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Chapter 3

The Role of the Coagulation System in Preterm Parturition

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54843

1. Introduction

Term and preterm parturition have a common pathway that includes irregular uterine contractions, cervical effacement and dilatation, along with decidual activation and rupturing of the chorioamniotic membrane. This pathway is observed in the physiologic labor at term as well as in the pathological processes leading to premature delivery. Indeed, the clinical presentation of preterm parturition involves all components of this common pathway: 1. Preterm contractions in women with spontaneous preterm labor with intact membranes; 2.cervical effacement and dilatation in women with cervical insufficiency; and/or 3.decidual activation and rupture of membranes in those with preterm PROM.

The syndrome of preterm parturition is the clinical presentation of several underlying mechanisms, not all of them being fully understood. Among the well establishes etiologies for preterm parturition are: intra amniotic infection/inflammation, cervical insufficiency, increased thrombin generation and vascular pathology of the placenta, as well as multiple gestations. The study of the maternal fetal interface and the placenta contributes to the deciphering of the mechanism leading to preterm birth. Placental and decidual vascular lesions have been reported in about 20-30% of patients who deliver preterm. There are accumulating evidence that preterm parturition is associated with an increased activation of maternal hemostatic system which also interacts with the acute inflammatory processes observed in this syndrome. Moreover, higher rates of fetal growth restriction and placental vascular lesions were observed among women with preterm labor who delivered at term suggesting that some vascular insults may not be severe enough to cause preterm birth but still inflict some effect on fetal growth.

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The following chapter will summarize the changes in maternal hemostatic system during normal pregnancy and those associated with preterm labor and preterm PROM. In addition, we will review the vascular changes associated with preterm parturition. The last section of this chapter will address the role of the hemostatic and angiogenic markers for the prediction of spontaneous preterm birth.

2. The physiology of hemostasis

Hemostasis is crucial for the maintenance of the vascular tree integrity.

The major components of the hemostatic system, which function in concert, are the following: 1) the vessel wall and endothelium; 2) platelets and other formed elements of blood, such as monocytes and red cells; and 3) plasma proteins (the coagulation and fibrinolytic factors and inhibitors). These components act altogether in a synchronize fashion to generate the hemostatic plug, preserve the integrity of the vascular tree in the body, and avoid uncontrolled clot formation and thrombosis (See figure 1).

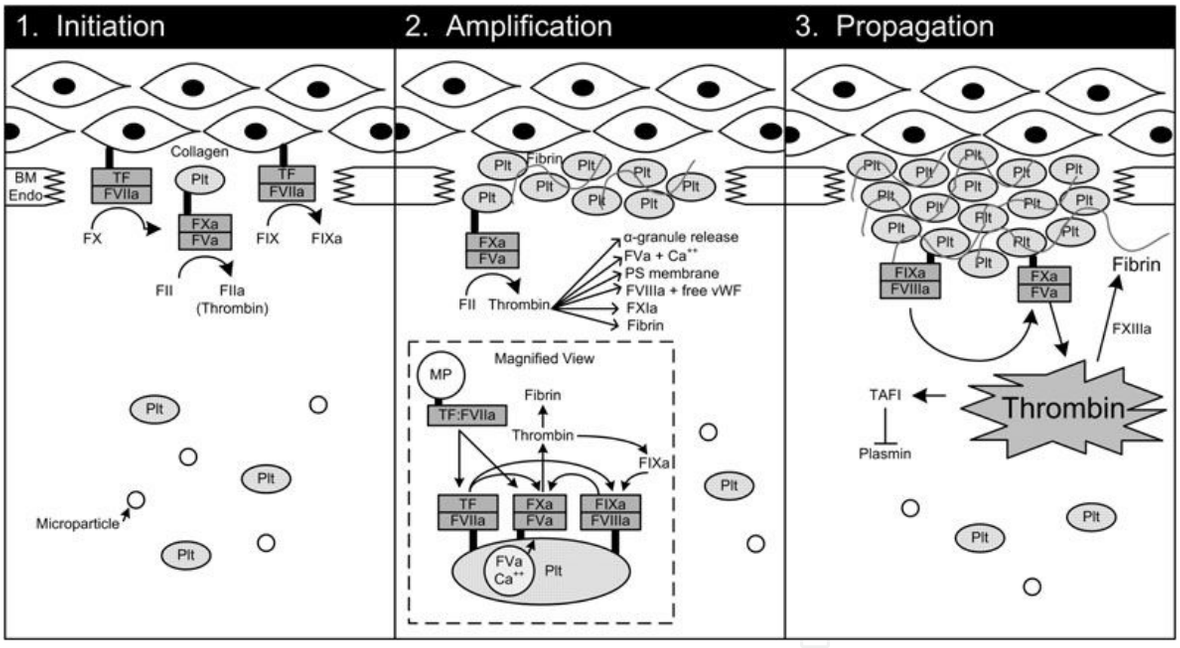


Figure 1. Initiation of coagulation by endothelial injury and exposure of tissue factor to the extrinsic pathway. Then, the platelets aggregate by activation of intrinsic pathway and platelet activation. And finally propagation and clot stabilization by thrombin – fibrin balance formation (from reference #12 with permission).

The vessel wall: Endothelial damage or activation is a crucial event that launches the cascade of reactions leading to thrombin generation and fibrin clot formation. The vascular endothelium is the focal point for both initiation and inhibition of the coagulation process. During endothelial damage the sub endothelial tissue factor molecules are exposed and initiate coagulation by activation of the extrinsic pathway. This is relevant also for the maternal fetal

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interface since the villous and exteravillos trophoblast of the human placenta adopt the properties of endothelium and vessel wall in order to allow laminar flow of maternal blood through the placental bed without unnecessary activation of the coagulation cascade; and any damage in their integrity will activate the coagulation cascade.

Platelets activation and plaque formation: Following vascular injury platelets initially adhere to sub-endothelial collagen via von Willebrand factor (vWF) (figure 2). These vWF ''bridges'' are anchored at one end to sub-endothelial type IV collagen molecules and at the other end to the platelet GPIb/IX/V receptor [1,2]. The adherent platelets can also attach to other sub-endothelial extracellular matrix proteins (e.g. laminin, fibronectin, and vitronectin) via cell-membrane bound integrins [3]. The binding of these receptors activates the platelets through calcium-dependent cytoskeletal changes.

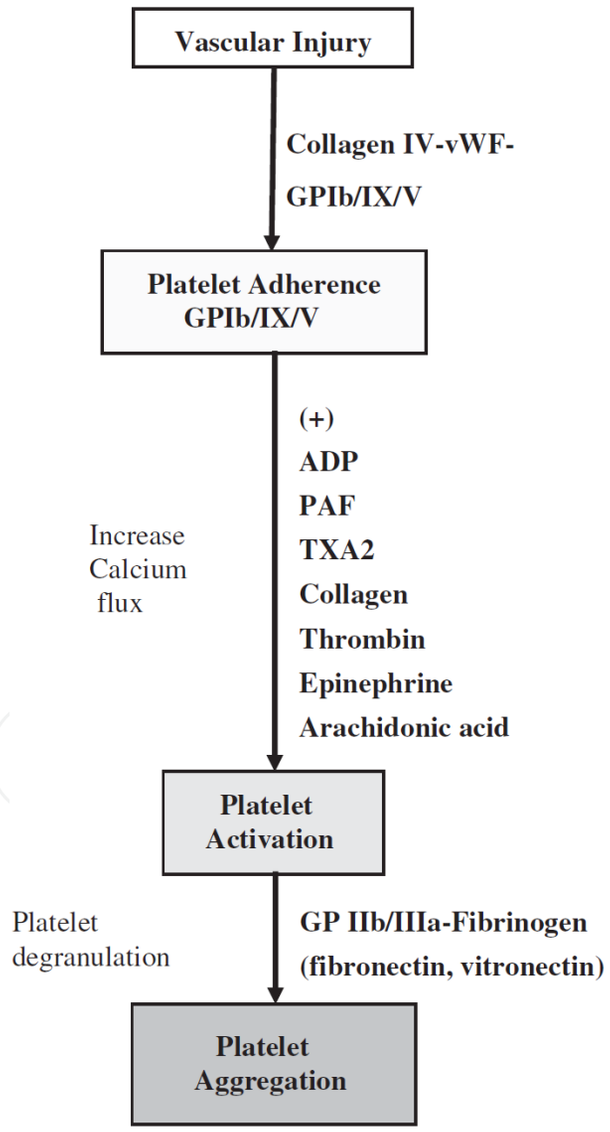


Figure 2. Mediators of platlet activation and agregation (from reference #5 with permission).

Activated platelets form pseudopodia that further enhance vWF coupling to the sub endothelium. Moreover, ADP induces a conformational change in the GPIIb/IIIa receptor on the platelet membrane causing platelet aggregation via the formation of a high affinity fibrinogen bridges anchored at either end by GPIIb/IIIa receptors on 2 different platelets [4]. Thus, Platelet activation converts the normally inactive Gp IIb/IIIa receptor into an active one, enabling binding to fibrinogen and VWF. Because the surface of each platelet has about 50,000 Gp IIb/IIIa-binding sites, numerous activated platelets recruited to the site of vascular injury can rapidly form an occlusive aggregate by means of a dense network of intercellular fibrinogen bridges. Since this receptor is the key mediator of platelet aggregation, it has become an effective target for antiplatelet therapy [5].

2.1. Plasma proteins

Coagulation factors: Plasma coagulation proteins (*clotting factors*) normally circulate in plasma in their inactive forms. The sequence of coagulation protein reactions that culminate in the formation of fibrin was originally described as a *waterfall* or a *cascade*. Two pathways of blood coagulation have been described in the past: the extrinsic, or tissue factor, pathway and the intrinsic or contact activation, pathway (figure 3). However, the current approach is a more unify view in which the coagulation cascade is normally initiated through tissue factor exposure and activation of the *extrinsic pathway* that generates thrombin and activates the elements of the classic *intrinsic pathway*. These reactions take place on phospholipid surfaces, usually on activated platelets.

The initial phase of coagulation is the exposure of tissue factor to coagulation factors, caused either by endothelial damage or activation [6]. Tissue factor (TF) is a 47kDa cell bound trans-membrane glycoprotein and member of class 2 cytokine superfamily [7], that functions as: 1) a receptor, with signal transduction resulting in the induction of genes involved in inflammation, apoptosis, embryonic development and cell migration[8]; and 2])as an activator and cofactor for factors VII/VIIa in the coagulation cascade. It is constitutively expressed by many extravascular tissues, especially perivascular ones, and it is highly expressed in the brain, heart, lungs, kidneys, testis and placenta [9-11], reflecting the importance of these tissues to the organism[12]. TF expression can be induced in monocytes and platelets, and has been detected on circulating microparticles (MP) derived from these and other cell types [7,13]. The expression of this coagulation factor can also be induced on endothelium in response to inflammatory stimuli including exposure to: 1) bacterial lipopolysaccharide (LPS) in sepsis; 2) adhesion molecules (P-selectin expressed on platelets, CD40 ligand expressed on white blood cells); and 3) inflammatory cytokines (interleukin- 6, tumor necrosis factor), and oxidized low-density lipoprotein(LDL) [14].

Tissue factor activates the coagulation cascade by binding to the serine protease factor VIIa; the complex of TF+FVIIa activates factor X to factor Xa and initiating the converting factor IX to factor IXa in the intrinsic system leading to further formation of factor Xa. Thus, this factor is formed through the actions of either the tissue factor/factor VIIa complex or factor IXa (with factor VIIIa as a cofactor), and converts pro-thrombin to thrombin, the pivotal protease of the coagulation system. Thrombin is a multifunctional enzyme that converts soluble plasma fibrinogen to an insoluble fibrin matrix. Thrombin also activates factor XIII (fibrin-stabilizing factor) to factor XIIIa, which covalently cross-links and thereby stabilizes the fibrin clot.

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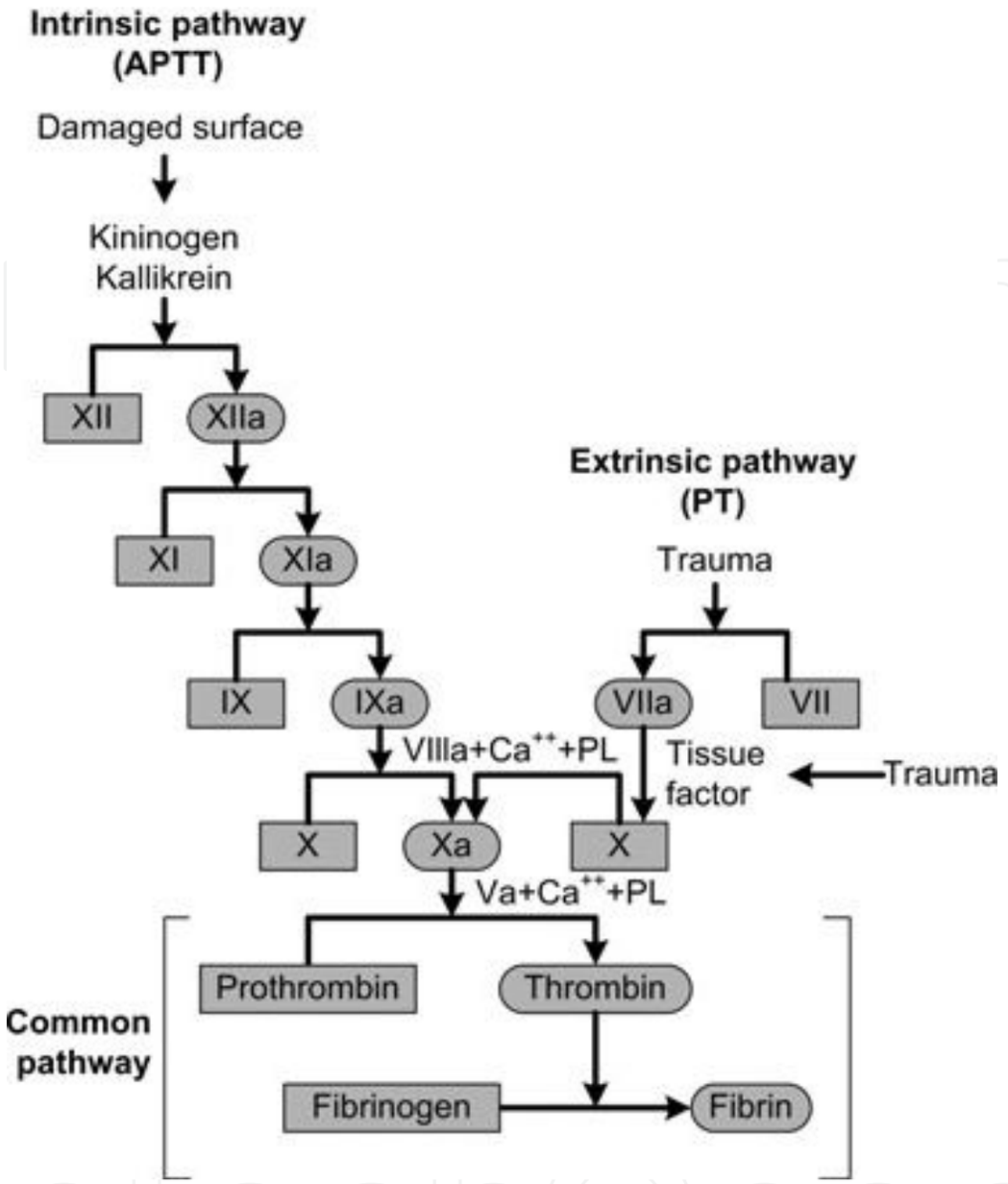


Figure 3. The extrinsic and intrinsic pathways of coagulation are a model for simplifying the coagulation system. This model is reflected in the laboratory PT and PTT measurements (from reference #12 with permission).

An additional mechanism in which the activation of the coagulation cascade can take place is through microparticles. Circulating microparticles are an area of intense research, as increased levels of them were shown to be pro-coagulant, even in the absence of TF expression [14-17]. These microparticles are tiny (<1 mm) membrane-bound vesicles and express membrane antigens that reflect their cellular origin[18]. The concentration of circulating microparticles is increased during platelet activation, inflammation, or apoptosis. Elevated concentrations of microparticles are encountered in diseases with vascular involvement and hypercoagulability such as disseminated intravascular coagulation, diabetes, and immune-mediated thrombosis [12].

Anti-coagulation protein:

Thrombin also plays a crucial role in activating the inhibition of the coagulation cascade.

Following its activation thrombin binds to thombomodulin causing a conformational change that activates the endothelial receptor of protein c, which in turns activates protein C. The latter is bound to its cofactor protein s together this complex inactivates factor Va and factor VIIIa of the intrinsic pathway, reducing substantially thrombin generation13. In addition to protein c and protein s there is the tissue factor pathway inhibitor (TFPI) which is the main inhibitor of the extrinsic pathway of coagulation, this protein inhibits the activity of factor VIIa and factor Xa reducing by this thrombin generation by the extrinsic pathway. the complex of protein z and Protein Z-dependent protease inhibitor (ZPI) inactivates factor Xa, and can also directly inhibit factor XIa. However, by far the most active inhibitor of both factor Xa and thrombin is antithrombin (AT) (previously known as antithrombin III). The AT molecule binds to either thrombin or factor Xa and then complexes with vitronectin which causes a conformational change that facilitates heparin binding. The resultant quaternary structure augments thrombin inactivation 1000-fold. The function of these anticoagulation protein is essential for maintaining the homeostasis between coagulation and adequate blood flow in the vascular tree, and deficiency in these protein is associated with increase risk for thromboembolic diseases and other complications.

Fibrinolysis factors and inhibitors: The process of fibrinolysis (i.e., clot lysis) is also crucial to the prevention of thrombosis (Figure 4). Fibrin is degraded to its degradation products (FDPs) by plasmin [19], that is generated from plasminogen by the action of tissue-type plasminogen activator (tPA) embedded in fibrin. This process is accelerated when plasminogen itself is bound to fibrin. Endothelial cells produce a second plasminogen activator, urokinase-type plasminogen activator (uPA). The latter's activation requires high molecular weight kininogen, kallikrein, and plasmin. This helps explain why deficiency of the former two ''intrinsic pathway'' clotting factors (ie, activators of factor XI) paradoxically lead to thrombosis and not bleeding.

There are series of inhibitors of premature fibrinolysis and, thus, hemorrhage. Plasmin is directly inhibited by a2-plasmin inhibitor. This inhibitor is also bound to the fibrin clot where it is positioned to prevent premature fibrinolysis. Type-1 plasminogen activator inhibitor (PAI-1) is synthesized by endothelial cells and platelets in response to thrombin binding to (protease activated receptor) PARs. In pregnancy, the decidua is a rich source of PAI-1, while the placenta produces PAI-1 and PAI -2, and serve as the primary source for the latter [20,21]. In the initial stages of platelet plug and fibrin clot formation, endothelial cells release PAI-1 but after a delay, endothelial cells release tPA and uPA to promote fibrinolysis.

Thrombin-activatable fibrinolysis inhibitor (TAFI) is another antifibrinolytic factor which acts by cleaving the C-terminal lysine in fibrin, to render it resistant to cleavage by plasmin [22,23]. Levels of TAFI are increased in the third trimester [23]. Interestingly, TAFI is also activated by the thrombin-thrombomodulin complex, once again implicating thrombin as the ultimate arbiter of hemostasis. The fibrinolytic system can influence coagulation in several ways. For example, FDPs inhibit thrombin action, a major source of hemorrhage in disseminated

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intravascular coagulation. In addition, PAI-1 bounded to vitronectin and also to heparin can directly inhibit thrombin and factor Xa activity [5,24].

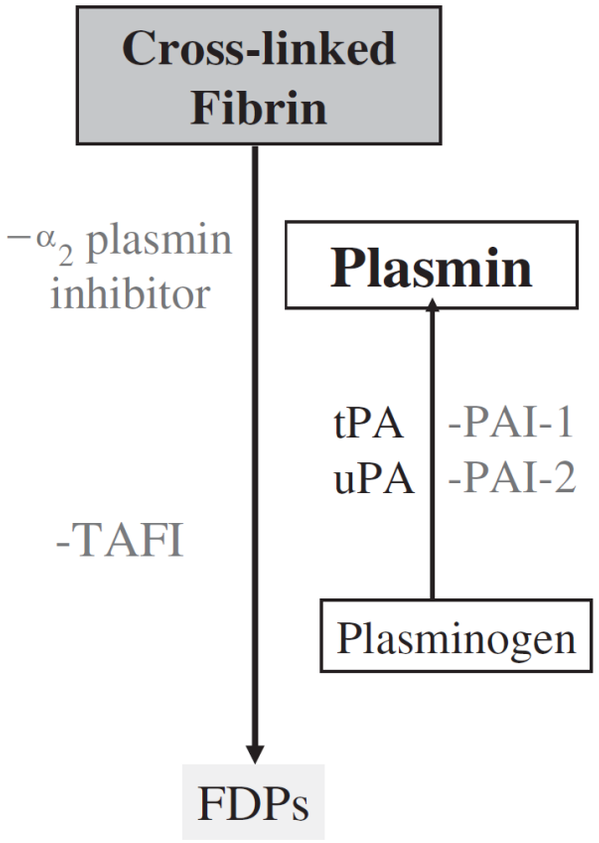


Figure 4. Fibrinolysis factors and inhibitors. The following scheme shows the process of fibrin degradation and plasmin generation (from reference #5 with permission).

3. Pregnancy associated changes in the hemostatic system

Pregnancy is a challenging time period for the hemostatic system. The demands from this system changes in different sites and are somewhat contradictory. The formation of the placental bed in which the maternal blood is running outside the maternal vessels necessitate the mother to address two challenges, the first one is to protect herself from a life threatening bleeding, and the second is to enable a continues blood flow through the placental bed outside the maternal blood vessels without activating the coagulation cascade. These challenges have been addressed by the formation of three compartments: 1) The maternal compartment which becomes adaptive and pro-coagulant to prevent severe bleeding during delivery; 2) The fetus that develops his coagulation system during gestation while floating in the pro-coagulant amniotic fluid; and 3) The maternal fetal interface of which the intervillous space is hypocoa-

gulated in order to ensure the extravascular laminar flow of maternal blood and the maternal decidua is rich with tissue factor to prevent bleeding.

During gestation, changes in the coagulation system are considered to be adaptive to prevent hemorrhage at the time of delivery [25-29]. Indeed, normal pregnancy has been associated with excessive maternal thrombin generation [28,30] and a tendency for platelets to aggregate in response to agonists [31,32] (TABLE 1). Pregnancy is accompanied by 2 to 3-fold increase in fibrinogen concentrations and 20% to 1000% increase in factors VII, VIII, IX, X, and XII, all of which peak at term [33]. The concentrations of vWF increase up to 400% by term [33]. By contrast, those of pro-thrombin and factor V remain unchanged while the concentrations of factors XIII and XI decline modestly[34]. Indeed there is evidence of chronic low-level thrombin and fibrin generation throughout normal pregnancy as indicated by enhanced concentrations of pro-thrombin fragment 1.2, thrombin-antithrombin (TAT III) complexes, and soluble fibrin polymers[23]. Free protein S concentration declines significantly (up to 55%) during pregnancy due to increased circulating complement 4B-binding protein its molecular carrier. Protein S nadir at delivery and this reduction is exacerbated by cesarean delivery and infection [33,35]. As a consequence, pregnancy is associated with an increase in resistance to activated protein C [23,33]. The concentrations of PAI-1 increase by 3 to 4-folds during pregnancy while plasma PAI-2 values, which are negligible before pregnancy reach concentrations of 160 mg/L at delivery [33]. Thus, pregnancy is associated with increased clotting potential, as well as decreased anticoagulant properties, and fibrinolysis [5]. Therefore, it can be defined as a prothrombotic state.

		Increased	Decreased	No change
Systemic changes	Procoagulant factors	I,V,VII,VIII,IX,X	XI	
	Anticoagulant factors	Soluble TM	PS	
	Adhesive proteins	vWF		
	Fibrinolytic proteins	PAI-1,PAI-2	t-PA	TAFI
	Microparticles and APLA	MP		APLA
Local placental changes		TF	TFPI	

Table 1. Hemostatic changes in pregnancy [42].

In contrast to the maternal circulation and the decidua, the establishment of the uteroplacental circulation challenges the hemostatic system. Indeed, fibrin deposition sites were identified in

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decidual veins at sites of trophoblast invasion, where villi are implanted into veins [36]. Compared with endothelial vasculature, the trophoblasts lining decidual spiral arteries have a reduced capacity to lyse fibrin, and recent studies have shown that this is caused by high concentrations of plasminogen activator inhibitors [37] that affects it fybrinolytic capabilities. In addition, perivascular decidualized human endometrial stromal cells are ideally positioned to prevent postimplantation haemorrhage during endovascular trophoblast invasion by expressing TF, which is a primary cellular mediator of hemostasis [38,39]. In vivo and in vitro studies have demonstrated that estradiol (E2) enhances TF expression during progesterone induced decidualization. It was demonstrated that paracrine factors, such as endothelial growth factor (EGF) are involved with steroid-enhancing TF expression in decidualized human endometrial stromal cells through the EGF receptor [40]. The trophoblast and the placenta have distinct anticoagulation properties that aimed on one hand to prevent bleeding and on the other hand to allow laminar flow of maternal blood through the intervillous space [41,42]. Accumulating evidence suggest that the trophoblast acquires properties of vascular epithelium and expresses coagulation inhibitors such as tissue factor pathway inhibitor 2[43-45] (also known as placental protein 5 [46,47]), heparin co-factor II, dermatan sulfate [48, 49], and thrombomodulin [50-53] as well as pro-coagulant proteins such as tissue factor [38,54]. Moreover, a knockout mouse model for the endothelial receptor of protein C was lethal in-utero and the embryos died on the 10.5 day of gestation, and fibrin deposition was found around their giant trophoblast cells of these embryos [55]. Moreover, a recent report demonstrated that the placenta is an extra-hepatic source of the anti-coagulant proteins including protein C, protein S, as well as protein Z, and their expression is constitutive irrespective of obstetrical conditions [85].

4. The hemostatic system and preterm parturition

The involvement of the hemostatic system in the pathophysiology of preterm parturition is becoming more and more apparent. Indeed, changes in maternal and fetal gens, abnormal placental vascular finding and increased thrombin generation in the maternal circulation were all reported in association with preterm parturition.

Genetic studies: During parturition there is remodeling of the extra cellular matrix of the uterine cervix. Recently increased expression of the tissue type plasminogen activator gene was reported during labor at term [56]. This finding was supported by the role of plasminogen activation in the remodeling of the extracellular matrix in human amnion, chorio-decidua, and placenta during and after labor [57]. Moreover, in a genetic association study that tested maternal and fetal genes in women with preterm labor reported this gene to be highly express in fetuses of Hispanic patients who delivered preterm.

Single nucleotide polymorphisms of the coagulation genes are associated with increased risk for preterm birth. Indeed, in a study that aimed to identify the impact of genetic polymorphisms with pro-thrombotic and anti-thrombotic effects on the occurrence of preterm birth in a large cohort of very-low-birth-weight (VLBW)-infants and their mothers, and term-born-

infants and their mothers, maternal factor VII-121del/ins and the infant's factor VII-121del/ins polymorphisms were more frequent in the group of singleton VLBW and their mothers. Furthermore, the frequency of the factor XIII-Val34Leu polymorphism was significantly lower in singleton VLBW than in term infant controls; and in a multivariate regression analysis, previous preterm delivery, the maternal carrier status of the factor-VII-121del/ins polymorphism (OR=1.7, 95% CI: 1.12-2.5, p=0.007) and the lower frequency of infant's factor-XIII-Val34Leu polymorphism (OR=0.53; 95% CI: 0.29-0.96; p=0.038) were found to be independently associated with preterm delivery [58]. The association between Polymorphisms in factor VII and preterm birth was also reported among Caucasian in the USA. This study included maternal and fetal DNA from 370 patients. For maternal data the strongest associations were found in genes in the complement-coagulation pathway related to decidual hemorrhage in preterm birth. In this pathway 3 of 6 genes examined had SNPs significantly associated with preterm birth, including factor V, factor VII, and tissue plasminogen activator. The single strongest effect was observed in tPA marker rs879293 with a significant allelic and genotypic association with preterm delivery (OR- 2.80, CI 1.77–4.44, for a recessive model). Finally, exploratory multi-locus analyses in the complement and coagulation pathway were performed and revealed a potentially significant interaction between a marker in Factor V (rs2187952) and Factor VII (rs3211719) ($p<0.001$); the authors concluded that "These results support a role for genes in both the coagulation and inflammation pathways, and potentially different maternal and fetal genetic risks for preterm birth"[59].

Collectively the evidence brought here suggest that genetic polymorphism of the coagulation genes may predispose a subset of women to an increased risk for preterm birth. What is the role of gene environmental interaction and in what mechanisms these polymorphisms of the coagulation genes affect the risk for preterm parturition are still unknown and are an area of future research.

Changes in maternal circulation: Increased thrombin generation in the maternal circulation, above that reported during normal pregnancy, has been reported in all the great obstetrical syndromes including preeclampsia [60-66], fetal growth restriction [61,62,67,68], fetal death [69], preterm labor (PTL) [30,70], and preterm PROM [30,69,71]. There are several possible explanations for the increased thrombin generation reported in women with preterm parturition: 1) increased activation of coagulation cascade in the maternal circulation due to pathological processes including bleeding or inflammation; and 2) depletion of anticoagulation proteins that subsequently leads to increased thrombin generation.

Increased activation of the coagulation cascade among women with preterm parturition is well supported by the current literature. Indeed, women with preterm PROM and preterm labor have a higher median maternal plasma concentration of thrombin-anti-thrombin (TAT) III complexes [30,70]. In addition, in women with preterm labor elevated maternal plasma TAT III concentration was associated with a higher chance to deliver within <7 days from admission [69] (figure 5, and figure 6). Median maternal plasma Tissue factor, concentration is higher in women with preterm PROM, but not in those with PTL, than in those with normal pregnancies [72]. Nevertheless, women with preterm labor as well as those with preterm PROM had both increased tissue factor activity in comparison to normal pregnant women.

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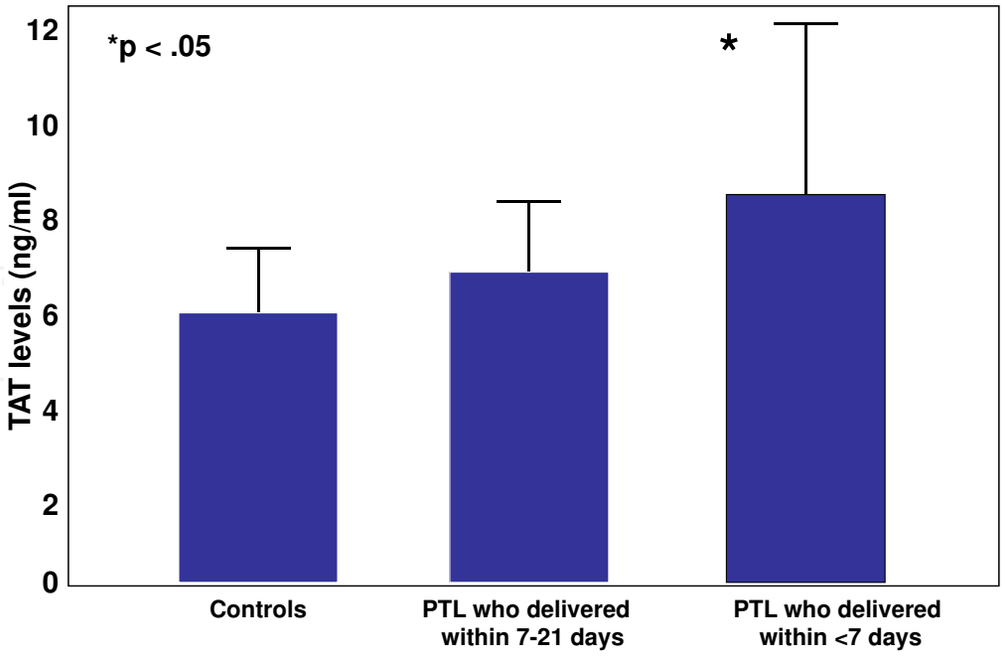


Figure 5. Thrombin–antithrombin III (*TAT*) levels in control patients, patients with preterm labor who delivered within 3 weeks, and patients with preterm labor who delivered after 3 weeks. *Open diamonds,* Mean levels; *black error bars,* SD. **P* <.05, Student-Newman-Keuls method (from reference #70 with permission).

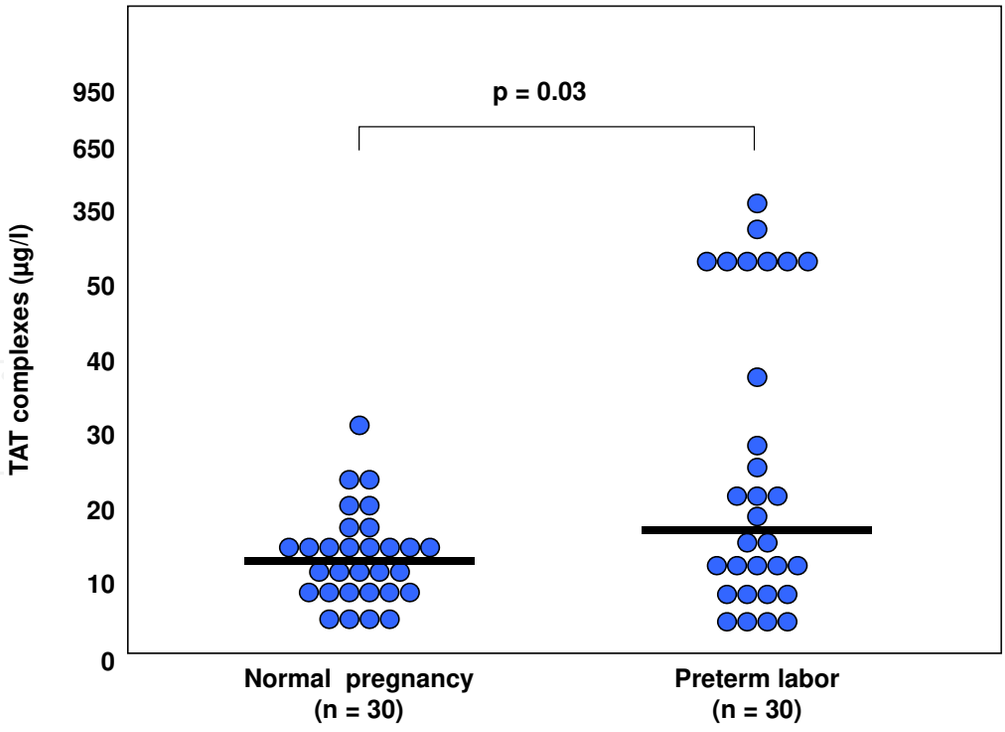


Figure 6. Maternal plasma TAT III concentration in women with preterm labor (PTL) and those with a Normal pregnancy (from reference #30 with permission).

The activation of the coagulation system in the placental and maternal compartment of patients with preterm parturition can result from the following underlying mechanisms: 1(decidual hemorrhage that leads to a retro-placental clot formation [73]; 2) intra-amniotic infection which can induce decidual bleeding and sub-clinical abruption [74], as well as increased intra-amniotic TAT complexes [69]; and 3) an increased maternal systemic inflammatory response [75] that may activate the extrinsic pathway of coagulation due to the expression and release of tissue factor (TF) by activated monocytes [76]. These mechanisms result in an increased thrombin generation, which has been associated with the following: 1) stimulation of decidual cell secretion of matrix metalloproteinase (MMP) (i.e. MMP-1 and MMP-3) that can degrade the extracellular matrix of the chorioamniotic membranes [77,78](as is in preterm PROM); and 2) myometrial activation and uterine contractions generation that may lead to preterm labor with or without rupture of membranes and a subsequent preterm delivery [70,79,80]. While thrombin is generated as a consequence of activation of the coagulation cascade, TF, the most powerful natural pro-coagulant, is abundant in the uterine decidua in the normal state [81,82], as part of an efficient hemostatic mechanism in the uterine wall, which is activated in the course of normal pregnancy during implantation[83] and after delivery[84]. However, this hemostatic mechanism may also be activated due to pathological decidual bleeding in pregnancies complicated by placental abruption [73,85] and intra-amniotic infection [74].

A novel mechanism that may lead to an increased thrombin generation in women with preterm parturition is depleted or insufficient anticoagulant proteins concentration. Indeed, women with preterm labor without intra-amniotic infection or inflammation and those with vaginal bleeding who delivered preterm had a lower median maternal plasma protein Z, a co-factor that participate in the inhibition of factor Xa, concentration than women with normal pregnancy and those with vaginal bleeding who delivered at term [86]. Moreover, both patients with preterm labor and preterm PROM had a lower median maternal plasma concentration of total tissue factor pathway inhibitor (TFPI), the main physiological inhibitor of the TF pathway, regardless of the presence of infection or gestational age at delivery. These observations suggest that the increased thrombin generation observed among these patients may derive not only from an increased activation of the hemostatic system, but also from insufficient anti-coagulation. The latter can be due to either low concentrations of the anticoagulant proteins, or as a result of an abnormal balance between coagulation factors and their inhibitors.

The overall balance between the concentration and activity of the coagulation factors and the anti-coagulation proteins is one of the determining factors of thrombin generation. In the normal state, the immunoreactive concentrations of TFPI in the plasma are 500 to 1000 times higher than that of TF [87], suggesting that an excess of anti-coagulant proteins closely controls the coagulation cascade activity [87]. Although preterm labor was not associated with a significant change in the median maternal plasma tissue factor concentration, the TFPI/TF ratio was lower than that of normal pregnant women, mainly due to decreased TFPI concentrations. Along with the reports that patients with preterm PROM [72], as well as those with preeclampsia [88], have a lower median maternal plasma TFPI/TF ratio than that of normal pregnant women. The lower TFPI/TF ratio in patients with preeclampsia occurs despite the increase in the median maternal plasma TFPI concentration observed in these patients. This

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suggests that the balance between TF and its natural inhibitor may better reflect the overall activity of the TF pathway of coagulation, than the individual concentrations of TF or TFPI. Collectively, these observations suggest that our attention should be focused not only on the coagulation protein but also on their inhibitors since an imbalance between them may contribute to increased thrombin generation leading to the activation of preterm parturition.

Inflammation is a major process in term and pre term parturition. In recent years it has become apparent that tight and reciprocal interactions exist between coagulation and inflammation [90]. Originally, much attention was given to mechanisms by which inflammatory mediators, most notably cytokines, can activate coagulation. More recent investigations have revealed that, in turn, mediators involved in the regulation of coagulation and anticoagulation have major effects on the inflammatory processes.

Inflammation elicits coagulation primarily by activating the tissue factor pathway [89] and the generation of thrombin and fibrin. The pivotal role of tissue factor in activation of coagulation during a systemic inflammatory response syndrome, such as produced by endotoxemia or severe sepsis, is well established, and attenuation of the activation of the tissue factor/factor VIIa pathway in endotoxemic humans and chimpanzees and in bacteremic baboons abrogated the activation of the common pathway of coagulation [90-92] and decreased the morbidity associated with these systemic inflammatory conditions.

During preterm PROM and preterm labor, there is a moderate maternal systemic inflammation that results in monocyte and granulocyte activation [75]. Activated monocytes express TF on their membrane [93-97] and shed micro-particles containing TF into the plasma [93]. In addition, the lack of association between intra-amniotic infection/inflammation, as well as the placental histologic findings and median maternal plasma concentrations of TF and TFPI, suggest that the pro-coagulant changes observed in patients with preterm PROM may be due to a systemic rather than a local (i.e. placental, intrauterine) inflammatory process.

Moreover, preterm PROM is associated with an increased activation of the decidual component of the common pathway of parturition [98]. Thus, in pregnancies complicated by abnormal placentation or intrauterine infection, decidual bleeding may lead to a higher expression of TF and activation of the coagulation cascade, resulting in increased thrombin generation. The latter has uterotonic properties that may generate uterine contractions that could initiate labor [70,79,80]. Moreover, thrombin can mediate the activation of MMP-1 [78], MMP-3 [77], and MMP-9[99] that can digest components of the extracellular matrix, weaken the chorioamniotic membranes and predispose to preterm PROM.

The mechanisms described above are localized to the maternal-fetal interface. The lack of association between median maternal plasma TF concentrations and the presence of intra-amniotic infection/inflammation or vaginal bleeding in patients with preterm PROM suggest that the systemic maternal inflammatory response during preterm PROM[75] may contribute the increase median maternal plasma TF concentration in these patients regardless to the presence of infection or inflammation in the amniotic cavity or the occurrence of vaginal bleeding [100].

In addition to the maternal circulation intra-amniotic infection and/or inflammation is associated with an increased amniotic fluid TAT III complexes (figure 7). This is important since it represent an increased thrombin generation in the amniotic cavity during infection and or inflammation that may contribute to uterine contractility and the development of preterm birth [99]. Of interest, elevated intra-amniotic TAT III concentrations were associated with a shorter amniocentesis to delivery interval and an earlier gestational age at delivery only inpatients with preterm labor without intra-amniotic infection or inflammation [99]. This observation suggest that in a subset of patients with preterm labor activation of the coagulation system can generate preterm parturition and delivery; while in those with intra-amniotic infection and or inflammation the activation of the coagulation and thrombin generation is a byproduct of the inflammatory process leading to preterm birth.

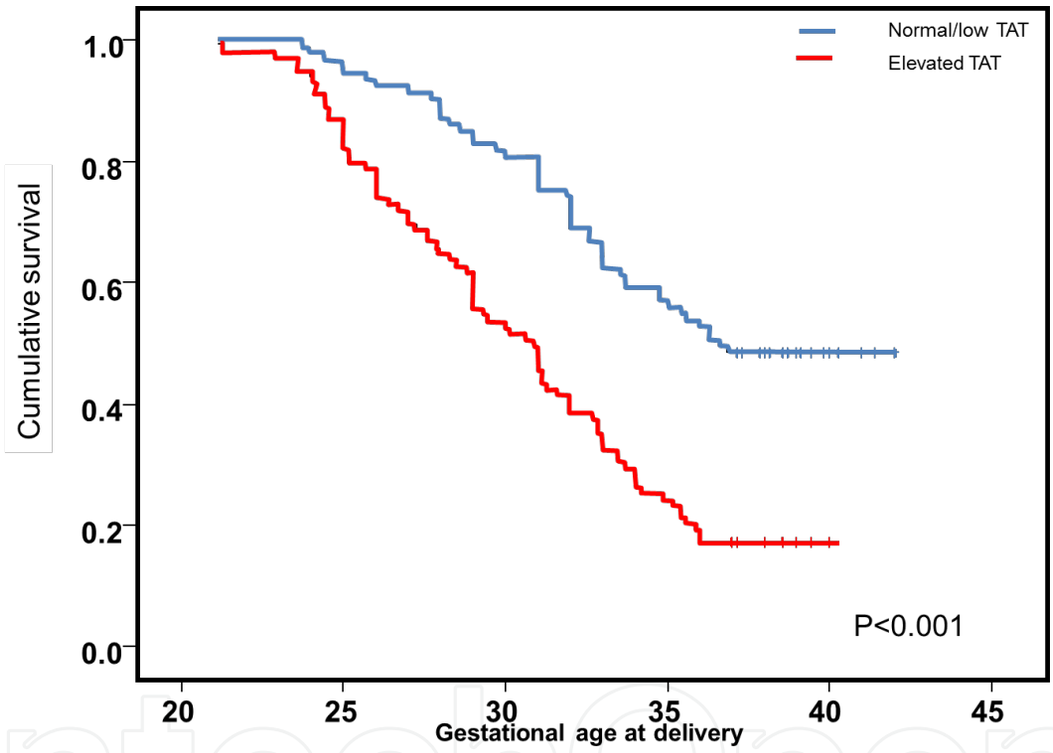


Figure 7. The effect of amniotic fluid thrombin-antithrombin (TAT) III concentrations on gestational age at delivery (from reference #69 with permission)

5. Placental vascular changes in women with preterm parturition

Accumulating evidence from studies of the placenta [101,102], uterine artery Doppler scans [103], and animal experiments [104], suggest a role for uteroplacental ischemia in preterm birth. Indeed, Arias et al reported that about 20% of the placentas of patients who delivered preterm following preterm labor or preterm PROM had vascular lesions [105].

The invasion of trophoblast cells into the decidual and myometrial segments of the spiral arteries is a key point of normal placentation. This process results in reversible changes of the normal spiral arteries wall architecture [106]. The ''disappearance of the normal muscular and elastic structures of the arteries and their replacement by fibrinoid material in which trophoblast cells are embedded'' was originally termed physiologic transformation by Brosens et al in 1967. This process progressively remodeled, starting from the end of the first trimester onward, the uterine spiral arteries to form dilated conduits lacking maternal vasomotor control, ensuring the delivery of a constant supply of blood to the maternal-fetal interface at an optimal velocity for nutrient exchange [107]. Notably, several coagulation components, such as TF and thrombomodulin, are involved not only in hemostasis but also with placental blood vessel differentiation [38,42], affecting thereby the generation of different pathological condition affecting pregnancy and parturition; A higher rate of failure of transformation of the spiral arteries was reported in placentas of patients with preterm labor and preterm PROM than in those of normal pregnant women. This lesion has been implicated in the increased vascular resistance in the placental bed and the reduction of blood flow to the intervillous space [108,109], this is considered as a marker for defective placentation. Failure of transformation of the spiral artery was first reported in women with preeclampsia [110]. Indeed, the extent of this lesion in placenta of women with preeclampsia is more extensive than what is detected in women with preterm labor or preterm PROM [111-113], suggesting when extensive failure of physiologic transformation is present, narrowed uteroplacental arteries predispose to reduced perfusion of the intervillous space, ischemia, and compensatory maternal hypertension. If these lesions are less extensive, the degree of ischemia may be insufficient to induce maternal hypertension, but may predispose to preterm labor/preterm delivery by itself or in association with other pathologic processes, such as intrauterine infection. A report that support the concept that clinical presentation is somewhat reflecting the extent of the disease is the study by Espinoza et al who found that women with an episode of preterm labor who delivered at term had a higher rate of SGA neonates and increased frequency of placental vascular lesions in comparison to those with preterm labor who delivered preterm [114]. This finding suggests that in some cases the vascular lesions that lead to development of preterm labor is not severe enough to cause preterm birth, however the "price" for the continuum of the pregnancy to term is decrease fetal growth.

6. The future — Hemostatic markers for preterm parturition?

In light of the association between maternal plasma TAT III concentrations in women with preterm labor and preterm birth within a week; and the association between amniotic fluid TAT III concentrations, the interval from amniocentesis to delivery, and gestational age at delivery. The question of the role of hemostatic markers as predictors for preterm birth is relevant. A preliminary report by Vidaeff et al found that increased concentrations of amniotic fluid TAT III concentration during mid-trimester amniocentesis of asymptomatic patients is associated with subsequent preterm delivery [115]. Aside the amniotic fluid new assays that

study the thrombin generation potential in maternal blood may offer similar answer in less invasive methods [116].

7. Conclusions

The understanding of the homeostasis system and coagulation process is crucial for understanding the physiological and pathological parturition. The significant impact of placentation abnormalities caused by those same changes in the haemostatic system, on maternal and fetal wellbeing is yet to be studied.

The aim of this chapter was to provide a window to the complexity of the normal homeostasis and pregnancy and a view of the different pathological conditions that may emerge during parturition. The inflammation as well as the coagulation and placental implantation are all part of the total picture of parturition.

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