

## Haemostatic system changes during pregnancy and puerperium

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### Abstract

**Background:** The activity in the hemostasis system is determined by two opposite processes that function simultaneously – blood clotting (fibrin clot formation) and fibrinolysis (the process of fibrin clot breakage). A normal balance between the processes of coagulation and fibrinolysis produces neither coagulation nor lysis, and vice versa, the imbalance of these processes is potentially dangerous in the development of coagulopathic or lytic events. Both systems (coagulation and fibrinolysis) undergo substantial changes in the physiological pregnancy, changes in an increase of coagulation factors concomitant with a decrease of anticoagulants and suppression in the fibrinolysis system. The predominance of prothrombotic activity gives the pregnancy a hypercoagulable status, with an increased risk of intravascular thrombi formation and thromboembolic complications (e.g. venous thrombosis, DIC syndrome). On the other hand, physiological hypercoagulation during pregnancy contributes to preventing the loss of blood during the immediate postpartum period by providing hemostasis in placental wounds and birth pathways.

**Conclusions:** The hemostasis system in pregnant women is marked by an increase in coagulation at each stage (from endothelium to circulatory factors of coagulation) which presumes the risk of thrombo-embolic complications, and the inhibition in the fibrinolytic system prevents peripartum bleeding.

**Key words:** haemostatic system, pregnancy, puerperium.

### I. Changes in the coagulation system in pregnant women

The blood coagulation involves the interaction of the vascular endothelium, platelets, plasmatic coagulation factors and consists of two stages: primary hemostasis (involves the vascular wall, vascular endothelium and platelets) and secondary hemostasis (activation of the coagulation cascade). The vascular endothelium is the component of the vascular wall with an important hemostatic function at local and systemic level through the secretion of substances with various actions (e.g. procoagulant, anticoagulant, fibrinolytic, antifibrinolytic, etc.), the molecular interactions of which favour coagulation in the subsequent stages and fibrinolysis.

Endothelial cells secrete:

- ◆ Prothrombotic factors (tissue factor, von Willebrand (fvW) factor, plasminogen activator inhibitor (PAI 1 and PAI 2), platelet activator factor (PAF), endothelins, fibronectin, collagen);
- ◆ Antithrombotic factors: protein S, protein C, thrombomodulin, tissue factor pathway inhibitor (TFPI), heparan, antithrombin III, tissue plasminogen activator, urokinase, nitric oxide (NO), prostacyclin (PGI<sub>2</sub>);
- ◆ Vasodilating factors: prostacyclin (PGI<sub>2</sub>), NO;
- ◆ Vasoconstrictor factors: endothelins (ET-1, ET-2, ET-3).

The role of vasoactive substances (thromboxane (TX) and PGI<sub>2</sub>) in maintaining hemostasis is their mutual annihilating actions on thrombocyte functions (TX and PGI<sub>2</sub> counteract each other's actions to maintain homeostasis with respect to platelet function). PGI<sub>2</sub> inhibits platelet aggregation and TX is a strong platelet aggregator and contributes to the activation of other platelets. In addition, PGI<sub>2</sub>

is a potent vasodilator and contributes to increased blood flow in the utero-placental complex and TX has a vasoconstrictor action. Endothelial dysfunction is accompanied by a reduction in PGI<sub>2</sub> synthesis, and the platelet aggregation-increasing TX effects and induction of vasoconstriction are determinant [1-3].

An important source of TX and PGI<sub>2</sub> during pregnancy are placenta, placental vessel endothelium, umbilical cord and uterus; ductus arteriosus; derivatives of placenta – amnion, chorion and decidua. The healthy placenta produces an almost equal amount of TX and PGI<sub>2</sub>, that is why their biological action on vascular tone, platelet aggregation and uterine contractility is balanced. It should be mentioned that in physiological pregnancy the concentration of both substances increases – PGI<sub>2</sub> (middle of pregnancy) and TX (towards the end of pregnancy). TX is primarily produced by trophoblast and stroma tissues, and PGI<sub>2</sub> is the primary product of endothelial cells of placental vessels and in smaller amounts of trophoblast (fig. 1). The increased serum concentration of TX derivatives and β-thromboglobulin (increased in the wall of the spiral arteries and in the intervillous space of the placenta) in the third trimester of pregnancy is further evidence of platelet activation.

In comparison with the physiological pregnancy in pre-eclampsia TX production increases and PGI<sub>2</sub> production decreases, so that the balance of the biological actions of these substances tend to favour TX actions. Decreased PGI<sub>2</sub> is also found in complicated pregnancies with intrauterine fetal development delay.

Another component of the coagulation system is platelets. Generally the number of platelets does not change during normal pregnancy (tab. 1), but it varies considerably within the normal baseline (50-70x10<sup>9</sup>/L) (tab. 1). Gesta-

tional thrombocytopenia is defined as a reduction in platelets below  $150 \times 10^9 / L$  determined in 5-12% of healthy pregnant women. Gestational thrombocytopenia occurs at an advanced gestational age (3rd trimester), rarely enough to have an impact on postpartum bleeding, and is secondary to the dilution effect in pregnancy when the plasmatic volume increases (at the end of the second trimester of pregnancy); reduction of platelets survival in pregnancy; increase in platelets breakage, etc. Restoration of normal platelets number occurs within the first 2 months after childbirth [4-6].

A peculiarity of the coagulopathic changes is related to platelet functions. The platelet membrane is composed of glycoproteins, phospholipids and cholesterol. Some glycoproteins act as membrane receptors (the most important complexes Ib-IX and IIb-IIIa). Transmembrane complex Ib-IX – role of thrombin receptor and von Willebrand factor in platelet adhesiveness. Complex IIb-IIIa – receptor for fibrinogen (essential in platelet aggregation) for  $Ca^{2+}$ , von Willebrand factor.

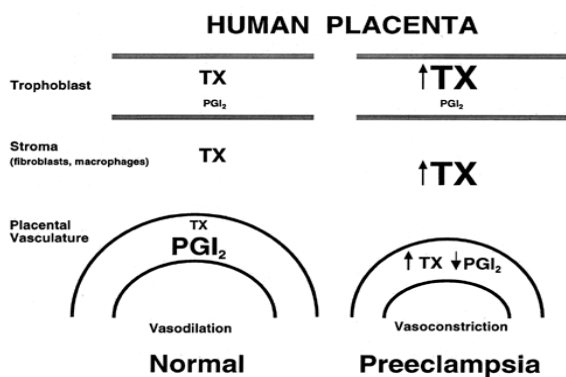


Fig. 1. Secretion distribution of vasoactive substances (PGI<sub>2</sub>, TX) by placenta in normotensive and with preeclampsia pregnant women.

Hemostatic functions of platelets:

1. Adhesion – the property of adhesion, their attachment to subendothelial structures (collagen, microfibrils, basal membrane). The adhesion process requires the presence of von Willebrand factor that binds the platelets to the subendothelial structures.

2. Platelet activation – follows thrombocyte adhesion and consists in synthesis and release of thrombocyte factors and some active substances (histamine, serotonin, adrenaline, immune complexes, PAF, arachidonic acid, TXA<sub>2</sub>, thrombin, etc.). All the released substances are designed to attract other platelets to the source, to activate them and determine platelet aggregation and promote coagulation.

3. Aggregation – represents the property of platelets to join together to form conglomerates.

Increased adhesion, activation and aggregation of platelets is marked in complicated pregnancy induced by hypertension, preeclampsia, placental abruption, HELLP-syndrome, prolonged retention of the dead fetus in utero, massive intra- and postpartum bleeding. Changes in adhesion, activation and aggregation functions of platelets are described differently in normotensive pregnant women [7, 8].

Von Willebrand factor as well as platelets is a component of coagulation that occurs at the primary hemostasis stage. FvW is the vascular (endothelial) component of the coagulation system and has a mediator function in the platelet adhesion process to endothelial injured structures. In addition, it is the transporting protein of VIII factor. The fvW level increases progressively during the physiological pregnancy (tab. 1). A parallel increase of fVIII is marked out. The increase in fvW far exceeds its normal level from a normal pregnancy in obstetric complications, the appearance and development of which are attributed to endothelial dysfunction (e.g. from preeclampsia) [9].

Essential changes in the blood coagulation system in pregnant women are determined by an increase of coagulation factors and a concomitant decrease of inhibitors of blood coagulation (anticoagulants). Factors with direct contribution to blood hypercoagulability (with the exception of XI and XIII factors) during pregnancy are: fI (fibrinogen); fVII (proconvertin); fVIII (antihemophilic A factor circulating in plasma associated with von Willebrand factor); fX (Stuart-Prower factor); fXII (Hageman factor); fvW (von Willebrand) (tab.1). The IX (antihemophilic B factor or Christmas factor), II (prothrombin), and V (proaccelerin) factors increase insignificantly or remain unchanged (tab. 1) [2, 6, 9, 10]. The high serum concentration of coagulation factors is reflected on the diagnostic parameters of blood coagulation during pregnancy, marked by shortening of coagulation time; shortening of PT and aPTT (sometimes below lower reference limits); increase of thrombo-elastographic parameters such as maximum clot firmness (MCF) and maximum amplitude (MA) [4, 11-14].

The serum level of fibrinogen in pregnancy at term constitutes (4–6 g/l) (tab.1), a double exceeding as against its reference values outside the pregnancy (2-4 g/L). Thus, the fibrinogen level considered normal for non-pregnant status – 2 g/l, in postpartum bleeding (hypo-atonic) may indicate the loss of a significant amount of blood [1, 15-17].

Increased formation of thrombin-antithrombin complexes (TAT), prothrombin fragments 1 and 2 in the second and third trimester of pregnancy is another indicator of hypercoagulability in pregnant women. The TAT complex is formed as a result of the interaction of these factors; it is a non-active complex, the formation of which is followed by the loss of activity of both components, thrombin and antithrombin. The presence of serum complexes TAT is a marker of increased thrombin formation and their progressive increase may indicate a possible depletion of antithrombin. Prothrombin fragments 1+2 (FP1+2), as well as TAT complexes, are indicators of thrombin formation. FP1+2 fragments are generated during prothrombin transformation into thrombin (tab. 1) [3, 18-20].

With the evolution of pregnancy the fibrinopeptid A concentration increases. Fibrinopeptid A is a marker of fibrin formation. Under the proteolytic action of thrombin the fibrinogen is cleaved into fibrinopeptids A, B and fibrin monomers. The serum level of fibrinopeptid A is maximal in the last trimester of pregnancy, the increase of which in

plasma indicates increased formation of thrombin and fibrin generation in physiological pregnancy (tab. 1).

Table 1

## Changes of hemostasis system in pregnancy

Physiological components of blood	Out of pregnancy	In pregnancy
Platelets	150-350x10 <sup>9</sup>	Unchanged
Von Willebrand (fvW) factor	100%	Increases
Fibrinogen (fl)	2.0-4.5 g/l	4.0-6.5 g/l
F II (prothrombin)	75-125%	100-125%
F V (proaccelerin)	75-125%	100-150%
F VII (proconvertin)	75-125%	150-250%
F VIII (antihemophilic A factor)	75-150%	200-500%
F IX (antihemophilic B factor or Christmas factor)	75-125%	100-150%
F X (Stuart-Prower factor)	75-125%	150-250%
F XI, antihemophilic globulin C (Rosenthal factor)		Does not change
F XII (Hageman factor)	75-125%	100-200%
F XIII (fibrin stabilizing factor)	75-125%	35-75%
Prekallikrein		Does not change
Kininogen with high molecular weight		Does not change
Protein S	100%	Decreases(↓)
Protein C	100%	Does not change/ increases resistance to protein C
Antithrombin III	80-130%	Does not change
Heparin cofactor II		Increases
Complexes TAT		Increase
Fragment 1 of prothrombin		Increases
Fragment 2 of prothrombin		Increases
Fibrinopeptid A		Increases
Complexes PAP		Increase
Tissue plasminogen activator(t-PA)	1.6-13µg/l	3.3-9.2 µg/l (↓)
TAFI		Increases
Inhibitors of plasminogen activator (PAI-1, PAI-2)	100%	Increase
Thrombomodulin		Increases
Fibrin degradation products (FDP)		Increase
D-dimers	<0.5 mg/l	0.13-1.7 mg/l

There are a number of factors with inhibitory action on blood coagulation preventing in such a way the formation of thrombi. Some of the important physiological inhibitors are antithrombin, protein C, protein S, heparin cofactor II, tissue factor pathway inhibitor or coagulation extrinsic pathway inhibitor (TFPI). Hypercoagulability during pregnancy is favoured/supported by changes of anticoagulants marked by a significant reduction (40-50% decrease in protein S) or neutrality (e.g. antithrombin, protein C, which remain unchanged). Antithrombin III – powerful inhibitor of blood

coagulation by inactivating most enzymes: thrombin (f II), fIX (antihemophilic B or Christmas factor), fX (Stuart-Prower), f XI, fXII (Hageman factor), and of VIIa complex factor and tissue factor.

Protein S is an anticoagulant that works in association with protein C. The decrease of protein S during pregnancy reduces the amount of thrombomodulin-thrombin-protein C and S complexes formation, thus diminishing their inhibitory action on V and VIII factors with increased procoagulant activity of the blood. In pregnancy the level of thrombomodulin increases [2, 21-23].

Out of pregnancy the interaction of the mentioned anticoagulants works differently. At the endothelial cells level thrombomodulin binds thrombin. The formed complex activates the protein C which in the presence of proteins S and Ca<sup>2+</sup> leads to a decrease in blood coagulation through activation of factors V and VIII.

One of the important mediators of blood coagulation is the tissue factor (TF). In pregnancy a substantial increase in tissue factor concentration in decidua, myometrium, placenta, fetal membranes (especially in amnion) and amniotic fluid is determined. Inhibition of TF activation is accomplished by the tissue factor pathway inhibitor (TFPI) which has anticoagulant impact, the placenta being an important source of TFPI production and release in the maternal circulation. Thus, the concentration of TFPI increases significantly and progressively in the physiological pregnancy, the maximal level of which is reached in the pregnancy at term, with a dramatic decrease close to the non-pregnant level in the first postpartum day [1, 20, 21, 24].

## II. Fibrinolysis and fibrinolytic activity in pregnancy

Fibrinolysis is a mechanism of prevention of thrombosis, consisting of a set of reactions that lead to fibrin degradation with a repermeabilization of the injured vessels and resumption of blood circulation. Plasmin is the enzymatic key of fibrinolysis that plays the role of thrombus lysis. The plasmin is formed from the activated plasminogen (in circulation the plasminogen is inactive). The activation of plasminogen (under the influence of fibrinolysis activators) is accompanied by its transformation into plasmin, and the plasmin acting on fibrin degrades it into fragments until final products are formed (fig. 2).

Plasmin is inactivated by antiplasmins (inhibitors of fibrinolysis with action on plasmin) – α<sub>2</sub>-antiplasmin and α<sub>2</sub>-macroglobulin (fig. 2), with the formation of plasmin-antiplasmin complexes (PAP), the concentration of which increases in the physiological pregnancy. The increased PAP complexes concentration during pregnancy is also due to the increase in antiplasmins. Plasmin in the formed complexes (PAP) loses the ability to destroy the fibrin.

Fibrin degradation product (FDP) increases progressively in pregnancy through increased formation of fibrin and secondary enhancement of fibrinolysis. Excessive production of FDP (e.g. in obstetrical complications that involve coagulation system activation, preeclampsia, abrupt-

tion placentae, DIC syndrome, etc.) has an anticoagulation impact and inhibits blood coagulation [5, 25].

A more specific indicator for the fibrinolysis process than FDP is D-dimers. The level of D-dimers begins to gradually increase from the 1st trimester of pregnancy, so that at the end of pregnancy its levels may be 3-4 times higher than the initial level. Significant increase in D-dimers is determined in pregnant women with complications of pregnancy (e.g. DIC syndrome, thrombosis of deep veins, thromboembolic complications in pregnancy, etc.) (tab. 1). Excess concentration of D-dimers in such complications indicates activation of fibrinolysis preceded by the activation of coagulation cascade with excessive fibrin formation.

D-dimers and PAP complexes are markers of the fibrinolysis process. Thus, hemostasis markers change during pregnancy, reflecting the increase in thrombin generation (fragment 1 and 2 of prothrombin, TAT complexes, fibrinopeptid A) on the one hand, and increase of fibrinolysis (D-dimers, PAP complexes) on the other hand [21, 26-28].

Similar to the coagulation system, the fibrinolytic process is the result of the interaction of activators and inhibitors. At the action of fibrinolytic activators the endovascular deposits of fibrin are removed, but the inhibitors prevent premature lysis of the hemostatic thrombus that could lead to a prolonged bleeding. The fibrinolysis can be activated in two ways – extrinsic and intrinsic [10, 11, 23, 24].

The activators of extrinsic fibrinolysis are tissue plasminogen activator (t-PA); U-PA urokinase and activators of bacterial origin (streptokinase, staphylokinase, proteolytic enzymes, e.g. trypsin). The activation of intrinsic fibrinolysis is triggered by fXII (Hageman), kallikrein. The final effects of the activators of both pathways of fibrinolysis are unanimous, to transform the plasminogen into plasmin.

The fibrinolysis inhibitors act upon the enzymes (plas-

minogen and plasmin) involved in the most important fibrinolysis reactions: 1. The inhibitors of the tissue activator of plasminogen (t-PA) impede in such a way the transformation of plasminogen into plasmin; 2. Inhibitors with direct action on the plasmin (the effect of stopping the thrombus lysis) (fig. 2).

The fibrinolysis inhibitors to neutralize the tissue activator of plasminogen are collectively called PAI (plasminogen activator inhibitors): PAI-1 – produced by endothelial cells, platelets, hepatocytes and stimulated by proinflammatory cytokines; PAI-2 – is met exclusively in pregnant women, produced by the cells of chorionic villositities, progressively increases in pregnancy, returning to normal values 6 weeks after childbirth; PAI-3 – a powerful inhibitor of protein C.

Both substances, PAI-1 and PAI-2, can inhibit the activators of the intrinsic pathway of fibrinolysis (t-PA and U-PA).

The inhibitors with direct action on the plasmin are  $\alpha_2$ -antiplasmin,  $\alpha_2$  macroglobulin,  $\alpha_1$  antitrypsin. The fibrinolysis inhibitor activated by the thrombin TAFI. TAFI modifies fibrin filaments, inhibiting the binding of plasminogen to the fibrin network and implicitly its activation to plasmin;

The activity of the fibrinolysis system is opposed to the activity of coagulation system, marked by the decrease in activators and increase in inhibitors, with subsequent suppression in the fibrinolytic system in pregnancy.

Changes in fibrinolysis activators during pregnancy:

- ◆ Plasminogen increases but its fibrinolytic activity decreases;
- ◆ Decrease in tissue plasminogen activator (t-PA) due to the increase of the levels of inhibitors of plasminogen activators during pregnancy – PAI-1 and PAI-2.

Changes in coagulation inhibitors in pregnancy:

- ◆ Increase in inhibitors of plasminogen activator – PAI-

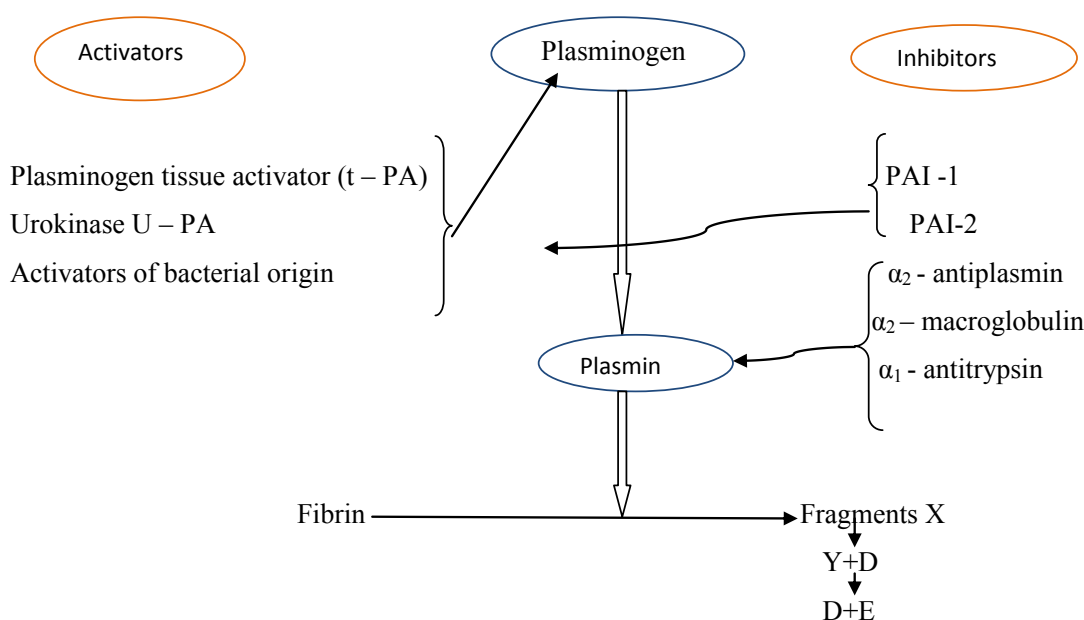


Fig. 2. Fibrinolysis and regulation of activity in fibrinolytic system.



1 and PAI-2. In particular, the inhibition of fibrinolysis in pregnancy is due to the increase of inhibitor of type 2 (PAI-2) of the plasminogen activator.

- ◆ Significant increase of inhibitors with direct action on plasmin –  $\alpha_2$  antiplasmin;  $\alpha_2$  – macroglobulin,  $\alpha_1$  – antitrypsin.
- ◆ Increase of the fibrinolysis inhibitor, activated by the thrombin – TAFI. TAFI reaches maximal values up to 35-39 SA with a rapid decrease in 24 hours after childbirth.

### Conclusions

The hemostasis system in pregnant women is marked by an increase in coagulation at each stage (from endothelium to circulatory factors of coagulation) which presumes the risk of thrombo-embolic complications, and the inhibition in the fibrinolytic system prevents peripartum bleeding.

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