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REVIEW

Disseminated intravascular coagulation in obstetric disorders and its acute haematological management

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SUMMARY

As activation of the coagulation pathway is a physiological response to injury, the development of disseminated intravascular coagulation (DIC) is a warning signal to the clinician that the primary pathological disease state is decompensating. In pregnancy, DIC can occur in several settings, which include emergencies such as placental abruption and amniotic fluid embolism as well as complications such as pre-eclampsia. Whilst the acuteness of the event and the proportionality in the coagulant and fibrinolytic responses may vary between these different conditions, a common theme for pregnancy-associated DIC is the pivotal role played by the placenta. Removal of the placenta is the linchpin to treatment in most cases but appropriate blood product support is also key to management. This is necessary because DIC itself can have pathological consequences that translate clinically into a worse prognosis for affected patients. This article will describe how pregnancy-associated DIC can be diagnosed promptly and how treatment should be managed strategically. It also discusses the latest developments in our understanding of haemostatic mechanisms within the placenta and how these may have relevance to new diagnostic approaches as well as novel therapeutic modalities.

Introduction

Disseminated intravascular coagulation (DIC) occurs when the finely controlled process of haemostasis becomes disrupted. As a result, coagulant responses can change from being naturally protective to the host into a maladaptive response with pathological consequences. Clinically, this is reflected in the increased morbidity and mortality that is associated with DIC. The recognition that DIC arises as a complication of different disease states reflects the variety of ways in which clinical events can uncouple normal haemostasis. In sepsis for example, the predominant force appears to be the unchecked cytokine response to infection leading into a cyclical cross-talk between the processes of inflammation and coagulation.[1,2] This is played out systemically due to the involvement of the vast endothelial surface in the haemostatic response. In pregnancy however, the rheostat for coagulation is already adjusted to a higher level in order that any excess risk of bleeding is diminished at the mother–baby interface and at parturition.[3] The inherent risk of such a physiological response is the increased susceptibility to dysregulation in the event of intercurrent obstetric pathology. In this article, we will review the evidence for this and how identification of DIC can improve the quality of clinical care for both mother and child. A key issue is recognising that the placenta is in a heightened state of coagulation activation. In addition, awareness that systemic manifestations of the coagulopathy may be reflecting an overspill from a more localised event can be helpful in targeting treatment. DIC can be life-threatening and evidence for its haematological management will be presented.

Causes of DIC in obstetrics

The causes of DIC in obstetrics are listed in Table 1. Some of these conditions would require re-consideration in the present diagnostic age. For example, the onset of amniotic fluid embolism is so abrupt that although DIC has been reported in up to 83% of cases, its diagnosis can be difficult under such situations.[4] A recent review from June 1976 to October 1999 concluded that amniotic fluid embolism can neither be predicted nor prevented and that there are no standardised investigations or protocols for confirmation.[5] However, if abnormal coagulation tests are noted in relation to symptoms and signs of acute hypotension or hypoxia within 30 min of delivery, the diagnosis of DIC may be considered as possibly secondary to amniotic fluid embolism.

Intrauterine foetal demise (IUD) has been classically described as frequently associated with DIC. However, the incidence of

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Table 1
Commonly described causes of DIC in obstetrics.

Amniotic fluid embolism
Intrauterine foetal demise
HELLP syndrome
Pre-eclampsia/eclampsia
Placental abruption and placenta praevia
Septic abortion and intrauterine infection
Postpartum haemorrhage
Acute fatty liver of pregnancy

undiagnosed IUD is likely to be rare in the well-resourced obstetric environment. This is because spontaneous delivery would usually ensue within the first two weeks whilst marked coagulation disturbances only tend to occur after a month of foetal demise.[6] If the foetus were retained longer, up to 25% of cases develop a coagulopathy that is mediated by release of thromboplastin-like material from dead products of conception.[7] These defects may correct spontaneously before evacuation although this can be a slow process.[6] Even when pregnancy is complicated by death of one foetus and survival of another, derangements in coagulation are rare.[8]

Pre-eclampsia is a significant contributor to maternal as well as neonatal mortality and morbidity.[9] Occurring in 3–5% of all pregnancies, it is considered to be a consequence of an abnormal maternal response to placentation. As such, its clinical severity depends on the extent to which abnormal placental sensing provokes inflammatory signals.[9] The abnormal placentation could be caused by a form of maternal–paternal immune maladaptation that is initiated at the time of semen deposition in the female genital tract. This provokes a cascade of cellular and molecular events resembling a classic inflammatory response.[10] Subsequent increase in syncytiotrophoblast shedding would further augment this inflammatory response.[11] Endothelial dysfunction secondary to an exaggerated maternal inflammatory response towards the trophoblast would result in decreased vasodilator prostaglandins, especially prostacyclin and nitric oxide.[12,13] This could potentiate platelet aggregation and utero-placental ischaemia to cause pre-eclampsia.[14]

Placental abruption results from a rupture in the maternal decidual artery to cause dissection of blood at the decidual–placental interface.[15] DIC in this situation was first described by De Lee in 1901 as a state of "temporary haemophilia".[16] The precise pathophysiology is unknown in many cases but impaired placentation, placental insufficiency and utero-placental hypoperfusion are considered as key mechanisms.[17] As these changes have also been observed in placentas of women with pre-eclampsia, the two conditions may share some common pathophysiological denominators.[15] As in pre-eclampsia, immunological defects and an increased production of pro-inflammatory cytokines have been implicated in premature placental detachment.[18,19] Abruptio placenta also demonstrates the important role played by thrombin, which has potent uterotonic properties in addition to its pivotal role in coagulation. Placentae from women with pre-term labour often demonstrate evidence of old placental bleeding to support the concept of thrombin production in potentiating placental abruption and spontaneous pre-term birth.[20] The consequent haemorrhage upon premature placental separation can also allow entry of placental tissue factor into the circulation to promote thrombin generation and coagulation.[15] The degree of placental separation has been shown to correlate with the extent of fibrin formation and thrombocytopenia, suggesting that coagulation is initiated from the placenta bed.[21]

Post-partum haemorrhage (PPH) is another cause of bleeding-associated DIC. The coagulopathy arises mainly from the excessive blood loss, consumption of clotting factors and the further effects of massive transfusion in the setting of acidosis and hypothermia.[22] This is discussed separately later. Septic abortion and intrauterine foetal infection also cause DIC with mechanisms similar to those in sepsis whereby inflammatory processes dysregulate coagulation. This is well-reviewed elsewhere.[2,23]

The syndrome with haemolysis, elevated liver enzymes and low platelets (HELLP) is characterised by prominent endothelial cell damage within the liver. It may be considered as a placenta-mediated and liver-targeted acute inflammatory condition whereby Fas-dependent apoptosis of hepatocytes has been observed.[24] Endothelial dysfunction, platelet and complement activation with release of inflammatory mediators are the different factors that predispose towards DIC in this condition[25] Another liver-specific but mechanistically distinct condition is acute fatty liver of pregnancy (AFLP). This is usually seen in the third trimester of pregnancy and is often fatal. A genetic deficiency of fatty acid beta oxidation has been described in its pathogenesis and the coagulopathy is mainly caused by severe hepatic dysfunction.[26] Notably, there is marked antithrombin deficiency in AFLP to further drive procoagulant changes and DIC.[27]

Pathophysiology of DIC in obstetric disorders

It is important to understand the normal coagulation process in order to characterise the abnormalities observed during DIC. The coagulant response begins with exposure of tissue factor (TF) and binding of factor VIIa to activate factor X for conversion of prothrombin to thrombin (Fig. 1).[28] Thrombin generation is further propagated through the intrinsic pathway and the explosive burst of thrombin results in cleavage of fibrinogen into fibrin.[29] Clot formation is homeostatically regulated to achieve the desired haemostatic effect and this involves a number of regulatory responses that are spatially and temporally differentiated. Normal endothelium at the margins of injury switches from thrombin procoagulant to anticoagulant activity via its binding to the endothelial receptor, thrombomodulin (TM).[30] The thrombin–TM complex activates protein C bound to the endothelial protein C receptor (EPCR).[31] The generated activated protein C (APC) degrades activated factor V and VIII with co-factor support from protein S to inhibit further clot formation.[32] Other important anticoagulants involved are antithrombin and tissue factor pathway inhibitor (TFPI). The former inactivates thrombin and factor Xa whilst TFPI forms a quaternary complex with tissue factor, factor VIIa and Xa to inhibit the cascading effect towards thrombin generation.[33] Normal clot formation is followed by its own regulated dissolution. This process of fibrinolysis involves thrombin-induced tissue plasminogen activator (t-PA) dependent generation of plasmin from plasminogen.[34] Regulation of fibrinolysis is mainly through plasminogen activator inhibitor (PAI)-1 and thrombin activatable fibrinolysis inhibitor (TAFI).[35] PAI-2 is also involved physiologically in pregnancy.

Whilst these protein–protein interactions are key to the formation and regulation of coagulation, the availability of an assembling surface critically affects the magnitude of the reaction. *In vitro*, the availability of negatively charged phospholipid surfaces can accelerate the prothrombinase reaction by 250,000-fold.[36] *In vivo*, the relevance of this is demonstrated by the observation that factor Xa infusions alone are not thrombogenic unless co-infused with negatively charged phospholipids.[37] Increasing the phospholipid content was shown to convert this haemostatic response into that of DIC.[38] Whilst phosphatidylserine (PS) behaves as a procoagulant phospholipid, phosphatidylethanolamine (PE) enhances APC activity to promote anticoagulation.[39]

Central to the development of DIC is the excessive generation of thrombin *in vivo*. Whilst thrombin generation is generally dependent on prothrombinase complex assembly on platelet surfaces,

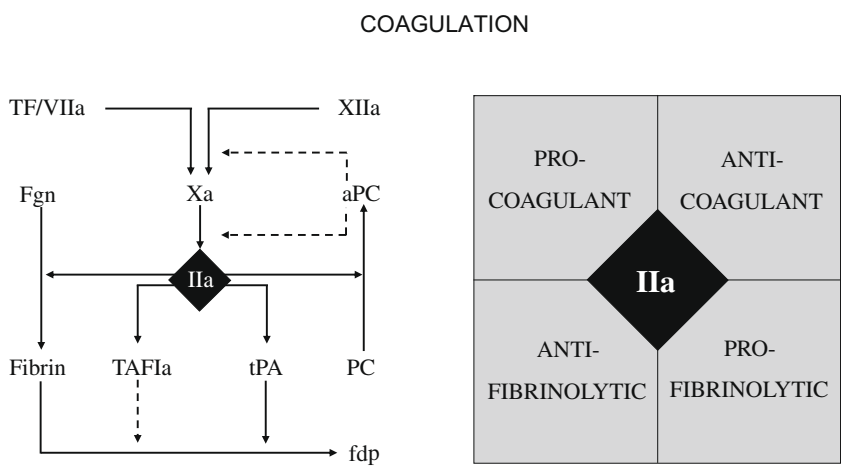


Fig. 1. Pivotal role of thrombin in the balance between coagulation and fibrinolysis. Normal clotting begins with the exposure of tissue factor (TF), which enables factor VIIa to activate factor X and lead to thrombin (IIa) generation. Thrombin is procoagulant in converting fibrinogen (Fgn) to fibrin but also controls anticoagulation through generation of activated protein C (aPC) to degrade activated factor V and VIII. Clot dissolution to generate fibrin-degradation products (fdp) occurs through thrombin-induced tissue plasminogen activator (tPA) and regulation of fibrinolysis involves activation of thrombin activatable fibrinolysis inhibitor (TAFI). Thrombin is therefore central to the balance between pro and anticoagulant functions as well as pro and antifibrinolytic activities. Dotted lines denote inhibition.

cell-free phospholipid can also support such reactions *in vivo*.[40,41] These form as a result apoptosis or damaged cell membranes to externalise the inner leaflet and expose PS. Microparticles which carry the externalised PS are generally procoagulant and their circulating levels increase in pregnancy.[42]

Of relevance too is the provision of phospholipid surfaces by lipoproteins such as oxidised low-density lipoprotein and very low-density lipoprotein (VLDL), the latter of which can increase several fold in DIC.[43,44] In addition, lipoprotein dysregulation can influence thrombin activity through the relative loss of high-density lipoprotein (HDL) with its anticoagulant-promoting properties.[45] Circulating lipoproteins have been shown to correlate with a higher incidence of pre-eclampsia.[46] Women with pre-eclampsia exhibited threefold increase in VLDL, with significantly lower HDL concentrations. This imbalance between the pro and anti-coagulant lipoproteins may contribute to endothelial dysfunction and the pathogenesis of pre-eclampsia.

Placenta as an activated coagulation system

The vascular bed of the placenta contains foetal trophoblast cells, which have an endothelial cell-like ability to regulate haemostasis. These cells have several distinct haemostatic properties that are important for homeostatic maintenance in normal pregnancy (Fig. 2). These include the (i) TF expression, (ii) altered anticoagulant function, (iii) suppression of fibrinolysis, and (iv) exposure of anionic phospholipids.

Tissue factor expression

Syncytiotrophoblast membranes from normal human placenta strongly express TF activity.[47] Aharon et al. identified high TF levels in syncytiotrophoblast cells compared to low levels in human umbilical vein endothelial cells (HUVEC).[48] In contrast, syncytiotrophoblast expressed lower TFPI levels than HUVEC. Of interest is that a correct balance between TF and TFPI in different organs is required to maintain haemostasis during embryonic development.[49] For example, TFPI-/- mice embryos can be rescued from lethality by reducing TF expression, while haemostasis can be restored in low TF expressing mice through abolishing TFPI expression.

Altered anticoagulant function

TM is expressed on placental trophoblasts as much as on the endothelial surface of blood vessels.[50] Boffa et al. identified that soluble TM levels at the 12th week of gestation are similar in both normal and abnormal pregnancies with a wide range thereafter to make a reference curve difficult to establish.[51] EPCR is also expressed on the syncytiotrophoblast to enable APC-dependent ligation of protease-activated receptor-1 to block the apoptosis of placental cells.[52] Growing evidence supports a role for EPCR in pregnancy maintenance, since EPCR knockout mice experience placental thrombosis and early embryonic mortality.[53] Furthermore, high levels of antibodies to EPCR are associated with a higher risk of a first episode of foetal death.[54] Anti-EPCR autoantibodies can activate the complement to cause pro-inflammatory trophoblast destruction and foetal loss. Systemically, PC activity appears to be unaffected by gestation while a progressive fall in total protein S has been reported with increasing gestation age.[55,56] APC resistance is increased during pregnancy with up to 45% of pregnant women having a ratio below the 95th percentile of the normal range for non-pregnant women of similar age.[55,57] Antithrombin levels however do not change during pregnancy.[58] But, altogether, systemic anticoagulation appears to be less active than in the non-pregnant state and suggests an overall procoagulant shift in normal pregnancy.[59]

Suppression of fibrinolysis

The placenta produces PAI-2 to augment increases in PAI-1.[58,59] In normal pregnancy, PAI-1 gradually increases to become markedly elevated in the third trimester.[60] This overwhelming increase compared to relatively unchanged t-PA levels contributes to a state of decreased clot lysis and a prothrombotic bias in the pregnant woman.[61] This "heightened protection" against clot lysis is further mediated through TAFI. TAFI is a carboxypeptidase B-like proenzyme, which is synthesised in the liver and activated by the thrombin–thrombomodulin complex.[62] Once activated, it down-regulates fibrinolysis and Chabiloz et al. have reported a significant increase of TAFI antigen levels during pregnancy, peaking in the last trimester.[63] Mousa et al. confirmed this and also demonstrated that unlike other coagulant-related factors in pregnancy, which would take up to 6 weeks to normalise post-partum, TAFI

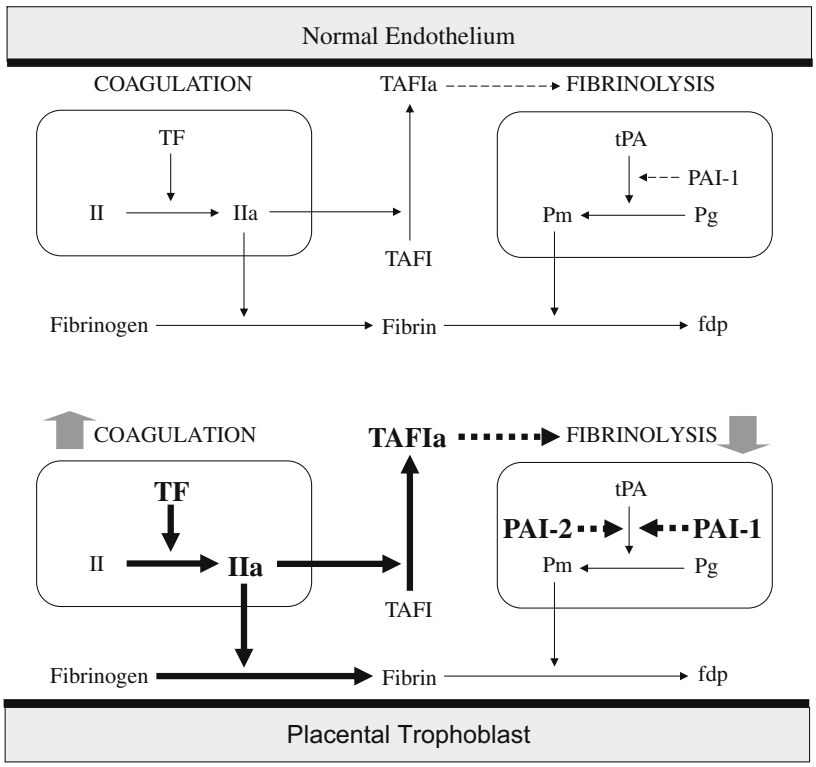


Fig. 2. Comparison between normal endothelium (top) and placental trophoblast (bottom). The placenta is in a heightened state of coagulation activation through increased tissue factor (TF) production. This increases prothrombin (II) to thrombin (IIa) conversion for cleavage of fibrinogen into fibrin. Increased amounts of activated thrombin activatable fibrinolysis inhibitor (TAFIa) is generated, which together with increased levels of plasminogen activator inhibitors (PAI) 1 and 2, reduce fibrinolytic activity that would normally occur through tissue plasminogen activator (tPA)-induced generation of plasmin (Pm) from plasminogen (Pg) in generating fibrin-degradation products (fdp). The bold arrows signify increased generation and the dotted arrows signify inhibition.

levels corrected abruptly within 24 h of parturition.[64] In DIC, the excessive thrombin generation could further increase TAFI levels to inhibit fibrinolysis.

Exposure of anionic phospholipids

Phospholipids have also been shown to be important in the growth of the placental surface by differentiation and intercellular fusion of the villous cytotrophoblast into the syncytiotrophoblast.[65] PS externalisation appears to be an essential component of this intertrophoblast fusion process.[66] Differentiation of the villous cytotrophoblast results in redistribution of membrane phospholipids with enrichment of PS on the syncytiotrophoblast surface.[66] The contribution of this PS rich trophoblast surface to the pathological states of obstetrical DIC is therefore plausible but remains to be fully investigated.

Diagnosis of DIC

Commonly available tests of haemostasis

The diagnosis of DIC is reliant on the interpretation of several haemostatic parameters rather than on an isolated test. The classically characterised findings of DIC are prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), low platelet counts, low fibrinogen and elevated products of fibrin breakdown, e.g. D-dimer. However, all these tests have limitations in the pregnancy because the concentrations of almost all coagulation factors with the exception of factor XI rise significantly.[67] This results in marked shortening of the PT and aPTT. Any consumption of coagulation factors would prolong these measurements but the overall clot time might still be within normal non-pregnant ranges. It is therefore important to assess serial changes in the PT and aPTT to be aware of the ongoing DIC process. Likewise, the physiological thrombocytopenia of pregnancy needs to be considered before interpreting the platelet count in DIC.[68] A serial drop is more significant than a single measurement in indicating the likelihood of increasing thrombin generation.[69]

Measurement of fibrinogen, an acute-phase reactant, can also be problematic. In an analysis of 535 patients with overt DIC (unrelated to pregnancy), only 46 patients (8.6%) showed low plasma fibrinogen levels (less than 1 g/L) and this suggests that it is not sensitive for DIC.[70] This is likely to be more of a problem in pregnancy when fibrinogen levels can double from non-pregnant states. This would confound the interpretation of "normal fibrinogen levels" in a patient suspected of having DIC.[71] However, fibrinogen can be used a predictor of PPH severity as demonstrated by Charbit et al. The PPH study group from France analysed data from 128 women, of whom 50 had severe PPH.[72] Serial coagulation tests were performed at enrolment and up to 24 h thereafter. Multivariate analysis showed fibrinogen as the only marker associated with the occurrence of severe PPH. The negative predictive value of a fibrinogen concentration greater than 4 g/L was 79% and the positive predictive value of a concentration less than or equal to 2 g/L was 100%.

D-Dimer levels are considered useful in DIC as a marker of increased cross-linked fibrin formation. However, they are inherently high in normal pregnancy and an increased level cannot always be due to DIC.[50] For practical purposes, a single high D-dimer value is not meaningful but a continued increase may help in a clinical situation where DIC can be a complication. However, it should be noted that the accuracy of high D-dimer levels is not well standardised at the present time.[73]

Hence, results within the normal range for tests that are routinely used for diagnosing DIC in a non-obstetric setting cannot be immediately extrapolated to pregnancy-associated DIC. Serial

Table 2
International society on thrombosis and haemostasis diagnostic scoring system for overt DIC.

1. Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?
If yes: proceed
If no: do not use this algorithm
2. Order global coagulation tests (prothrombin time, platelet count, fibrinogen, fibrin related marker)
3. Score the test results
Platelet count (>100 = 0, <100 = 1, <50 = 2)
Elevated fibrin marker (e.g. D-dimer, fibrin-degradation products) (no increase = 0, moderate increase = 2, strong increase = 3)
Prolonged prothrombin time (<3 s = 0, >3 but <6 s = 1, >6 s = 2)
Fibrinogen level (>1 g/L = 0, <1 g/L = 1)
4. Calculate score:
⩾5 compatible with overt DIC: repeat score daily
<5 suggestive for non-overt DIC: repeat next 1–2 days

coagulation tests are more helpful than single time points of assessment. A scoring system that uses simple and widely available laboratory tests has been established by the Scientific and Standardization subcommittee on DIC of the International Society on Thrombosis and Haemostasis (ISTH) (Table 2) whereby a score of 5 or more was considered as compatible with DIC.[74] Subsequent prospective validation studies showed a high accuracy of this scoring system for the diagnosis of DIC.[75]

Specialized tests

Excessive thrombin generation in DIC can be measured using molecular markers of its activation and function, which include prothrombin activation fragment 1 + 2, thrombin–antithrombin (TAT) complexes and fibrinopeptide-A.[76] These also increase in normal pregnancy to make estimations difficult in aiding the diagnosis of DIC.[77] However, patients with pre-eclampsia have higher median TAT concentrations than normal pregnant women.[78] In reality, such tests are presently impractical and expensive in the acute diagnostic setting.

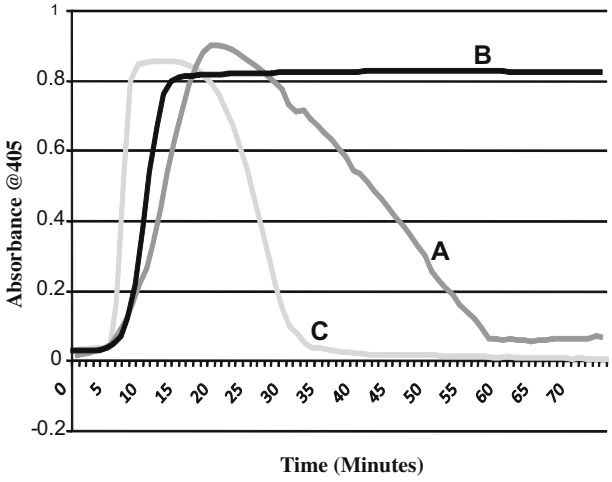
Plasma levels of antithrombin or PC have been shown to be useful in DIC and potentially predictive of outcome in patients with sepsis and DIC. Although both are unaffected by gestation, antithrombin is decreased in pre-eclampsia and AFLP independent of DIC development. This is probably due to consumption in the former and decreased synthesis in the latter.[79] From a laboratory perspective, the availability of chromogenic assay systems for both PC and antithrombin allow greater practicality for diagnostic application.

Soluble TM levels also increase in DIC. Whilst variability in these levels beyond 12 weeks in normal pregnancies precludes a referenceable standard range, a sudden increase from baseline in a given individual can be predictive of underlying placental vascular pathology.[51] Magriples et al. found that in a prospective cohort study of 25 pregnancies, soluble TM was significantly elevated in those who had placental abruption confirmed after delivery.[80] The sensitivity and specificity of soluble TM level of greater than or equal to 60 ng/ml was 87.5% and 76.5%, respectively. Mutations in the TM genes have also been associated with increased late foetal loss although this maybe a modifier effect in combination with other variants.[81,82]

With regard to molecular markers of fibrinolysis, patients with significantly elevated PAI-1 levels in early pregnancy have been noted to develop pre-eclampsia later.[78] Estelles et al. suggested that this may be induced by increased placental tumour necrosis factor-alpha, which will also induce TF to promote pro-thrombotic events.[83] This would suggest an inflammatory component in pre-eclampsia, as in sepsis, with pathological coagulation activation. An increase in the PAI-1/PAI-2 ratio in maternal plasma has also been demonstrated as a biochemical marker of pre-eclampsia.[84] Clinical studies have also highlighted the relevance of TAFI levels in pre-eclampsia.[64] TAFI can contribute to impaired clot lysis and increasing APC resistance in the coagulation-related problems of pregnancy.[85]

More global tests of the fibrinolytic contribution to overall haemostasis have also been described. He et al. devised a simple laboratory method that can screen the overall haemostatic potential in plasma to assess the state of coagulability.[86] A fibrin time curve was generated with the addition of thrombin and t-PA to plasma and analysed spectrophotometrically to record both fibrin generation and its consequent lysis. The area under the curve correlated with the concentrations of different factors involved in global haemostasis. In a case-control study, which included 33 women who had a normal vaginal delivery and 20 women who had PPH (blood loss > 1 l) placental TF (1:40,000), thrombin (0.09 iu/ml) and t-PA (660 ng/ml) were added to citrated blood collected 0–6 h after placental delivery and re-calcified. In PPH patients, two distinct profiles were observed in addition to normal fibrinolysis (Fig. 3). Whilst one group demonstrated enhanced clot lysis, no clot lysis was observed in the other group. TAFI levels were low in the former group and PAI-1 levels were increased in the latter. Though further studies are warranted, this simple method may be used to determine the role of pro-haemostatic agents, such as recombinant factor VIIa in the former group with enhanced fibrinolysis.

Another area of testing that can convey quantitative as well as functional data is in microparticle analysis. Although the total numbers of circulating microparticles are not significantly altered from normal pregnancy, the numbers of T-cell and granulocyte-derived microparticles are increased in patients with pre-eclampsia.[87] In addition, trophoblast-derived microparticles and exosomes have been shown to contribute to the systemic inflammatory responses of pre-eclampsia.[88] Circulating microparticles therefore provide more than just diagnostic relevance and present an opportunity to examine function as well as phenotype of originating endothelial cells, which are otherwise inaccessible for investigative understanding.



A) Normal Vaginal Delivery: 33/33 (100%), PPH : 8/20 (40%)

B) Hypofibrinolytic PPH: 6/20 (30%)

C) Hyperfibrinolytic PPH: 6/20 (30%)

Fig. 3. Overall haemostatic potential in post-partum haemorrhage (PPH). Patients with PPH show three different clot lysis profiles – [A] normal pattern (8/20 patients) similar to women with uncomplicated vaginal delivery (33/33 women), [B] no evidence of clot lysis, suggesting hypofibrinolysis (6/20 patients), and [C] a group demonstrating hyperfibrinolysis (6/20 patients).

While the above studies highlight that changes in the coagulant and fibrinolytic pathways occur in pregnancy-associated DIC, they do not clarify whether this represents a systemic process or a more localised pathology of the utero-placental bed that could have overspilled into the circulation. Higgins et al. determined haemostatic changes in both the utero-placental and peripheral circulations in normotensive and pre-eclamptic pregnancies.[89] One study-group included peripheral blood samples from normal pregnancies and those complicated by pre-eclampsia. The second group consisted of patients who underwent Caesarean section for both normal and pre-eclamptic pregnancies with additional blood samples obtained from the uterine vein. The end-products of coagulation (soluble fibrin and TAT) and end-products of fibrinolysis [plasmin–anti plasmin and fibrin-degradation products (FDP)] were measured in both groups. The findings of increased levels of activated coagulation markers in the uterine vein as compared to the peripheral circulation suggested that the systemic findings originated form placental site-specific changes.

Management

In pregnancy-associated DIC, the primary approach is to address the obstetric abnormality. Once this is corrected, the DIC will usually subside. Nonetheless, additional supportive treatments that are specifically aimed at the coagulation abnormalities may be required in some cases. The following section is focussed on this aspect of the management.

Replacement of blood products

Blood product therapy should be instituted on the basis of the clinical condition in combination with laboratory results (Table 3). However, most of the recommendations in terms of management are based on clinicians' experience and case studies. In general, platelets are administered to patients with a count of less than 50×10^9/l, who are actively bleeding. A much lower threshold ($<30 \times 10^9$/l) may be used if there is no active bleeding. There is no justification for administering coagulation factors or plasma if there is no associated haemorrhage. However, in the presence of active bleeding and prolonged PT and aPTT, administration of fresh frozen plasma (FFP) (10–20 ml/kg) can be useful. Further doses may be necessary and this should be guided by the clinical condition of the patient in conjunction with repeated laboratory results. If FFP transfusion is not possible due to fluid overload, prothrombin complex concentrate (PCC) (25–30 U/kg)) may be tried. These concentrates will only partially correct the defect because they only contain vitamin-K-dependent coagulation factors, whereas the deficiency in DIC is much more global. It should also be borne in mind that it is the non-activated PCC that should be used rather than activated PCCs as these can potentiate DIC.[90,91]

Specific coagulation defects, such as an isolated low level of fibrinogen, also need correction. A fibrinogen level of 1 g/L is considered to be haemostatically adequate although a higher threshold for replacement would be advisable in patients with DIC as fibrinogen can be consumed rapidly. Fibrinogen is usually given as cryoprecipitate. Due to the potential for viral contamination, pasteurised fibrinogen concentrates are increasingly used. Its efficacy and safety has been shown in both congenital and acquired deficiencies of fibrinogen.[92,93] A recent analysis of 30 adult patients who received fibrinogen concentrate for acquired hypofibrinogenaemia (fibrinogen <1.5 g/L) showed that 46% stopped bleeding without the need for surgery or radiological interventions. There were no adverse effects, including thromboembolic events and the cost of using the concentrate was comparable to using cryoprecipitate.[94] The usually administered dose of 4 g fibrinogen concentrate raises plasma levels by around 1 g/L.

Anticoagulants

Heparin has been used in the treatment of DIC in the setting of IUD on the basis of an activated coagulation process. Though the effectiveness of this therapy has not been negated, neither are there studies to substantiate its benefit. There are reports of improvements in laboratory abnormalities through heparin use[95,96] but whether this translates into clinical benefit is unclear. It cannot be recommended in patients who are bleeding or at high risk of doing so.

As regards to anticoagulant factor concentrates, antithrombin has been used as monotherapy in a single report of patients with obstetrical DIC and antithrombin levels of less than 70%. In a randomized controlled trial, antithrombin concentrates or placebo was given to severely pre-eclamptic patients (1500 U/day for seven days) along with a continuous infusion of unfractionated heparin.[97] Improvement was significantly greater in the antithrombin-treated group in terms of biophysical score profile and coagulation parameters and there were no associated adverse events. Further trials appear warranted to confirm these findings.

APC, a physiological inactivator of factor Va and VIIIa, has been shown to be effective in patients with sepsis-induced DIC. In a large multicentre trial, recombinant human APC at a dose of 24 μg/kg/h was administered intravenously for 96 h. Compared to placebo, this treatment achieved a 19.4% relative-risk reduction

Table 3
Guide to blood product replacement in massive obstetric haemorrhage.

1. Control bleeding using surgical and/or radiological interventions
2. Aim to try and restore circulating blood volume using fluids and blood products
3. Control exacerbating factors for abnormal coagulation especially, hypothermia and acidosis
4. Blood product support as follows
Red cells
Use O negative red cells first
If no record of red cell antibodies, ABO and Rh compatible, cross matched blood should be available within 30 min (maximum of 45 min)
Replace red cells as required to maintain circulating blood volume
Use blood warmer to avoid hypothermia
Fresh frozen plasma
Transfuse one unit of plasma to every one unit of red cell
Aim for PT & APTT less than 1.5 times normal (normal for PT ~15 s and APTT ~ 35 s)
Platelet transfusion
One to two adult doses after 1.5–2 blood volume replacement (equivalent to 8–10 bags of red cells)
Aim for a platelet count over 50×10^9/l
Fibrinogen
Cryoprecipitate (dose = two donation pools)
Fibrinogen concentrates (4 g)
Aim for fibrinogen level over 1 g/L

and a 6.1% absolute risk-reduction. The incidence of serious bleeding was however higher with APC treatment.[98] Kobayashi et al. used plasma derived APC (5000–10,000 units for 2 days) in 16 patients with moderate to severe placental abruption and achieved significant improvement in fibrinogen levels, FDP and PT.[99] The authors did not comment on bleeding or any adverse events. Once again, large trials are required before specific recommendations for its use in certain sub-groups of obstetric DIC.

Management of massive haemorrhage

Obstetric haemorrhage is the most common cause of maternal mortality. Amongst survivors, morbidity due to haemorrhage has more long-term sequelae than most other obstetric complications.[100] Aggressive resuscitation is the key to a positive outcome. Massive amounts of blood loss is most common in PPH where surgical control can be difficult and where occasionally, drastic measures such as hysterectomy need to be performed. The usual management of PPH includes medical, mechanical and surgical methods with blood product support in large quantities.[101] It is therefore useful to have a hospital policy for massive transfusion with regular drills for relevant personnel to be constantly prepared.

Recommendations for blood product replacement in obstetric haemorrhage can be drawn from studies in clinical situations associated with extensive trauma[102] (Table 3). The aim of resuscitation is to establish normotensive, normothermic patients with adequate coagulation factors. The initial step requires the insertion of two large-bore intravenous cannulae to administer fluids quickly to prevent shock. The choice of crystalloids or colloids is still debated but there are concerns that colloids can affect coagulation.[103] Rapid administration of volume expanders can cause dilution of the coagulation factors and it is therefore important to replace these with blood as quickly as possible. Universal 'O' Rh negative and Kell negative blood should be made available as soon as possible from the blood bank.[102] If no antibodies are detected, group-specific blood should be made available in a maximum time of 45 min.

Further resuscitation needs to include plasma and platelet support as Hirshberg et al. found that resuscitation with more than five units of red blood cells inevitably caused a dilutional coagulopathy.[104] As such, a 1:1 ratio of red blood cells to FFP should be used and this has been associated with improved survival.[105,106] Prophylactic platelet therapy is also required, which can reduce the need for other blood products.[107] It is now considered safe practice to transfuse at least one or two adult doses of platelets with every 8–10 units of administered blood and plasma.

Fibrinogen deficiency is dealt with by infusion of cryoprecipitate or fibrinogen concentrates. Cryoprecipitate should be transfused as two pools when the fibrinogen drops below 1.5 g/L. A retrospective study using fibrinogen concentrate (Haemocomplettan) was associated with a significant reduction in transfusion requirement for red cells, FFP and platelet concentrates as well as a significant reduction in blood loss and improvement in coagulation parameters.[108] This study included mainly obstetric cases (12/43) and supports the use of these concentrates in abruption placentae and placenta praevia.

Regular blood tests that include full blood count and coagulation parameters should dictate continuation or cessation of blood product support, in addition to clinical evidence of haemostatic control. The role of a "person in charge" to coordinate all the resuscitation measures, testing and record the blood products transfused (legally required according to new European directive on traceability of blood products) has been emphasised.[102] Equally, awareness of the deleterious effects of acidosis and hypothermia from transfusion of cold blood components is important because acidosis interferes with coagulation factor complex assembly whilst hypothermia can reduce enzymatic activity and impair platelet activation.[109]

The role of activated factor VII

There has been increasing experience in the use of recombinant factor VIIa (rFVIIa) in cases of intractable bleeding, including massive obstetric haemorrhage. At supra-physiological concentrations, rFVIIa can directly activate factor X on the surface of locally activated platelets.[110] In situations of massive obstetric haemorrhage, a response rate of approximately 90% has been shown in several reports. In one of the larger studies, the Northern European FVIIa in Obstetric Haemorrhage Registry recorded 83% improvement followed rFVIIa administration.[111–113] The effectiveness of rVIIa in these reports has been measured with various endpoints that include reduced red cell transfusions, avoidance of uterine artery embolisation and the need for hysterectomy. Despite the often-dramatic response, the use of rFVIIa has several unresolved issues. First of all, its dose in massive obstetric haemorrhage is not yet optimised as different groups have used doses ranging from 15 to 120 μg/kg. Secondly, patients with a platelet count over 100×10^9/L and those with less severe coagulopathy are more likely to respond to rFVIIa and this supports the need for early blood product resuscitation in optimising outcomes.[114] Acidosis and low fibrinogen can also retard the optimal function of rFVIIa.[109] As a pro-haemostatic agent, rFVIIa has been associated with thromboembolic complications and this can be a particular problem in the hypercoagulable state of pregnancy. However, only one thromboembolic complication has been reported in a recent review of 48 treated cases.[113] Another consideration about rFVIIa is its high cost although the cost of blood products, surgical measures and prolonged hospitalisation including intensive care stay need to be considered in balance. rFVIIa remains a reasonable and effective management option in massive obstetric haemorrhage but further studies are required to determine the correct dose, frequency and the most appropriate timing or stage of resuscitation for its use. A recent review of the usage of rFVIIa in PPH went through the available evidence and data from two registries to conclude that there is a lack of high quality evidence and highlighted the need for randomised controlled trials.[115]

Summary

The heightened state of coagulation in the placental bed increases the vulnerability of the pregnant female to thrombotic disorders. In abnormal pregnancies, this prothrombotic state can be further accentuated by mechanisms that include pro-inflammatory forces and the release of procoagulant material. The spill over of localised coagulation activation from the placenta into the systemic circulation can disseminate thrombin generation and precipitate organ damage. Key to management is in early recognition to facilitate timely intervention. Diagnosis of DIC associated with obstetrical disorders is possible through a scoring system as proposed by the ISTH and serial testing is recommended to increase diagnostic precision. Treatment often includes supportive blood product replacement therapy in addition to removal of the placenta. However, there is a need for new therapeutic agents in this setting and advances in diagnostic and biomarker profiling might facilitate more effective approaches. With regard to massive obstetric haemorrhage, a well-prepared approach is crucial and collaborative trials to include pro-haemostatic agents could translate into improved prognosis and outcome.

Practice points

The placenta represents a vascular bed where the coagulation system is in an activated state to prevent catastrophic bleeding during delivery.

Disseminated intravascular coagulation (DIC) in obstetrical disorders can arise from the spill over of heightened placental coagulation activation into the systemic circulation.

The diagnosis of DIC should be made if at all possible using serial blood tests as recommended by the International Society on Thrombosis and Haemostasis DIC diagnostic criteria.

The management of DIC related to obstetrical pathologies involves delivery of the placenta, wherever feasible, and adequate, tailored blood product support.

Recent availability of the pro-haemostatic agent, recombinant human activated factor VII may be considered in post-partum haemorrhage.

Research agenda

The role played by inflammation and exposure to anionic phospholipid surfaces to promote coagulation in obstetrical disorders needs to be explored.

Understanding and improved profiling of perturbations in the coagulant–fibrinolytic axis to improve pathogenic understanding and targeted therapeutic intervention.

Prospective studies to determine the efficacy of the International Society on Thrombosis and Haemostasis DIC scoring system in the different obstetrical disorders.

Randomised controlled trials are required in the massive haemorrhage of obstetrics to determine the rate, volume and type of blood product replacement.

The appropriate time and use of recombinant human activated factor VII needs clarification through multinational randomised controlled trials.

Conflict of interest statement

None

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