decreased to <540 000 mm^{-3} (95% confidence interval 40–75 000 mm^{-3}), suggesting that changes in MA were more likely to be a result of changes in platelet count or function. Based on their study, they suggested that a platelet count of 75 000 mm^{-3} should be associated with adequate haemostasis. However, there is no clinical evidence that a normal MA is correlated with safe epidural analgesia, and these results should be confirmed with more data before widespread acceptance. Although viscoelastic assays have their advantages over traditional tests, there are some gaps in their diagnostic abilities. In general, they tend to be insensitive to specific factor deficiencies, especially when used as single tests.[53] Therapeutic interventions can improve variables, disguising other deficiencies. For example, treating a patient with fibrinogen can increase MA and MCF but disguise a developing thrombocytopenia.[54] Additionally, tests are performed at 37°C, which means that the effect of hypothermia on coagulation is not measured.[55]

Another tool that can be used to monitor haemostasis is platelet function testing. Although automated platelet counters can provide practitioners with absolute platelet counts, they are neither sensitive nor specific for platelet function. The standard test for platelet function is considered to be aggregometry, which uses spectrophotometry to measure density changes induced by the addition of adenosine diphosphate (ADP) and arachidonic acid (AA) to platelet-rich plasma.[56] This test has limitations, including difficult preparation of reagents, operator dependence, and corrections that must be applied to results based on the concentrations of reagents and platelet count. Furthermore, the test takes days to obtain results.[57] As such, point-of-care platelet function-testing devices have been developed and used in the clinical arena. These machines monitor platelet function by different methods, including the counting of platelets pre- and post-activation with ADP and AA[58] (Plateletworks®), measurement of the time to development of high shear forces by whole blood blocked by platelet plug closure[59] (PFA-100®), and measurement of the increase in electrical impedance caused by the aggregation of platelets[60] (Multiplate®). The utility of these tests thus far has been to aid in diagnosis and management of patients with platelet disorders, such as Bernard–Soulier or Glanzmann's thromboasthenia,[61 62] and in the areas of cardiac surgery[63] and interventional cardiology[64] to monitor patients who are on multiple platelet-inhibiting agents, such as clopidogrel and aspirin. The utility of these tests for the parturient has been investigated because obstetric anaesthetists are often confronted with disorders of both platelet count and function. Beilin and colleagues[65] investigated the correlation between platelet closure (CT) times with the PFA-100 and platelet count and did not find a correlation. Davies and colleagues[66] investigated PFA-100 CT and found that patients with severe pre-eclampsia have significantly longer closure times than those with mild pre-eclampsia or control subjects. There are currently no investigations demonstrating values of a platelet function test for the safe placement of neuraxial anaesthesia. Platelet function testing has also been examined in the setting of the bleeding patient to aid management, especially in the arena of cardiac surgery[67] and trauma.[68] Experience using these tests for obstetric haemorrhage is limited to one case report.[69] More research is needed in this area to determine the clinical utility of these tests for the parturient.

Inherited disorders of coagulation

Owing to the low prevalence of inherited coagulation disorders, routine screening for inherited coagulation disorders is not recommended except in the face of a personal or immediate family history of bleeding.[20] However, parturients who present with known disorders or bleeding history (mucocutaneous bleeding or menorrhagia) are at increased risk of bleeding complications during pregnancy and childbirth.[70 71] Investigation into coagulation disorders is warranted in patients with a history of PPH without other known cause.[20] In general, patients who present with bleeding disorders should be treated by a multidisciplinary team consisting of an obstetrician, anaesthetist, haematologist, and support personnel (such as a haemophilia nurse to aid in dispensing of medication and neonatologists to care for the potentially affected neonate) when indicated. Factor levels should be checked at confirmation of pregnancy, at 28 and 34 weeks of gestation, and before invasive procedures based on expert consensus.[71] Not all factor deficiencies correct with pregnancy, nor do normal factor levels exclude the possibility of bleeding.

A delivery plan (birth plan) should be made in advance, with a copy given to the patient to carry with her. The plan should include the patient's wishes for the delivery that are not necessarily influenced by her disease state (such as skin to skin or the use of formula) and information regarding the patient's disease state and treatment plan (such as prophylactic factor administration or plan of mode of delivery). There are no current recommendations on mode of delivery for these patients;[72] the presence of a bleeding disorder does not preclude normal spontaneous vaginal delivery with a neuraxial anaesthetic.[20 73] Patients should be

Table 5 Von Willebrand disease types. A, absent; ↔, unchanged; ↓, decreased; ↑, increased; DDAVP, desmopressin; Plt, platelet; Rco, resitocentin-induced aggregation; RIPA, ristocentin-induced platelet aggregation; VWF, von Willebrand factor; VWF Ag, von Willebrand antigen

VWD type	VWF concentrations	Plt count	VWF Ag/RCo ratio	RIPA	vWF high density multimer	DDAVP effective?
1	↓	↔	>0.7	↔,↓	↔	Yes
2A	↓	↔	<0.7	↓↓, A	A	Variable
2B	↔	↔, ↓	<0.7	↑	↓	Do not use
2M	↔	↔	<0.7	↓↓, A	↔	Variable
2N	↔	↔	↔	↔	↔	Variable
3	↓↓, A	↔	↓↓, A	↓↓, A	↓↓, A	No

treated on n individual basis, with a thorough discussion of the risks and benefits of the obstetric and anaesthetic interventions. Patients with severe disorders should have factor levels normalized as close to labour and delivery as possible, with maintenance of factor levels for 3–5 days after vaginal delivery or 5–7 days after Caesarean delivery.[74] Treatment regimens can consist of tranexamic acid (TXA), 1-desamino-9-d-arginine vasopressin (DDAVP), recombinant proteins, and blood components such as plasma and cryoprecipitate. Their mechanisms and utility in specific disorders are discussed below. When possible, recombinant proteins are preferred, as they carry no risks of viral transmission. Plasma-derived specific factors are treated with virucidal agents to minimize transmission of certain viruses, such as human immunodeficiency virus, but can still transmit hepatitis A, parvovirus, and others.[75–79] Even though the risk of infection has decreased, risk still exists. Therefore, when plasma is used, pathogen-reduced plasma should be considered. Common techniques include treatment with riboflavin, photo-irradiation, solvent detergent (SD FFP), or methylene blue. Dosing of plasma can vary, because factor levels from each unit can vary greatly.[80] Solvent detergent processing decreases the activity of certain factors, such as factor V, by as much as 30%, so dosing should be adjusted and follow-up studies should be done.[81] Cryoprecipitate is not virally inactivated and should be used only if no other products are available[74]

For management of labour, avoidance of prolonged labour (>20 h in nulliparous women or >14 h in multiparous women)[82] and instrumentation for delivery of the fetus are advisable. When it is unknown whether the neonate is at risk or has inherited the disorder, invasive fetal monitoring (fetal scalp electrodes and blood sampling) should be avoided, and vacuum-assisted delivery is contraindicated.[71] The levels of several factors decrease greatly in the postpartum period (see specific disorders below). As such, it is prudent to recheck levels before removal of epidural catheters if a significant amount of time has passed (6 h).[73] For patients in whom neuraxial anaesthesia is contraindicated, analgesia for labour can be accomplished with controlled inhalation of nitrous oxide[83] or patient-controlled analgesia with medications such as remifentanil.[84] Although patients with bleeding disorders can be at risk for PPH, it should be noted that once haemostasis is achieved or in the situation where the patient does not require prophylactic treatment, the use of anticoagulation for prevention of deep venous thrombosis should be considered. It is beyond the scope of this review to discuss all known coagulation disorders, so we will focus on the most common disorders affecting the parturient.

Von Willebrand disease

Von Willebrand disease (VWD) is the most common bleeding disorder encountered in the general population, with an estimated prevalence of ~1%,[85] although the prevalence of clinically significant disease is much lower (around 1 in 10 000 patients),[86] and complicates more than 50 000 deliveries per yr.[87 88] Von Willebrand factor works at the site of injury by adhering to injured tissues and causes platelet adherence.[89 90] Additionally, it stabilizes factor VIII, which degrades rapidly when not attached to VWF. Von Willebrand disease results from either quantitative or qualitative defects in VWF and has several subtypes (Table 5). Many patients with VWD are asymptomatic and commonly present only after a traumatic insult. The most common type of VWD is type 1, which accounts for 70–80% of all patients with VWD and is a purely quantitative deficiency.[91 92] Type 2 VWD results from qualitative deficiencies that can also be complicated with quantitative deficiency and accounts for ~20% of patients with VWD.[92 93] Each letter subtype has a specific loss or gain of function of VWF, in which the end result is a bleeding tendency. Of note, type 2B is a gain-of-function change, in which the binding of VWF to platelets is abnormally enhanced. This leads to platelet aggregation and clearance, which leads these patients also to be thrombocytopenic. Desmopressin (DDAVP) is contraindicated in this form of VWD because it will exacerbate thrombocytopenia.[93 94] The remainder of VWD patients are type 3 (<10%), in which no VWF is present. These patients present in a similar way to a haemophiliac, because they have little or no circulating factor VIII as a result of the absence of VWF.[95]

In normal pregnancy, VWF can increase 200–375%.[90] As such, most patients with type 1 disease will attain normal factor concentrations as pregnancy progresses, and bleeding after the first trimester is rare.[96] Patients with type 2 disease have similar increases in VWF; however, given that their mutations are functional in nature, many of these patients are still at risk for peripartum bleeding. Additionally, those with subtype 2B may have worsening thrombocytopenia. Patients with type 3 disease do not have an increase in VWF during pregnancy (because they make no VWF) and are at increased risk of PPH.[93 97]

Treatment and prophylaxis of these patients depends on their presentation, timing, and subtype. Patients with known VWD should have testing to determine the type of VWD, which should include testing factor VIII concentrations and a von Willebrand ristocetin cofactor activity assay (VWF:RCo) test to determine the functional concentration of VWF.[85] Goal concentrations at the time delivery include a VWF:RCo and factor VIII concentrations >50 IU dl^{-1}, while those below this concentration require treatment.[88] Some clinicians monitor peak and trough concentrations daily around the time of delivery.[85] Risk factors for PPH in this patient population include having type 2 or 3 disease, or having less than 50 IU dl^{-1} VWF activity around the time of delivery.[98 99] Extra care should be taken in patients with VWD in the postpartum period because VWF concentrations rapidly return to their pre-pregnancy concentrations. One patient in the

literature went from 100% VWF activity to less than 10% in the first 24 h postpartum.[91]

Prophylaxis and treatment in selected patients can be achieved with TXA, DDAVP, antihaemophilic factor–von Willebrand factor complex (Humate-P), plasma, cryoprecipitate, or a combination of these. Tranexamic acid blocks the binding of plasminogen to fibrin, thus stabilizing formed clot.[88] Although TXA causes no change in factor concentrations, there is evidence of its efficacy when treating bleeding,[100–102] including areas where fibrinolytic activity may be increased, such as the uterus in the postpartum period.[103] Dosing is oral or i.v.[104] The i.v. dosing regimens for treating PPH are 1 g i.v. with repeat dosing as needed.[104] ε-Aminocaproic acid, another antifibrinolytic, can also be used; however, its efficacy and safety profile in obstetrics have not been studied.

Unlike TXA, DDAVP can be used to increase factor concentrations. Responses to DDAVP vary by subtype. Concentrations of VWF can increase two- to three-fold in 15 min, peaking at three to five times baseline in 90 min, by causing a temporary release of VWF from the Weibel Palade bodies in endothelial cells.[90] Dosing regimens usually start at 0.3 μg kg^{-1} up to a maximum of 25–30 μg i.v. based on previous response and should be given i.v.[88] Duration of effect varies but is typically 8–10 h. Dosing can be repeated every 12 h, although tachyphylaxis is common.[88] Side-effects from DDAVP administration include flushing, tachycardia, hyponatraemia, headaches, and tachyphylaxis.[91] Fluid intake should be monitored and restricted for 24 h after dosing. Initial concerns regarding its use in the obstetric population pertaining to the potential vasopressor effect (through cross-reaction with the vasopressin 1 receptor) of DDAVP decreasing uterine blood flow,[105 106] or an oxytocic effect causing preterm labour have not been recognized.[93] Patients may breastfeed after dosing.[107] As stated before, DDAVP will have limited utility in patients with type 2 disease (functional mutations) or type 3 VWD, and is contraindicated in patients with type 2B.

Low responders to DDAVP and type 3 patients require direct factor replacement. Direct factor replacement can be accomplished with recombinant and plasma-derived concentrates, including Alphanate SD/HT, Humate-P, and Wilate. Although these agents differ, in general they are virally inactivated, and administering 1 IU kg^{-1} increases both factor VIII and VFW:RCo by ~2 IU dl^{-1}.[88] Re-dosing might be needed every 8–24 h to maintain activity concentrations above 50 IU dl^{-1}. In the absence of plasma-derived or recombinant products, plasma or cryoprecipitate can be used, although it is a pooled product without viral inactivation. Owing to its higher concentration per volume (8.6 *vs* 0.9 U ml^{-1}),[108] cryoprecipitate is preferred. Dosing regimens vary, with a reasonable dose considered to be 10–12 units of cryoprecipitate every 12 h for an adult.[109]

Multiple case series report the safe use of spinal, epidural, and combined spinal–epidural anaesthetics in this patient population.[87 90 96 110] Most of these case series are fewer than 100 patients, and the majority of patients have type 1 disease. Recommendations for factor tests and concentrations have varied; however, most agree that patients with normalized VWF:RCo, factor VIII, and VWF antigen concentrations are candidates for neuraxial anaesthesia,[90] and that is our practice. The epidural catheter should be removed as soon after delivery as possible because factor concentrations decrease rapidly after delivery. If the catheter is maintained *in situ* after delivery, documentation of normal factor concentrations should be obtained before removal.[71]

Haemophilia A and B carriers

Although haemophilia A and B (severe factor VIII and IX deficiency, respectively) are extremely rare in females, carrier status is much more common.[111] Although most carriers are asymptomatic, 35% of carriers have factor concentrations below the normal threshold.[112] Up to 4% of patients who present for evaluation of menorrhagia are found to be carriers.[113] As such, known carriers should have factor concentrations checked at conception, and if abnormal, repeated at 28 and 34 weeks according to expert consensus.[71] Although some carriers of either haemophilia A or B are at risk for antepartum bleeding, factor VIII concentrations usually increase by term into the normal range.[107] Factor IX concentrations do not change with pregnancy; therefore, patients with low factor concentrations or positive bleeding history should be treated before delivery or invasive procedures.[71] In patients requiring treatment with factor products, factor concentrations should be supplemented to at least normal non-pregnant concentrations (50 IU dl^{-1} for both factors VIII and IX).[74] Specific factor concentrates are the treatment of choice for these patients; however, patients with haemophilia A carrier status with borderline factor concentrations can be given DDAVP for bleeding prophylaxis.[107] Desmopressin has no effect for carriers of haemophilia B.

Owing to the high risk of delivering children with carrier or full disease states, having a birth plan as discussed in the general inherited disorders section is strongly encouraged, as is pre-delivery testing of the neonate. If parents do not want to risk invasive testing, fetal DNA from maternal venous sampling can at least determine the sex of the baby. Although no specific mode of delivery is recommended, there is consensus that in the situation where the mother is a haemophilia carrier delivering a male child with the disease, elective Caesarean delivery is the safest option.[114]

Factor VIII concentrations decrease rapidly after delivery; therefore, secondary PPH rates for carriers are much higher than normal (11 *vs* 0.8%).[115] Factor concentrations should be supplemented to remain within the normal range for at least 3 days for vaginal deliveries and 5 days for Caesarean delivery.[71 107] In patients with refractory bleeding (despite administration of TXA and recombinant or plasma proteins), recombinant activated factor VII (rFVIIa) has been successfully used.[116]

Recombinant activated factor VII is a potent pro-coagulant that directly activates the extrinsic system, binds platelets, and generates a dose-dependent thrombin burst (Fig. 1) that can normalize thrombin formation in haemophilia A and B.[117 118] Dose regimens and intervals are highly variable; however, for patients with haemophilia doses of 90 μg kg^{-1} every 3 h until haemostasis is achieved have been used.[116 117 119] Recombinant activated factor VII is expensive and carries a significant risk of major thrombosis in patients, and should only be used when other treatment options have failed.

In the rare instance where factor VIII inhibitor has developed, the use of an anti-inhibitor coagulation complex, such as FEIBA (Factor Eight Inhibitor Bypassing Activity), should be considered.[120] FEIBA contains mostly non-activated factors II, IX, X, and VII. It also contains small amounts of both factor VIII coagulant antigen and factors of the kinin-generating system.[121] The dosage of FEIBA should be confirmed with a haematologist, and is usually in the range of 100 U kg^{-1} every 12 h in patients with severe bleeding.[122]

Several case series (~100 anaesthetics)[87] document the safe placement of neuraxial anaesthetics in haemophilia carriers, both in pregnant and in non-pregnant patients. Although the management was not standardized, in all instances where the

patient was a known carrier the factor concentrations of VIII/IX were normalized (>50 IU dl^{-1}) before placement. In about half of the patients, normal factor concentrations were documented before catheter removal.[73 123 124] As stated above, prophylactic factor replacement is recommended for 3–5 days after delivery to keep concentrations in the normal range, and should be documented as normal before removal of the catheter by either specific factor concentrations or aPTT.

Factor XI deficiency

Factor XI deficiency (also known as haemophilia C) is a bleeding disorder found predominantly in the Ashkenazi Jewish population, although it has also appeared in several other patient populations.[125 126] Its role in coagulation is not well understood, but it is believed to be both procoagulant and antifibrinolytic.[127] 'Normal' concentrations of factor XI depend on the laboratory used but are ~50 IU dl^{-1}, although patients with concentrations of 50–70 IU dl^{-1} can have positive bleeding histories.[128] Treatment thresholds differ based on mode of delivery. In women opting for vaginal delivery with concentrations of 15–70 IU dl^{-1}, expectant management is sufficient. Those with concentrations of 15–70 IU dl^{-1} and a bleeding history should receive TXA for vaginal delivery.[107 129] In other patients, factor replacement is required and can be accomplished with factor XI concentrate or plasma.[107] It should be noted that factor XI concentrate is not universally available. Careful dosing of factor XI concentrate is required to prevent thrombosis, with avoidance of peaks >70 IU dl^{-1} and a maximal dose of 30 IU kg^{-1}. The half-life of factor XI is long (52 h), so daily dosing might not be needed.[126 127] Factor concentrations should be maintained for 3 days after vaginal delivery and for 5 days after Caesarean delivery.[71] A rare subset of patients who have factor XI inhibitors can be treated with rFVIIa (for mechanism, see Haemophilia A and B section) although this is an off-label use.[130] Dose regimens vary between 30 and 60 μg kg^{-1} every 3–4 h.[131] In these patients, plasma exchange can also be used.[132]

The use of neuraxial anaesthesia in this patient population is controversial because of the unknown risk of epidural or spinal haematoma. However, several case series have demonstrated successful use of neuraxial techniques without negative sequelae. Bleeding history is more important than the factor concentrations, because factor concentrations do not predict bleeding. Strategies for ensuring haemostasis include taking a thorough bleeding history and demonstrating a normal coagulation profile (aPTT) before placement, or documenting correction of studies (aPTT, ROTEM) before placement. Correction was achieved through giving plasma or rFVIIa (30 μg kg^{-1} 10 min before block) in these patients.[73 126 133 134]

Acquired disorders

Platelet disorders

Platelet abnormalities can be qualitative or quantitative and are the most common haematological disorders during pregnancy. Most instances of thrombocytopenia during pregnancy (99%) are related to one of three causes: hypertensive disorders, such as pre-eclampsia; gestational thrombocytopenia; or idiopathic thrombocytopenic purpura (ITP). When evaluating the parturient with thrombocytopenia, there are two specific issues to consider. The first concern is whether the disorder is static or dynamic. If the disorder is static, as occurs during gestational thrombocytopenia or ITP, the platelet count is usually stable. If the disorder is dynamic, as occurs during pre-eclampsia, the platelet count can rapidly change and it is important to obtain serial platelet counts. The second issue is whether platelet function is normal or abnormal. Platelet function is typically normal in gestational thrombocytopenia and ITP, and may be abnormal in severe pre-eclampsia.[66]

Although the direct cause of thrombocytopenia in pre-eclampsia is unknown, it is hypothesized that microangiopathic endothelial injury results in the formation of multiple thrombi in the systemic vasculature, leading to platelet activation, aggregation, and consumption.[135] This may be complicated further by the subset of pre-eclamptic patients with hemolysis, elevated liver enzymes, low platelet syndrome, who can also manifest severe liver dysfunction and overt coagulopathy.

To our knowledge, there is only one case report in the literature of a parturient with pre-eclampsia who had thrombocytopenia (platelet count of 71 000 mm^{-3}) and developed an epidural haematoma.[136] The patient had an epidural anaesthetic with bupivacaine 0.5% 13 ml for uneventful Caesarean delivery, but had a seizure in the recovery room 1 h after the procedure. It was noted that her legs did not move, and a scan revealed an epidural collection of fluid. A laminectomy was performed 6 h after epidural catheter placement, at which time 4 ml of blood was drained. The patient recovered 72 h later. Whether the 4 ml of epidural blood was sufficient to cause her symptoms is unknown; it is possible that the symptoms were related to residual local anaesthetic effects.

In 1988, Cousins and Bromage recommended that one should not place an epidural catheter if the platelet count is <100 000 mm^{-3}.[137] Their recommendation has been challenged, primarily because thrombocytopenia occurs frequently during pregnancy,[138] and neuraxial anaesthesia is safer than general anaesthesia for the parturient.[139] Currently, most authors do not define a minimal platelet count below which it is unsafe to perform epidural anaesthesia. Indeed, each patient must be individualized, and the responsible anaesthetist must weigh the risks and benefits.

A routine platelet count is not necessary in the otherwise-healthy parturient and should be done based on patient history, physical examination, and clinical signs.[140] If the platelet count is found to be low it is important to confirm this finding because automated counters can be unreliable, especially at lower platelet counts. A manual count should be undertaken, because it is not uncommon to find that the platelets are clumping and the count is really greater than calculated.[141] Patient history and physical examination are key components when deciding whether to proceed with a neuraxial anaesthetic in the parturient with thrombocytopenia. Consultation with a haematologist, preferably before labour, can also help with assessing the aetiology of thrombocytopenia and determining whether platelets are functioning adequately. If there is any history of easy bruising or if the patient has evidence of petechiae or ecchymosis, neuraxial anaesthesia should not be offered. If the patient has no bleeding history, then our general practice is to obtain at least one additional platelet count as close in time to epidural catheter placement as possible to ensure that it is not decreasing. This is especially important for disease processes that are dynamic, such as pre-eclampsia. In pre-eclampsia, it is also important to demonstrate a normal PT/aPTT when the platelet count is <100 000 mm^{-3}. LeDuc and colleagues[142] demonstrated that as long as the platelet count in pre-eclampsia is >100 000 mm^{-3}, PT/aPTT remains normal.

There are no studies that define the lowest safe absolute platelet count for epidural catheter placement, nor are there

studies with TEG or ROTEM that define safe values. The risks of epidural placement *vs* general anaesthesia have to be individualized, and informed consent must be obtained. We will place an epidural catheter in a woman with a stable platelet count of 70 000–75 000 mm^{-3}, and some are comfortable with lower platelet counts, especially in women with ITP.[143] A recent survey highlighted this controversy, showing that 55% of anaesthetists polled would use neuraxial anaesthesia with a platelet count of 50–100 000 mm^{-3}.[144]

If the decision is made to place an epidural catheter, soft-tipped catheters should be used to minimize trauma to epidural vessels, and the epidural catheter should be placed in the midline.[145 146] The lowest concentration of local anaesthetics should be used, in order to preserve motor function. The patient should be examined every 1–2 h to assess the extent of the motor block, and these examinations should continue until after the anaesthetic has worn off and the catheter has been removed. In this way, if the patient develops a motor block out of proportion to what one would expect, or if the anaesthetic has a prolonged duration of action, the patient can be assessed immediately with magnetic resonance imaging for the development of an epidural haematoma.[147] Immediate evaluation is necessary because if the patient has an epidural haematoma, an emergent laminectomy and decompression must be performed within 6–12 h to preserve neurological function.[148]

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is an acquired disorder of unknown origin occurring once in 5000–10 000 pregnancies.[93] Although the cause is unknown, it is believed to occur secondary to an abnormality in the β-oxidation of fatty acids in mitochondria.[149] Patients present with vague abdominal symptoms that include pain, jaundice, vomiting, and anorexia.[150] Laboratory signs may include hyperbilirubinaemia, transaminitis, elevated serum creatinine, and coagulopathy. Outcomes for this disorder are directly related both to the time of recognition and to delivery of the fetus, and as such, induction of labour or Caesarean delivery is encouraged at the time of diagnosis.[150] Acute fatty liver of pregnancy has not been reported to resolve before delivery.[151]

Neuraxial anaesthesia has been used in patients with acute fatty liver of pregnancy. The largest retrospective review reported the use of neuraxial anaesthesia for 13 patients, using bleeding history, overt coagulopathy, or both as a guide for safety.[150] For coagulopathy, a threshold INR of 1.5 was used for current guidelines;[152] however, in two patients the INR was greater (2.4 and 2.3). No negative sequelae were seen.

The pregnant patient on anticoagulants

Fifty per cent of pregnant patients who die from a thrombotic event have an inherited thrombophilia.[153] A review of the most common mutations, including protein C and S deficiency, antithrombin III deficiency, factor V Leiden mutation, prothrombin gene G20210A mutation, methylenetetrahydrofolate reductase deficiency, and antiphospholipid antibody syndrome, is beyond the scope of this review. Other than an increased risk of thrombosis during labour and delivery, the anaesthetic implications of these disorders are not related to their pathophysiology, but to their treatment. The most commonly used anticoagulants are low-molecular-weight (LMWH) or unfractionated heparin (UFH).[154–156]

Low-molecular-weight heparin has gained widespread use in pregnancy and has certain advantages over unfractionated heparin. Both UFH and LMWH have similar haemorrhagic complication rates and antithrombotic efficacy; however, LMWH, unlike UFH, does not require laboratory monitoring. Also, there are fewer serious complications with LMWH, such as heparin-induced thrombocytopenia[157] and osteoporosis.[158] Low-molecular-weight heparin has sparked a new challenge for anaesthetists. Previously, spinal or epidural haematoma was a rather rare occurrence, <1 in 150 000–220 000 after neuraxial anaesthesia in the general population.[5] Within 1 yr of the introduction of enoxaparin' in the USA, two instances of epidural haematoma were reported. It became clear there were added risks with LMWH compared with UFH. This increased risk is primarily related to its long duration of action. Renal insufficiency prolongs the duration of action with LMWH and might have been a risk factor in at least one patient who developed an epidural haematoma after spinal anaesthesia.[159] Renal insufficiency, as an added risk factor, should be considered before placing neuraxial anaesthesia, although the guidelines (see below) are not altered based on renal insufficiency.

Both the American Society of Regional Anaesthesia and Pain Medicine (ASRA)[152] and the European Society of Anaesthesiologists (ESA)[160] published similar consensus guidelines in 2010 to help guide the safe placement of neuraxial anaesthesia in the parturient receiving UFH or LMWH.

Both the ASRA and the ESA recommended that with regard to UFH, if the dose is <5000 units twice a day no further testing is required before neuraxial anaesthesia. Doses of >5000 units twice a day require documentation of a normal PTT before placement. Also, a platelet count should be checked to rule out heparin-induced thrombocytopenia if the patient has been receiving heparin for >4 days.

With LMWH no testing is required, but neuraxial anaesthesia should be delayed by either 12 or 24 h from the last injection of LMWH depending on whether the patient is receiving prophylactic or therapeutic doses of LMWH, respectively. If the patient has an epidural catheter placed, LMWH administration should be delayed for 4 h after catheter removal.

Although it is rare for a pregnant woman to be taking the newer oral anticoagulants, such as dabigatran or rivaroxaban, if a patient taking these medications is encountered neuraxial placement should be delayed by 5 and 3 days, respectively.[152]

Conclusions

The parturient with coagulation defects presents a unique challenge to the anaesthetist. In addition to concerns of peripartum haemorrhage, one must be aware of the consequences of bleeding diatheses, factor replacement strategies, and anticoagulation on the safety profile of neuraxial anaesthesia. The risk of spinal or epidural haematoma in these patients has not been quantified fully, but is nevertheless a factor that one must consider on an individual basis in determining whether neuraxial anaesthesia is appropriate. Owing to the rarity of many of these disorders, consensus guidelines are lacking. More research is needed on optimal factor-replacement strategies, including the duration of treatment, how best to monitor patients with new point-of-care tests, and proper protocols to ensure both prevention of postpartum haemorrhage and neuraxial complications.

Authors' contributions

Substantial contribution to conception and design, drafting of the article and revising critically, verification and final approval of manuscript, agreed accountability for all aspects of work relating to accuracy and integrity: D.K., Y.B.

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