Haemostasis in normal pregnancy: a balancing act?

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Abstract

Pregnancy is a risk factor for venous thrombosis and the incidence of venous thromboembolism during normal pregnancy is 6-fold higher during pregnancy than in the general female population of child-bearing age. This incidence is, however, remarkably low given the increases in markers of haemostatic activation observed during normal pregnancy. During normal healthy pregnancy there are substantial changes in the haemostatic system, many of which are procoagulant and supposed to be in preparation for the haemostatic challenge of delivery. Normal haemostasis requires a balance between coagulation and fibrinolysis to maintain the integrity of the vasculature, and complex physiological changes are evident during pregnancy which appear to ensure a constant coagulation/fibrinolysis balance. This balance is maintained, at least partly, by an increase in fibrinolytic activity, but decreases in other factors such as factor XI and monocyte tissue factor expression may also serve to counterbalance procoagulant changes.

Introduction

Normal pregnancy is often referred to as a hypercoaguable state, with reported changes in the haemostatic system considered to be in preparation for the haemostatic challenge of delivery. Indeed, levels of markers of haemostatic activation such as F1 + 2 (prothrombin fragment 1 + 2), TAT (thrombin–antithrombin complex) and D-dimer similar to or higher than those found in patients following a thromboembolic event, have been observed in normal pregnancy [1]. The reported incidence of pregnancy associated VTE (venous thromboembolism) is estimated at approx. 1 per 1000 deliveries, 5.5–6 times higher than in the general female population of child-bearing age [2]. This incidence is, however, remarkably low given the increases in markers of haemostatic activation observed during normal pregnancy. It appears that the mechanism involved in maintaining this relatively low incidence of pregnancy associated VTE is not fully understood. This paper reviews venous thromboembolic disease in pregnancy and the haemostatic changes which occur during normal pregnancy, and proposes that in normal healthy pregnancy these changes represent a balancing act.

Venous thromboembolic disease in pregnancy

Pregnancy and the peripuerium are risk factors for venous thrombosis [3] and, although maternal death is rare, PE (pulmonary embolism) remains the leading cause of maternal death in the U.K. [4]. The incidence of venous thrombosis in pregnancy and the puerperium is between 0.62 and 1.88 per 1000 deliveries [2,5–7], with the incidence of DVT (deep vein thrombosis) and PE estimated at 0.71 and 0.15 per 1000 deliveries respectively [2]. The majority of DVT events occur antenatally and, although almost half of antenatal DVT in one study were detected before 15 weeks gestation, the puerperium should be regarded as the period of greatest thrombogenic potential in terms of women years at risk [2,6]. 

Virchow’s triad postulates the principal factors underlying venous thrombosis: venous stasis, vascular damage and hypercoagulability, all of which occur during pregnancy [8]. Venous stasis of the lower limbs occurs by the end of the first trimester [9], and the potential for vessel damage is present during delivery, whereas a hypercoaguable state is evident throughout pregnancy. Several clinical risk factors are associated with pregnancy-associated VTE, including advanced maternal age, weight, high parity, multiple birth, major current illness, pre-eclampsia and operative delivery [5,10]. There is also emerging evidence of a genetic predisposition to VTE, with personal or family history of thromboembolic disease recognized as risk factors for VTE; 30% of patients with confirmed VTE associated with pregnancy are reported to have a heritable thrombophilia [2]. Causes of inherited or congenital thrombophilia, include deficiencies of antithrombin, protein C and protein S, and the presence of factor V Leiden, prothrombin 20210, and homozygosity for the thermolabile variant of methylenetetrahydrofolate reductase [10]. Venous thrombosis is a disease of complex aetiology, with interaction between genetic and acquired risk factors [3]. The general strategy to reducing the incidence of pregnancy-associated VTE involves identification of women with multiple clinical
Figure 1 | Tissue factor pathway coagulation cascade (inhibited complexes are represented in boxes)
Modified from [47]. ©1999 Reproduced by permission of Edward Arnold.

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risks; however, 28% of pregnancy-associated VTE are not associated with either an established clinical risk factor for thrombosis or a thrombophilic defect [2,10]. Thus it is possible that other currently unknown factors may contribute to the increased risk of VTE in pregnancy, highlighting the need for further research into changes in haemostasis during pregnancy.

Haemostasis in normal pregnancy
Haemostasis involves a complex network of interactions with positive and negative feedback loops, integrating blood vessels, platelets, coagulation factors, coagulation inhibitors and fibrinolysis, and has evolved to maintain the integrity of the vasculature. The classical ‘cascade’ hypothesis formulated to explain coagulation has been replaced by the current revised scheme of blood coagulation, known as the TF (tissue factor) pathway (Figure 1). Normal pregnancy is associated with substantial changes in the TF pathway and in the wider haemostatic system. Traditionally, it is proposed that these changes are in preparation for the haemostatic challenge of delivery, with the haemostatic system returning to that of the non-pregnant state at approx. 4 weeks post-delivery [11]. In the current paper, alterations in coagulation factors, coagulation inhibitors, fibrinolysis and markers of haemostasis will be discussed in turn.

Coagulation factor changes
During normal healthy pregnancy there are physiological changes which result in increases in the majority of coagulation factors. Coagulation factor changes that occur during pregnancy are summarized in Table 1. Factor XIII, fibrin-stabilizing factor, increases in the early stages of pregnancy, returning to non-pregnant values in the third trimester [12]. Levels of factor XII, X and IX increase progressively during pregnancy [13–16]. In contrast, levels of factor XI decrease during pregnancy [13], and it has previously been suggested that this may be a consequence of increased factor XI consumption [17]. However, factor XI activation is a key step in driving thrombin generation, and it is also possible that, in normal pregnancy, levels of factor XI are physiologically lowered to counterbalance the increases in other coagulation factors.

Factor VIII levels and coagulation activity (VIIIc) increase progressively during pregnancy [13,15–19]. Levels of vWF (von Willebrand factor), which serves as a carrier for factor VIII and plays a role in platelet adhesion, also increase progressively in pregnancy [18,20]. Factor VII also increases gradually during normal pregnancy [14–17]. Increases in factor V concentration in early pregnancy are followed by a decrease and stabilization [15], whereas factor V coagulation activity (Vc) shows a gradual rise throughout gestation [18]. Studies of prothrombin (factor II) levels in pregnancy have yielded inconclusive results, reporting both an early increase in pregnancy followed by a progressive decrease back to non-pregnant levels over the course of pregnancy [15] or no change [18]. Fibrinogen levels show a steady increase during pregnancy [13,15,16,19,21,22].

The blood coagulation cascade outlined in Figure 1 is initiated by TF, which forms a proteolytically active complex with factor VII. TF is a transmembrane glycoprotein constitutively
Coagulation system changes in normal pregnancy

<table>
<thead>
<tr>
<th>Coagulation factor</th>
<th>System change</th>
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</tr>
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<tbody>
<tr>
<td>Factor XIII</td>
<td>Increases in early pregnancy, returns to non-pregnant values by third trimester</td>
<td>[12]</td>
</tr>
<tr>
<td>Factors XII, X, IX, VIII, VII, Vc</td>
<td>Increase throughout pregnancy</td>
<td>[13–19]</td>
</tr>
<tr>
<td>Factor V</td>
<td>Increases in early pregnancy, followed by a decrease and stabilization</td>
<td>[15]</td>
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<tr>
<td>Factor XI</td>
<td>Decrease throughout pregnancy</td>
<td>[13]</td>
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<tr>
<td>vWF, fibrinogen</td>
<td>Increase throughout pregnancy</td>
<td>[13,15,16,18–22]</td>
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<tr>
<td>Factor II (prothrombin)</td>
<td>Increases in early pregnancy, returns to non-pregnant values by third trimester/no change</td>
<td>[15,18]</td>
</tr>
<tr>
<td>Soluble TF</td>
<td>No change</td>
<td>[28]</td>
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<tr>
<td>Monocyte TF</td>
<td>Decreases throughout pregnancy, returns to non-pregnant values by 3 days post-partum</td>
<td>[29,30]</td>
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Table 1 | Coagulation system changes in normal pregnancy

Inhibitors of blood coagulation

Coagulation inhibitors are necessary to ensure that thrombin generation remains limited and localized. Antithrombin III, heparin, heparin cofactor II, α1-antitrypsin and TF pathway inhibitor are inhibitors of the serine proteases of the coagulation cascade such as thrombin, Xa and TF:VIIa. Alterations in the coagulation factors during pregnancy are accompanied by concomitant changes in coagulation inhibitors.

Levels of antithrombin III remain stable during pregnancy [13,15,21,31], whereas heparin cofactor II and α1-antitrypsin levels are increased during normal pregnancy [15,32]. Little is known about the effect of pregnancy on levels of TF pathway inhibitor, but lower levels during labour have been reported when compared with non-pregnant controls [33].

Protein C, TM (thrombomodulin), protein S, C4b binding protein and APC (activated protein C) inhibitor are all components of the protein C system. Activation of this system occurs when TM binds to thrombin, and rapidly degrades factors VIIIa and Va on the phospholipid surface of activated platelets. This reaction increases 10–20-fold when protein C combines with its cofactor protein S. Levels of TM increase throughout pregnancy, whereas levels of total and free protein S gradually decrease [18–22,34]. Levels of protein C remain constant during normal pregnancy [18,19,21,22], yet acquired APC resistance is reported in up to 50% of normal pregnancies [18,19,35]. This increase in APC resistance corresponds with increases in factor VIII and decreases in protein S and APC inhibitor [18,36]. Overall, pregnancy appears to be associated with a decrease in coagulation inhibitors, although there is also evidence of bi-directional changes in levels or activity of coagulation inhibitors, and it is probable that these complex changes occur to help maintain the coagulation/fibrinolysis balance during normal pregnancy.

Markers of coagulation activation

The hypercoaguable condition is difficult to detect with routine laboratory assays and requires the use of sensitive markers of coagulation activation. Prothrombin fragments 1 + 2 are cleaved from prothrombin after its activation by factor Xa, whereas TAT is formed during inactivation by its main inhibitor antithrombin and, as such, F1 + 2 and TAT are sensitive markers of coagulation activation.

During normal pregnancy, levels of TAT and F1 + 2 increase progressively, indicative of a substantial increase in coagulation activation [1,14,17–19]. Similarly, FPA (fibrinopeptide A), another marker of coagulation activation, is increased during pregnancy [17,28,31].

Fibrinolysis

Fibrinolysis controls fibrin deposition, thus maintaining a controlled procoagulant response. tPA (tissue plasminogen activator) converts plasminogen into plasmin, which cleaves fibrin and fibrinogen, yielding fibrin degradation products. α2-antiplasmin, a plasmin inhibitor, and PAI-1 and PAI-2 (plasminogen activator inhibitor type 1 and type 2), prevent excess fibrin degradation by plasmin. Endothelial derived PAI-1 increases during the later stages of pregnancy, whereas placenta derived PAI-2, detectable in the plasma during the first trimester, increases substantially throughout pregnancy [19,22,36]. Although levels of tPA antigen increase over the course of pregnancy [16,22,36,37], tPA activity in early pregnancy is close to the standard range seen in non-pregnant women, and there is a gradual decrease over the course of pregnancy [19,37]. This decrease in tPA activity is consistent with the increases observed in tPA inhibitors PAI-1 and PAI-2.
Taken together, the changes outlined above suggest that during normal pregnancy the fibrinolytic system is impaired. However, plasminogen levels are also increased during pregnancy, whereas levels of the plasmin inhibitor α2-antiplasmin are decreased [13,17]. These changes, together with increases in D-dimers and fibrin degradation products, which are products of fibrin breakdown by plasmin and, thus, markers of fibrinolysis [1,14,19,28,31,36], are indicative of a substantial increase in fibrinolytic system activation, possibly to counterbalance the increases in coagulation factors observed in normal pregnancy and thus leading to the relatively low incidence of VTE in normal pregnancy [17].

A balancing act?
A balance between coagulation and fibrinolysis is essential for normal haemostasis, and a shift in this haemostatic balance can result in either an increased risk of thromboembolism due to hypercoagulability or a bleeding tendency. Yet, despite the marked changes in haemostasis associated with normal pregnancy, the incidence of VTE remains relatively low. In one study, levels of coagulation and fibrinolytic indices in healthy third trimester pregnant women were similar to or higher than those found in patients following a DVT or PE, yet none of the women in this study developed clinical symptoms of VTE, leading the authors to conclude that the substantial increase in coagulation and fibrinolytic system activation indices during pregnancy has to be regarded as a physiological rather than a pathological process [1]. In this same study, the endogenous thrombin potential, an indicator of the plasma’s potency to generate thrombin in response to a thrombogenic stimulus, remained unchanged throughout pregnancy [1]. Moreover, the FPA/D-dimer ratio also remains constant throughout pregnancy, suggesting a constant coagulation/fibrinolysis balance [28]. In contrast, a high FPA/D-dimer ratio, suggestive of hypofibrinolysis, was observed in women with pre-eclampsia [38], thus highlighting the importance of coagulation/fibrinolysis balance during normal pregnancy and lending further support to the concept that haemostasis in normal pregnancy may indeed be a balancing act.

The haemostatic changes that occur during pregnancy are complex and little is known about the mechanisms involved in bringing about these changes. It is highly probable that hormonal changes play a significant role, given that the oral contraceptive pill and hormone replacement therapy are associated with increased risk of VTE [39]. One change that occurs is a reduction in monocyte TF activity and expression during normal pregnancy, possibly as a result of increased risk of VTE. Although the mechanisms involved in lowering monocyte TF expression during pregnancy are unclear, the physiological changes that occur during normal pregnancy may play a role in maintaining normal healthy pregnancy [40] and may play a role in inhibiting TF expression. Lower levels of IL-10 are associated with pathologic pregnancy, such as spontaneous abortion and pre-eclampsia [41,42], and given that such pregnancy complications are associated with thrombosis, it would be interesting to investigate if a failure to increase IL-10 is associated with VTE in pregnancy.

Homocysteine induces monocyte TF expression at physiological concentrations in vitro [26]. Plasma homocysteine concentrations are lower in normal pregnancy when compared with the non-pregnant state [43,44], with concentrations lowest in the second trimester before returning to non-pregnant levels at 3 days post partum [45], a pattern which mirrors that of monocyte TF expression in pregnancy [30]. It is possible, therefore, that reduced levels of plasma homocysteine during normal pregnancy play a role in down-regulating TF expression, and thus, in maintaining haemostasis in haemostasis. The reason for lower homocysteine in pregnancy is not clear, but since increased homocysteine is associated with prothrombotic changes and consequently with increased risk of pregnancy complications, one outcome of lower homocysteine may be the protection of the mother and foetus from VTE and pregnancy complications. Furthermore, given that hyperhomocysteinaemia can be modulated by folic acid, B 6 and B 12 [46], the question arises as to whether or not nutrition in pregnancy plays any role in maintaining haemostatic balance, an issue which can only be answered by large randomized controlled trials.

Conclusions
The balance between coagulation factors and coagulation inhibitors and between fibrinolytic factors and fibrinolytic inhibitors, ultimately resulting in coagulation/fibrinolysis balance, is an integral part of normal haemostasis. In normal pregnancy there are many changes in haemostasis, with a potential tilt towards the hypercoagulable state. However, haemostatic balance is maintained [1,28], at least partly by an increase in fibrinolytic activity. Other mechanisms, such as decreases in factor XI and monocyte TF expression, may also serve to counterbalance procoagulant changes. As well as increasing the risk of pregnancy associated VTE, disturbances in haemostatic balance may lead to inadequate maternal–foetal circulation and hence increase the risk of pregnancy complications such as placental abruption, foetal growth restriction and pre-eclampsia. Despite the many haemostatic changes in pregnancy, 28% of cases of VTE are not associated with a clinical risk factor for thrombosis or a thrombophilic defect [2,10], thus highlighting the necessity for further research into mechanisms involved in maintaining the haemostatic balance which appears to be central to normal healthy pregnancy.

References