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THE POTENTIAL ROLE OF CHANGES IN HEMOSTATIC IN PREGNANT WOMEN

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ABSTRACT

The parturient with coagulation defects presents a unique challenge to the anesthetist. In addition to concerns of peripartum hemorrhage, one must be aware of the consequences of bleeding diatheses, factor replacement strategies, and anticoagulation on the safety profile of neuraxial anesthesia. The risk of spinal or epidural hematoma 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 anesthesia 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 preventions of postpartum hemorrhage and neuraxial complications.

KEYWORDS: Hemostatic, pregnant women.

INTRODUCTION

The hemostatic system is made up of the coagulation and fibrinolytic systems, platelets and the vascular endothelium. The coagulation and fibrinolytic systems are responsible for the formation and destruction of insoluble fibrin. In the normal healthy individual, these systems are in dynamic balance and control fibrin deposition within the vascular compartment. Healthy endothelium acts as both an antithrombotic surface and a source of fibrinolytic enzymes and other vasoactive agents. Activated platelets adhere to damaged endothelium and form a platelet plug at the site of injury. The platelet plug is reinforced by strands of fibrin sealing the injured area and allowing the secretion of growth factors responsible for tissue repair.[1]

The production of fibrin can be initiated by either the intrinsic or extrinsic coagulation pathway. The intrinsic system operates as a cascade reaction of inactive zymogens which, when activated, promote the conversion of each subsequent zymogen into its active serine protease form, culminating in the conversion of Factor X to factor Xa (MacFarlane, 1964). The extrinsic system is activated when a surface, such as damaged endothelium, is exposed to the coagulation proteins. Tissue factor released at the site of injury forms a complex with calcium and Factor VII to produce Factor VIIa, which is responsible for the conversion of Factor X to Factor Xa. Factor Xa forms a complex with Factor V, phospholipid and calcium ions which converts inactive prothrombin to the active proteolytic enzyme, thrombin. The transformation of fibrinogen to fibrin involves the thrombin-catalyzed removal of fibrinopeptides from the amino-terminal ends of the alpha and beta chains of the fibrinogen molecule. These reaction products, for example, fibrinopeptide A and fibrin monomer, are useful as markers of in vivo fibrin production.[2]

During pregnancy, the risks of bleeding and of thromboembolic complications are both increased. The uteroplacental unit is unique; its most important function is to establish contact between maternal and fetal circulations, which is a requirement for fetal survival. This circulation must be established and maintained throughout pregnancy. The border between the maternal and fetal circulations must permit the exchange of gases such as oxygen and CO2 as well as nutrients. Bleeding and thrombotic events can interrupt this important function; therefore, several systems are involved in the repair of the uteroplacental circulation. Changes in the uteroplacental unit are a function of local conditions,1 but may also result from alterations in the maternal blood. Furthermore, there is an increased risk of bleeding during and following parturition. Therefore, the pregnant woman has an increased reserve of blood coagulation precursors and fibrinogen for use in connection with hemostasis activation at that time, although the contraction of the myometrium is the most important factor for achieving normal arrest of bleeding and preventing hemorrhagic catastrophes.[3]

Myometrial contraction initially stops bleeding and hemostatic mechanisms interrupt blood flow by producing clots in the blood vessels, which limits bleeding when myometrial contractions subsequently diminish and finally cease. The changes in hemostasis during pregnancy have been considered to be mainly the result of increased estrogen levels. Most of these hemostatic changes can also be observed in connection with other conditions entailing increased estrogen influence. However, maternal hemostasis differs from that in nonpregnant

females; it is important to master normal hemostasis during pregnancy to understand and treat obstetric complications associated with hemostatic changes. The following review presents changes in platelet function, blood coagulation, and fibrinolysis as well as in biochemical markers for activation of platelets, blood coagulation, and fibrinolysis during normal pregnancy and puerperium.[4]

BACKGROUND

Thrombocytopenia is the most common hemostatic abnormality observed in pregnancy. 1 In many healthy women (around 10%) late pregnancy is associated with thrombocytopenia. At least in part, this is due to haemodilution but the increase in mean platelet volume4 suggests that a compensated state of progressive platelet destruction occurs. Additional evidence of in vivo platelet activation in late pregnancy is the increased concentration of βthromboglobulin5 and of thromboxane A2 derivatives.[5]

During pregnancy the concentrations of coagulation factors VII, VIII, IX, X, XII, and normal range very early. The apparent fall in protein S during the first weeks of pregnancy does not allow a diagnosis of inherited protein S deficiency in pregnant women. Attempts to establish protein S normal levels during pregnancy are not recommended. Heparin cofactor II, another natural coagulation inhibitor, has been reported to increase in plasma during physiological pregnancy.[6] Protein Z is a vitamin-K-dependent plasma glycoprotein and inhibits the activation of factor X by serving as a cofactor to a plasma proteinase inhibitor. Protein Z deficiency has recently been reported in women with unexplained early fetal losses, and antibodies to protein Z can contribute to adverse pregnancy outcomes. Recent data show a progressive increase in protein Z levels with gestational age in normal pregnancies and a return to normal levels around 6 to 12 weeks postpartum.

The normal increase of protein Z during pregnancy may balance the increase of clotting factors to protect pregnant women from thrombosis. Activated protein C (APC) sensitivity is reduced during pregnancy; at term, 45% of pregnant women have an APC sensitivity ratio below the 5th percentile of the normal range for non-pregnant women of similar age. The reduction in APC ratio is directly related to its value in the non-pregnant state, being most pronounced in the women with the highest APC ratio.[7]

About 50% of the healthy women develop APC resistance, which reaches its lowest value by pregnancy second trimester with little further change. This behavior of the classical APC

resistance test has been called ‘acquired’ APC resistance. In a cross-sectional study no correlation was found between the decrease in the classical APC ratio and the free protein S levels; in another, a negative covariance was found between the APC ratio and FVIII levels in the first trimester and at delivery.[8]

Changes in the free protein S concentration are unlikely to contribute significantly to the development of APC resistance during pregnancy. Actually, protein S levels decline progressively during pregnancy and this differs from the pattern of reduction in APC anticoagulant activity, where little change in the APC ratio occurred between the second and third trimesters. In a prospective longitudinal study on healthy pregnant women19 no correlation was found between the total change in the classical APC ratio and the total changes in FVIII, fibrinogen or protein S. A modified APC resistance test, which includes sample dilution in FV-deficient plasma prior to the APTTbased assay, has been developed and shown to be useful in screening for factor V Leiden in patients on oral anticoagulants or with antibodies against phospholipids.[9]

When this modified APC resistance test was used, the gestation-dependent APC resistance that has been reported with the unmodified test was no longer observable. A significant, gradual increase in the levels of soluble fibrin, thrombin-antithrombin complexes, and prothrombin fragment 1+234 have been reported. The observed rise in F1+2 between the first and second trimester indicates that a degree of activation of coagulation occurs relatively early in normal pregnancy.[10] Thus an increased thrombin generation is a feature of normal pregnancy. A concurrent increase in the levels of the fibrinolytic inhibitor's plasminogen activator inhibitors 1 and 2 suggests a decrease in fibrinolytic activity. However, the levels of fibrin d-dimer, i.e. fibrin split products, also increases in parallel, so suggesting that fibrinolysis is present.[11]

GLOBAL TESTS

Global tests measuring hemostasis in whole blood or citrated blood with or without activators appear to most closely resemble the in vivo situation, although they do not reflect the interaction between blood and the endothelium. Until now, most studies about hemostasis and pregnancy have described blood coagulation factors, blood coagulation inhibitors, fibrinolytic factors, and platelet function separately. It seems more appropriate to study these factors and their cooperation together. Recently, reports on global tests and hemostatic changes during pregnancy have begun to appear in the literature. These tests reflect the in vivo situation in

whole blood and are important as bedside analyses, especially during delivery and obstetric complications, when the rapid analysis is crucial to provide immediate hemostatic treatment and to prevent thromboembolic complications. The Sonoclot signature, which provides information about the velocity of total fibrin formation and fibrin polymerization, fibrin-platelet interaction, platelet function, and fibrinolysis, was studied in pregnant women with normal pregnancies, deliveries, and healthy children.[12] Contact time and peak time were unchanged during pregnancy and statistically significantly shorter during pregnancy than 8 weeks postpartum. Clot rate and secondary rate were unchanged during pregnancy and statistically significantly higher during pregnancy than 8 weeks postpartum.[13]

The signature is easy to interpret and is of the same general shape for each patient over time. There is a clear state of hypercoagulability during pregnancy. There was a statistically significant correlation between Contact time and activated partial thromboplastin time (aPTT) and between clot rate and aPTT, respectively.

Like the Sonoclot signature, the Thromboelastogram shows platelet function, fibrin formation, and fibrinolysis, and is performed to evaluate hemostasis under conditions in which bedside information is important; for example, during liver transplantation and cardiac surgery. The TEG has been studied particularly during late pregnancy and, like the Sonoclot signature, reveals a hypercoagulable condition during pregnancy.[14]

Both methods are valuable in the delivery ward because results are available much faster than those of ordinary laboratory analyses. Although pathological signatures must be verified by laboratory analyses, treatment can be initiated as early as 10 to 20 minutes after blood sampling. More specific details about hemostatic disturbances may be necessary to achieve optimal treatment, but these global tests are valuable for initial diagnosis and treatment. Fibrin formation occurs more easily during normal and complicated pregnancy than during nonpregnant conditions. All these conditions have been studied with a new method analyzing the overall hemostatic potential in plasma (OHPP).[15]

The method measures properties of pro- and anticoagulants in plasma and the results verify those of earlier methods regarding hypercoagulability during pregnancy. OHPP may be useful in future studies of treatment of hypercoagulability during pregnancy. Endogenous thrombin generation has been studied to detect hypercoagulability.[16] Increased or unchanged capacity for thrombin generation has been reported during pregnancy as well as during

treatment with oral contraceptives and in patients with activated protein C resistance.[17] Activated protein C resistance caused by factor V polymorphism (factor V Leiden) is a well-known state of thrombophilia. Acquired activated protein C resistance has been reported during pregnancy; this condition can partly be explained by an increased factor (F) VIII:C levels and protein C inhibitors, but its significance is not fully understood. The aPTT is usually normal during pregnancy but tends to decrease slightly in late pregnancy and the PT is markedly shortened; INR is usually < 0.9 during the third trimester. Bleeding times, measured by template methods, is unchanged during normal pregnancy.[18]

Platelet Function

The number of platelets is comparable to that in nonpregnant individuals. The volume of platelets is reportedly unchanged during normal pregnancy.18,19 Studies of platelet life span have shown normal turnover during normal pregnancy.[19]

There can, however, be increased consumption of platelets in the uteroplacental unit resulting in decreasing platelet counts, occasionally < 150 109/L but exceeding 80 109/L, particularly during the third trimester. This benign gestational thrombocytopenia during pregnancy does not influence the outcome.[20] Increased platelet aggregation has been reported during pregnancy. There are contradictory results about the extent to which activated platelets exist in vivo during normal pregnancy.[21]

Activation of platelets and simultaneous release of vasoactive substances occur especially during repair of the uteroplacental unit and in connection with obstetric complications. Increased and unchanged levels of beta-thromboglobulin and platelet factor 4 in the circulation have, however, also been reported during normal pregnancy.[22]

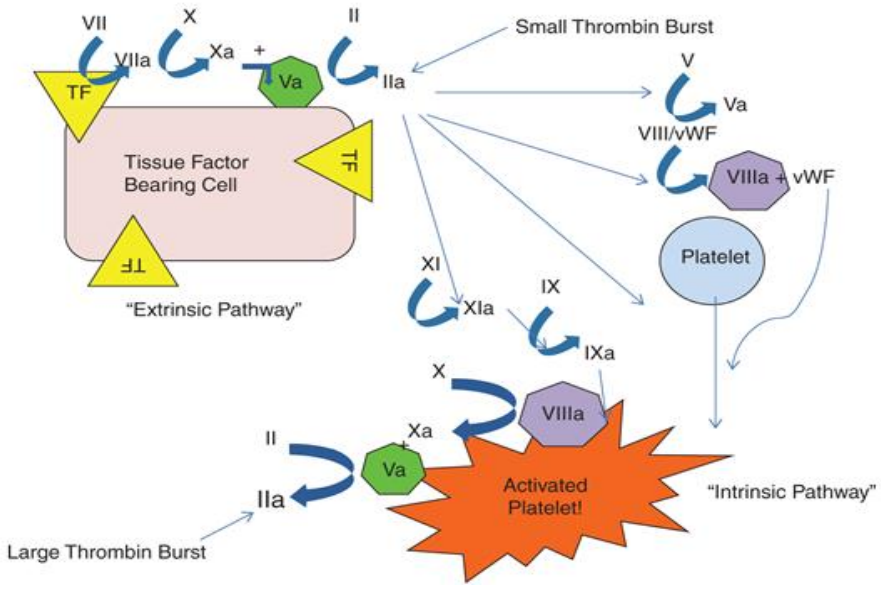
Coagulation system and changes in the parturient

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 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).[23] The formation of thrombin is broken down into initiation and propagation phases, in which tissue factor is the main initiator of coagulation(Fig. 1).[24] 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.[25]

The activated factors form on the surface of platelets, making the tenase complex (IXa, VIIa, and the substrate X), which in turn provides materials for the prothrombinase complex (Xa and Va), generating thrombin burst, ultimately forming fibrin from fibrinogen.[26] 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.

Fig 1



A 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. TF, tissue factor; vWF, von Willebrand factor.

Multiple changes occur to the coagulation system as pregnancy progresses, with the largest changes being seen at term gestation. 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 anemia of pregnancy. Platelet counts often decrease, both from dilutional effects and because of consumption by the uteroplacental unit. This decrease is rarely great enough to impact bleeding.[27]

Coagulation factor concentrations change dramatically throughout pregnancy. A comprehensive review is beyond the scope of this paper and can be found in other works.[28] 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.[29] Despite the significant changes that occur to the coagulation system, standard coagulation tests, such as prothrombin time (PT), the international normalized ratio (INR), and activated partial thromboplastin time (aPTT), do not change during pregnancy or are very slightly decreased.

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

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.[30]

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 tested to assess the body's ability to form a clot, because they focus almost exclusively on plasma factors.[31] 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.[32] As such, they are poor tests to assess clinical coagulopathy, especially in the bleeding patient.

Additionally, traditional coagulation tests take a long time to perform, typically with up to an hour turnaround time. Whole-blood point-of-care tests have been developed to overcome some of the disadvantages of traditional tests. For example, thromboelastography and thromboelastometry are two viscoelastic tests that can be run on whole or citrated blood and can measure clot kinetics and strength from formation to fibrinolysis.[33]

Thromboelastography was first introduced by Hartert in 1948 but was not used clinically until 1985. 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.[34] 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.[35]

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 available in a few minutes. Although the test can be run on whole blood, it is 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.[36]

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 labor intensive, new cartridge-based machines with a more favorable quality-control process are in development.[37]

Table 2.

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

DISCUSSION

The mechanisms of hemostasis 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.[38] This process is even more complex in the parturient, where changes such as physiological anemia and fluctuating coagulation factor concentrations alter the balance between bleeding and clot formation in preparation for peripartum blood loss. 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 hemorrhagic risk. It is crucial that anesthetists who care for pregnant patients have an understanding of these changes in coagulation; not only to ensure the safety of neuraxial anesthesia, the mainstay anesthetic for both labor and Caesarean delivery, but also for the management of hemorrhage, which is common in the parturient. The overall estimated risk of epidural or spinal hematoma after neuraxial anesthesia in the obstetric population is 1:168 000. Vandermeulen and colleagues reviewed 61 instances of anesthesia-related spinal hematoma in pregnant and non-pregnant patients and found that it most often occurred in patients with coagulopathies (68%).

CONCLUSION

The process of hemostasis 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 anesthetic options for labor and delivery is crucial to anesthetist caring for the parturient.

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