ORIGINAL ARTICLE

Pregnancy and Hemostasis: From Physiology to Pathological States

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ABSTRACT

The pregnancy infers important changes of the balance of the hemostasis, which associates one hypercoagulability acquired in an inflammatory state. The increase of the rate of coagulation factors, on the one hand, and the decrease of the fibrinolytic activity and the rate of the physiological inhibitors of the coagulation, on the other hand, are at the origin of the hypercoagulability. The aim of this paper is to put the point on the physiological modifications of the hemostasis during the pregnancy as well as the various pathologies which can arise. The specific pathologies of the pregnancy are defined by their appearance bound to the pregnancy status. Often the pathologies predisposing to the bleedings are bound to platelet abnormalities. Other pathologies of the coagulation are linked to hereditary deficits in factors of the coagulation or to deficits in Vitamin K. In these cases, the anomalies of the hemostasis are variably corrected and their coverage depends on the level of correction of every anomaly. The pathologies at thrombotic risk include the hereditary and acquired thrombophilia. An evaluation of risk thromboembolic is essential for the implementation of an etiological and/or anticoagulating treatment, the best adapted.

Key words: Pregnancy, hemostasis, physiological modifications, hemorrhagic and thrombotic complications

INTRODUCTION

A normal pregnancy is associated with very important hemostatic modifications with a change of numerous hematological parameters; it is marked by a physiological hypercoagulability described by certain authors as a disseminated intravascular coagulation (DIC) offset low grade.

This pro-coagulating state allows to decrease the hemorrhagic risk during the delivery and the post-partum. Besides, these modifications can engender hemorrhagic and/or thrombotic complications or then pathological pregnancies.[1]

PHYSIOLOGICAL HEMOSTASIS DURING THE PREGNANCY

All the aspects of the hemostasis can be disrupted during a normal pregnancy, like: A higher concentration of the majority of coagulation factors and/or lower concentrations of certain natural anticoagulants and decrease of the fibrinolytic activity with preservation of the placentary function during the pregnancy, this predisposes to hypercoagulability state [2-4].

Due to the hormonal changes during the pregnancy, this phenomenon would protect probably the woman of a lightning bleeding during the delivery, but in return, it would predispose to thromboembolism which is more marked around the term, around the immediate post-partum, and continues during at least 6 weeks.[4]

The normalization of the factors of coagulation is made in 3 in 6 weeks on average; the hypofibrinolysis becomes more marked at the end of pregnancy (30 min after the delivery).

After the immediate separation of the placenta and until the 3rd h of the immediate postpartum, the pro-coagulative,

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proplatelet, and hypofibrinolytic activity is in its peak, which explains the important increase of the rate of D-dimer.

HEMOGRAM OF THE PREGNANT WOMAN

The hemogram is a biological examination participating in the supervision of any pregnancy.

The interpretation of the results has to take into account the physiological modifications linked to pregnancy and the clinical context.

A variation of the rate of the hemoglobin is observed at the pregnant woman's; there is a physiological anemia, which is secondary compared with the independent and unequal variations of cell volume and plasma volume. A reduction in the rate of hemoglobin is noted from 8th weeks of amenorrhea (WA), and until 22th WA, date in which one it stabilizes is placed next of 11 g/dl at the time of the delivery.[5]

We note a progressive increase of the plasmatic volume with a stabilization toward 35th WA at a 50% rate upper to the basal volume and being able to achieve 1000 ml in 1500 ml during a twin pregnancy. This increase is favored by the maternal weight, the fetal size, and the multiparity.

The total spherical volume increases in a lesser, especially clear way from 36th WA and until the delivery, on average of 300 ml, representing one-third of the increase of the plasmatic volume. This conflict entails a false anemia by hemodilution.[6]

Further to the increase of the spherical volume and the maternal hypererythropoiesis. The nutrient need, the iron in particular, increased and become imperative, which explains the frequency of the anemia by military deficiency, especially in case of repeated or twin pregnancy or of insufficient contribution.

In contrast, changes in leukocytes during pregnancy are moderate; neutrophil leukocytosis is almost constant in the second trimester, remaining close to 10,000–12,000/mm^3.[2]

MODIFICATION OF THE PARAMETERS OF THE PRIMARY HEMOSTASIS

Platelets

A moderate decrease of the figure of platelets is the anomaly most collectively observed [Table 1]. According to various studies, this physiological decrease varies from 8% to 15%, between the 5th month and the term, without hemorrhagic complication.[7]

In most of the cases, it is about "gestational thrombopenia," characterized by a normal figure of platelets before the pregnancy, a spontaneous correction after the delivery, and the absence of neonatal thrombopenia. Its physiopathology is multiple: Dilution by an increase of the plasmatic volume, platelet, maximum activation in the third quarter, connected to a physiological DIC in the minimal.[2,3,8] This is going to give rise to a destruction of blood platelets, compensated partially with an intense reactional production with an increase of the platelet volume, which is going to pull a platelet reactivity to various aggregating agents bound to a greater synthesis of thromboxane A2.

Fibrinogens and von Willebrand factor (VWF)

Most coagulation factors increase during pregnancy resulting in a state of hypercoagulability. It is essentially fibrinogen, factor VII, and VWF, while coagulation inhibitors and fibrinolytic capacity decrease. An increase in the plasma concentration of fibrinogen compared to the normal state is observed with a doubling rate for fibrinogen and factor VII and by three for VWF.[9] During pregnancy and the 1st week postpartum, the VWF rate rises early from 10th to 11th WA and with rates at 34th –35th WA is reflecting those of the term.

The recently discovered VWF cleavage protein ADAMTS13 has been poorly studied during pregnancy. A recent review has shown a progressive decrease in its maximum activity at 36th WA and immediate postpartum which is associated with an increase in VWF, which constitutes an increase in thrombotic risk and obstetric pathology.[10,11]

Changes in coagulation parameters

Most coagulation factors increase during pregnancy; the rate of factor VIII increases gradually during pregnancy, and the

Table 1: Parameters of hemostasis decreasing during pregnancy (extreme and mean values and standard deviations)[3]

Parameters	11–15th WA	26–30th WA	36–40th WA
Platelets (g/L)	106–358	101–331	91–317
Factor XI (%)	93±23	77±18	56±14
Protein S activity (%)	62–112	43–70	34–60

WA: Weeks of amenorrhea

increase in factor VII and X, which can reach 120–180%, is responsible for the shortening of the prothrombin time (PT) observed in mid-pregnancy and until the end of pregnancy [Table 1].[7] Since the factor V and II levels do not change during pregnancy, the factor XI rate decreases on average by 20–30%, with a gestational deficit of up to 40% of normal [Table 2].

Physiological inhibitors of coagulation

Inhibitors of coagulation decrease during pregnancy, antithrombin is not modified by hormones, and however, a moderate decrease of about 15% is observed in the last weeks of gestation. This decrease is the witness of an activation of coagulation, with physiological formation of placental intervillous thrombosis.[12] The evolution of protein C (PC) is variable depending on the term, an increased rate in the second trimester, followed by a decrease in the third, and then a new increase in the immediate postpartum.[13]

Conversely, there is a gradual and significant decrease in protein S (PS), close to 50% at term and persisting for 2 months in the postpartum, longer in the case of breastfeeding, and the concentration of PS is hormonally sensitive. It is, therefore, recommended not to dose PS during pregnancy, even early. The deficit of this inhibitor is associated with the increase of the factors VIII, IX, X, and VWF. It is also responsible for resistance to active PC acquired during pregnancy. Therefore, the thrombotic risk increases significantly with all these variations.[14]

The fibrinolytic system

The fibrinolytic capacity gradually decreases during pregnancy, to be minimal in the third trimester.[15] This hypo-fibrinolysis certainly contributes to the prevention of bleeding at the time of separation of the placenta, so apparently paradoxical, the rate of plasma D-dimers, which should decrease due to hypo-fibrinolysis increases gradually throughout the pregnancy to reach up to 198–266 mg/L over time (N: min 80 mg/L).[16]

The increase in the level of fibrinogen is, in fact, the witness of an increase in the thrombin generation, with excessive formation of fibrin clots, which in turn leads to a reaction fibrinolysis. The increased production of thrombin is maximal at the end of pregnancy and contributes to the prevention of the hemorrhage of the delivery. It is associated with a significant and progressive increase in activation markers of coagulation (1 + 2 fragments of prothrombin, thrombin-antithrombin complexes, and D-dimer plasma) whose rates are multiplied by 3–8 in the third trimester.[15]

Pregnancy induces a decrease in tissue plasminogen activator (TPA) and an increase in plasminogen activator inhibitor (PAI)1 and the production of PAI2 by the placenta. This last also secretes urokinase which will partially compensate for the decrease of TPA, but overall there is hypofibrinolysis which favors the increase of D-Dimer.[16]

HEMOSTASIS DURING DELIVERY AND POSTPARTUM

The increase in thrombotic risk is maximal in immediate postpartum and persists for at least 6 weeks. This increased risk of thrombosis is related to the rapid correction of thrombocytopenia, along with increased PS deficiency and the persistence of high VWF.[9] At the same time, the levels of coagulation factors normalize (in 3–6 weeks on average), as well as hypofibrinolysis of late pregnancy (30 min after delivery). The peak of procoagulant, proplatelet, and hypofibrinolytic activity occurs immediately after delivery and persists for the next 3 h, indicated by a significant increase in D-dimer.[9]

Abnormalities of platelets

Thrombocytopenia and pregnancy

The discovery of thrombocytopenia (platelets <100 g/L) during pregnancy is a common situation that can result from many mechanisms.[17] A standard coagulation assessment should be performed and also, the time of bleed to explore a possible associated thrombopathy. Platelet counts >50 g/L are considered sufficient for vaginal delivery.

Table 2: Parameters of coagulation increasing or remaining stable during pregnancy and postpartum (mean values and extreme values)[7]

Parameters	11–15th WA	26–30th WA	36–40th WA	1 week PP	8 weeks' PP	>12 weeks' PP
Fibrinogen (g/l)	3.6 (2.6–5.2)	3.8 (2.6–5.4)	4.4 (2.9–6.2)	4.6	2.6	2.7
Factor VIII (%)	122 (53–283)	188 (67–528)	212 (75–570)	213	86	109
VWF (%)	133 (56–313)	210 (80–492)	376 (133–1064)	351	93	78
VWF (%)	111 (60–206)	158 (75–332)	171 (87–336)	104	94	91
Factor X (%)	103 (62–169)	126 (74–203)	127 (72–208)	101	91	92
Factor V (%)	93 (46–188)	82 (34–195)	85 (39–184)	98	80	84
Factor II (%)	125 (70–224)	120 (73–214)	115 (68–194)	98	106	107

WA: Weeks of amenorrhea, VWF: von Willebrand factor

Isolated thrombocytopenia should be distinguished from thrombocytopenia associated with other abnormalities. An attempt should also be made to determine whether thrombocytopenia is recent or pre-pregnancy.

Gestational thrombocytopenia

It is the most common abnormality during pregnancy (60–75%) and is not associated with fetal impairment. It is thought to be related to pregnancy hemodilution and platelet consumption in the placenta. It is usually isolated and moderate occurring during the second trimester of pregnancy without hemorrhagic manifestation.[2]

Immune thrombocytopenic purpura (ITP)

ITP is an autoimmune condition that can be discovered during pregnancy or worsen during pregnancy, particularly in the second trimester.[17] In contrast to gestational thrombocytopenia, thrombocytopenia can be severe, <30 g/L, and cause hemorrhagic manifestations in the mother, requiring the implementation of emergency treatment with corticosteroids or intravenous immunoglobulin.

There is no absolute correlation between the mother's platelet count and the risk of neonatal thrombocytopenia, but this risk is even higher when the mother is thrombocytopenic and the ITP has a severe course.[18]

Infectious thrombocytopenia

They occur mainly as a result of viral infections by cytomegalovirus in particular or the human immunodeficiency virus. These attacks can, sometimes, be revealed by a mononucleosis syndrome that the biologist must be able to evoke when reading the blood smear.[19]

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura is a rare and severe thrombotic microangiopathy characterized by the association of fever, renal failure, neurological involvement, and mechanical hemolytic anemia with schizocytosis and thrombocytopenia. These manifestations are due to the formation of platelet thrombi in the microcirculation, resulting from an initial endothelial aggression, and the pregnancy seems to be a particularly favorable ground.[19]

Thrombopathies

Thrombopathies or functional abnormalities of platelets are constitutional pathologies of very variable clinical expression. Few cases of pregnancy associated with severe thrombopathies, such as Glanzmann's disease (absence of a platelet receptor, GPIIbIIIa) or Bernard and Soulier syndrome (absence of platelet GPIb), have been reported in the literature. The risk of bleeding exists throughout the pregnancy with an increased risk of miscarriage, but this risk is, especially, important at the time of delivery and postpartum in the absence of treatment.[20]

Thrombocytosis

Reaction thrombocytosis

These thrombocytoses (platelets >400 g/L) are most often observed in an inflammatory context that may be infectious or accompanies iron deficiency.[20]

Essential thrombocythemia

It is a chronic myeloproliferative disorder that mainly affects platelets. The blood count most often shows a platelet count >400 g/L and persistent, reaching values above 1000 g/L. It can be found in young women of childbearing age. This rare condition can also cause spontaneous miscarriages during the 1st month of pregnancy. Venous or arterial thromboses sometimes aggravate the clinical picture. Platelet anti-aggregation therapy (low dose of aspirin 100 mg/day) improves the chances of completing the pregnancy.

Fibrinogen deficiency and pregnancy

Afibrinogenemia is a very rare hereditary disease of blood coagulation. The majority of pregnancies in women with afibrinogenemia end in a spontaneous abortion between the 5th and 8th WA. To avoid abortion, it is essential to increase the level of fibrinogen to at least 1 g/l from the 4th WA and to maintain this rate throughout the pregnancy. The level of fibrinogen is increased by the regular administration of fibrinogen concentrate.[19,20]

PATHOLOGIES OF COAGULATION AND PREGNANCY

Congenital factor VII deficiency

The constitutional factor VII deficiency is a hereditary inherited autosomal recessive disease that is associated with a combination of a normal activated Partial thromboplastin time (PTM). and a decreased PT, whereas in acquired deficits secondary to excessive consumption and/or insufficient production, the previous PT values are normal.[21,22]

Heterozygous deficits are moderate and more frequent, with factor VII levels generally >30%, whereas homozygous deficits are more severe with factor VII levels <10%.[22]

Hemorrhagic manifestations related to a factor VII deficiency can be seen before or after delivery, during genital lesions, after episiotomy, or during cesarean section.

Female driver of hemophilia

There is no risk of bleeding in the mother, but it is the diagnosis of the child at birth that is important to take into account.

Hypovitaminosis K and pregnancy

During pregnancy, the common etiology of hypovitaminosis K is a lack of Vitamin K intake, due to uncontrollable vomiting or malabsorption.[23]

Based on the studies of pregnant women with hypovitaminosis K, a correction of hemostasis disorders was observed after administration of 10 mg/day of Vitamin K alone subcutaneously for 3 consecutive days and a correction rapid response (TQ) and hepatic cytolysis after 10 mg intravenous Vitamin K.

DIC during pregnancy

DIC is a syndrome acquired with a severe prognosis. DIC is a result of systemic activation of coagulation mechanisms with multiple fibrin deposition. In the most severe forms, excessive activation of fibrinolysis is observed.[2]

It is biologically most often manifested by thrombocytopenia, a deficit in clotting factors mainly fibrinogen, factors II, V, VIII and an increase in degradation products of fibrin and D-dimer.

The diagnosis of DIC during pregnancy is difficult because of the physiological increase of most coagulation factors and it is the repetition of dosages that reveal their rapid decline.

Mechanisms of the DIC are not only apparent by the circulation of tissue procoagulant substances but also a massive cellular activation with release of cytokines. Hypovolemic shock due to major bleeding worsens the DIC and a vicious circle develops with fatal outcome in the absence of urgent treatment.[24] The clinic depends essentially on the etiology, which may range from minimal bleeding to lightning bleeding.

The etiologies of obstetric DIC are represented by infections and trauma during pregnancy, retroplacental hematoma, fetal death in utero, HELLP syndrome, amniotic embolism, and finally, hepatic insufficiency and acute steatosis, promoting the rapid development of a DIC.

DIC requires urgent management by first treating the cause and shock by transfusions of fresh frozen plasma, platelet, and globular pellets, sometimes with anti-fibrinolytic.[2]

Willebrand disease

WD is a constitutional hemorrhagic affection. Transmission is autosomal, most of the time dominant. It is the most common congenital hemostasis abnormality in women; its prevalence is from 0.6% to 3% of the general population.[10] It affects both the sexes, but women have a more marked clinical symptomatology because of the additional risks of hemorrhage during menstruation and childbirths. This inherited abnormality of primary hemostasis is due to a total, partial, or qualitative-quantitative deficiency of VWF, associated with a factor VIII deficiency defining three types: Type 1 is characterized by a partial deficit (represents 75% of cases), type 2 by a functional anomaly (20% of cases), and type 3 by a total deficit (<5% of cases).[11]

During pregnancy, there is an improvement of moderate forms of type 1 following the physiological increase of factor VIII and VWF, and also in late pregnancy, the normalization of factor VIII and VWF levels prevents hemorrhagic complications.

In the other types of WD, whether types 2 or 3, treatment must imperatively be implemented in a specialized environment because the risk of bleeding is major.

All studies report an increased risk of delivery and postpartum hemorrhage due to a rapid decline in factor VIII and VWF postpartum levels. The risk of early postpartum hemorrhage, occurring within the first 24 h, is 22% in women with WM versus 5% in the general population and secondary postpartum hemorrhage is 20–28% versus 0.7%. This hemorrhagic risk is greatly reduced by breastfeeding because it maintains high levels of factor VIII and VWF.[10,11]

Other rare deficits

The rare deficits in coagulation factors include the constitutional deficits isolated in factors II, V, VII, X, XI, and XIII, fibrinogen and the combined deficits in factors V and VIII, and vitamin-K-dependent factors. These are rare deficits accounting for 3–5% of congenital deficits of coagulation.[25]

Thrombophilia and pregnancy

Thrombophilias correspond to a constitutional and/or acquired abnormality of the coagulation at risk of venous and/or arterial thromboses. The occurrence of thrombosis at thrombophilic women can be favored by the pregnancy. Thus, the concept of thrombophilia at the pregnant women means added thromboembolic risk and must discuss the modalities of an anticoagulant prophylaxis.

Compensation for excess thrombin formation by natural inhibitors could be deficient in patients presenting a thrombophilia: Antithrombin deficiency, PC and PS, and factor V or factor II gene mutation.[26,27]

ANTICOAGULANT TREATMENT DURING PREGNANCY

The use of anticoagulants is essential at certain women's during pregnancy (mechanical prostheses, valvulopathies, and thromboembolic antecedents). The fetal complications of maternal anticoagulating treatment include fetopathies and hemorrhagic risk.[28]

Low molecular weight heparins are anticoagulants the most commonly used today because of their pharmacokinetic properties allowing a single daily injection. An extended

anticoagulating treatment can be indicated during the pregnancy in case of constitutional hemostasis disorder, mechanical prosthesis, etc.[29]

In general, anti-Vitamin K (AVK) is misadvised during the pregnancy. Indeed, under AVK, malformation syndrome was described in 4–7% of the pregnancies exposed between 6 and 9 WA.

During the pregnancy, the prescription of the AVK must be exclusively reserved for exceptional cases where heparin cannot be used or exposed to a thromboembolic risk upper to that of the AVK.

In case of treatment by AVK, the substitution with heparin is imperative from 36 WA. AVK can be taken back after delivery. In every case, the INR targets remain unchanged.[30]

All the reference tables recommend to favor the use of the LMWH to unfractionated heparin (UFH) for their lack of transplacental passage, their efficiency, their ease of administration, their slightest risk of osteoporosis, and thrombocytopenia inferred by heparin.

The daily doses of preventive LMWH are on average 4000 IU and increased in case of significant overweight. The curative doses are adapted to the weight of the patient and administered in one or two daily injections.[29,30]

Platelet count control is recommended before the prescription of UFH and LMWH. It must be continued under UFH. It is not recommended under LMWH in the Anglo-Saxon recommendations.[30]

CONCLUSION

Pregnancy is accompanied by modifications of the coagulation and fibrinolysis. To make a voucher followed by a normal or pathological pregnancy, we have to have, first of all clinical information, take into account impacts of this pregnancy in the interpretation of routine hemostasis tests and finally direct the clinician to the examinations adapted. In particular in front of the urgency of postpartum hemorrhage or the picture of pre-eclampsia, such are the assets of the biologist to contribute to a better care of the pregnant woman.

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