REVIEW PAPER

THROMBOPHILIA AND PREGNANCY

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ABSTRACT

Leading cause of death in pregnant women still remains venous thromboembolism, with an incidence of 1.4 to 4.9 per 100,000 pregnancies. A special group of inherited and acquired coagulation disorders associated with a susceptibility to thrombosis is thrombophilia. Physiological changes during the pregnancy also contribute to the occurrence thromboembolic diseases (VTE) in pregnancy. Total rate of venous thromboembolism is 100 per 100,000 pregnancies and 200 per 100,000 births. Etiopathogenesis of obstetric complications in thrombophilia is not clearly defined, which is one of the reasons for the occasional failure of therapy. In pregnancies with hereditary thrombophilia the oxidative stress is considered to be a cause of complications, similar to preeclampsia. Based on the findings so far, additional research should clarify questions regarding the anticoagulants role in pregnancy loss prevention. In this paper, we analyze the effect of the screening on pregnancy outcomes, consider the justification for the use of anticoagulation therapy in difficult situations, discuss about previous knowledge in the field and argue the use of new specific protocols. In short, we address the justification for prescribing anticoagulants and evaluation of their effect within thrombophilia therapeutic strategies.

Keywords: *Thrombophilia; thrombosis; pregnancy; anticoagulants; heparin; therapeutics.*

ABBREVIATIONS

acL- anti-cardiolipin antibodies
AFS- antiphospholipid syndrome
anti-b2GPI - anti-beta2-glycoprotein
DVT- deep-venous thrombosis
ELISA- enzyme-linked immunosorbent assay
HELP syndrome - hypertension, elevated liver enzymes and thrombocytopenia
HIT- heparin-induced thrombocytopenia
LAC- lupus anticoagulant
LVMH- low molecular weight heparin
MTHFR- methylenetetrahydrofolate reductase
PAI 1- plasminogen activator inhibitor 1
PAI 2- plasminogen activator inhibitor 2
TAF I- activating fibrinolytic inhibitor
UFH- unfractionated heparin
VTE- venous thromboembolic diseas

INTRODUCTION

Thrombophilia is not a disease by itself, rather it is a special group of hereditary and acquired coagulation disorders associated with a propensity for thrombosis. High risk of venous thromboembolic (VTE) disease in gestation occurs as a result of physiological and hormonal modifications during pregnancy. Total rate of venous thromboembolism in pregnancy is estimated on about 200 per 100,000 childbirths. Deep vein thrombosis is far more common than lethal pulmonary embolism (1, 2). However, the primary cause of death for pregnant women continue to be VTE events, with incidence from 1,4 to 4,9 per 100,000 pregnancies (1, 2). Hereditary and acquired thrombophilia contributes to enlarged thrombotic events susceptibility (3). Acquired thrombophilia and total impact of hereditary for women out of pregnancy is low and most of the patients never experience a thrombotic attack. It is known that about a half of patients with thrombosis during pregnancy basically has one of the variants thrombophilia. Increased thrombogenicity mainly occurs due to gestation-related physiological shift. As a consequence of hormonal changes during pregnancy, plenty of coagulation factor activity, like factor VII, VIII, X, XII and fibrinogen were increased. Antithrombin simultaneously increases impedance to protein C activation, while decreases protein C activity in the II and III second and third trimester of gestation (4). Concentration of fibrinolytic inhibitor (TAF I) and plasminogen activator inhibitor 1 and 2 (PAI-1 and PAI-2) is also increased (5).

Additional factors in pregnancy have a contribution to the enhanced thrombotic events risk. Increased pressure of the gravid uterus on pelvic veins and reduced blood perfusion in the flow in the lower extremities result in a decrease in the rate of flow through the blood vessels. Relative compression of the left iliac vein in the flow through the pelvis leads to increased possibility formation of a blood clot in the left iliac vein (6). This phenomenon is particularly noticeable in the third trimester. Concomitant diseases like systemic lupus erythematosus, thrombocytopenia, diabetes mellitus, Cushing's syndrome, hypothyroidism, nephrotic syndrome, surgery and injuries with different risk factors, including increased body weight, reduced mobility, aging and smoking can increase risk of thrombosis. Women with previously spontaneous thrombosis have an enlarged risk of second attack developing with assessed relapse rate of 10.9% during pregnancy (7).

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (AFS) is an autoimmune disease of uninflammatory genesis that is characterized by thrombosis or complications in pregnancy in the surrounding of autoimmune thrombocytopenia and antiphospholipid antibodies (lupus anticoagulant-LAC, anti-cardiolipin antibodies-acL, antibodies to beta-2 glycoproteins). It belongs to the group of acquired thrombophilia disorders, dividing on two types: the primary one, when the etiological cause of the syndrome is not known and the secondary one, when the cause is known. Numerous criteria have to be met in order to diagnose this AFS. It involves the following: a) one or multiple documented thrombosis events and / or recurrent (three or more) early fetal losses in the first ten weeks of pregnancy; b) one or multiple miscarriages occurring after ten weeks or premature birth within less than or 34 weeks followed by placental insufficiency or preeclampsia. Adequate and well-defined laboratory criteria are necessary to monitor these clinical events. The one of the first criteria is lupus anticoagulant (LAC) which has to be isolated in plasma in two independent cases at least 12 weeks apart and/or IgG or IgM class (or both) anti-cardiolipin (acL) antibodies in plasma, in medium to high titers (≥40 GPL and/or MPL or greater than the 99th percentile by ELISA). Moreover, IgG or IgM classes of anti-beta2-glycoprotein (anti-b2GPI) has to be detected in plasma in two or more repeated measurements, with surely 4 month distant. Pregnant women with AFS have 15.8 times increased risk of blood coagulation during pregnancy.

There is a strong and significant correlation between increased titer of antiphospholipid antibodies and the pregnancy loss (8). Mutation of prothrombin gene and factor V Leiden are the very common abnormalities in AFS. These mutations represent the main genetic abnormalities associated with VTE with total of 2-5% of these mutations in the Caucasian population (9). Mutation occurs as a result of adenine replacement by guanine and as a consequence factor V is not any more sensitive to protein C. It is estimated that about 40% of pregnant women who have the factor V Leiden will have one thromboembolic event (10). The risk of VTE is approximately 8 times higher if the person is heterozygous and 80 times if the person is homozygous (4). The mutation of prothrombin 20210 is the result from a guanine substitution by adenine in non-coding position 20210, which is leading to a prothrombin increase in plasma (1). Total of 17% of patients who develop venous thromboembolic disease during gestation, had the mutation of prothrombin G20210A. Previously conducted meta-analysis that included results of 79 studies, assessed the gestation related VTE (11). Another study valued that 1 in 200 pregnant women who are heterozygotes for prothrombin G20210A mutation 1 in 500 ones who are heterozygotes for factor V Leiden would experience thrombosis during pregnancy (11).

COAGULATION PROTEINS DEFICENCIES

Hypercoagulable condition may be due to normal coagulation proteins deficiency. During pregnancy, protein C, protein S, and antithrombin abnormalities are linked with thrombophilia. Like previously mentioned, alteration in coagulation factors happens due to physiological changes during pregnancy. Complete absence of mentioned factors leads to more intense changes in mechanisms of coagulation. Deficiency of these coagulation proteins increases the risk for VTE incidence in pregnancy. This ratio is 3.2 higher for women with protein S, 4.7 for antithrombin and 4.8 for protein C deficiency (12). Moreover, at female with protein C deficiency the possibility for the thrombotic event

manifestation during pregnancy is 1 in 113 women, 1 in 3 women for antithrombin type 1 deficiency and 1 in 42 women for type 2 antithrombin deficiency (12).

OTHER GENE MUTATIONS

The association of mutations in MTHFR with thrombophilia with remains debated. Higher concentration of homocysteine which crucial for vitamin B9 and B12 metabolism is a result of C667T mutation in the MTHFR gene. Deficiency of homocysteine in gestation can be natural physiological consequence of pregnancy (1). Moreover, increased VTE risk during gestation is not related with the homozygous mutations in the MTHFR gene (1, 8, 13). According the aforementioned, all hereditary thrombophilia, except the MTHFR mutation, may be related with a higher VTE risk during gestation. Hereditary disorders which are considered the low-risk for thrombophilia events during the pregnancy are: heterozygosity for factor V Leiden, heterozygosity for prothrombin G20210A and protein C or protein S deficiency (13). Hereditary disorders which are considered the high-risk for thrombophilia events during the pregnancy are: deficiency of antithrombin, factor V Leiden homozygosity and prothrombin G20210A mutation homozygosity. The most common hereditary thrombophilia is factor V Leiden heterozygosity, a gene mutation of prothrombin G20210A, homozygosity for 4G/4G (PAI-1) and hyperhomocysteinemia (methylenetetrahydrofolate reductase mutations F677T) (14).

INFLUENCE OF THROMBOPHILIA ON DETRIMENTAL PREGNANCY OUTCOMES

The impact of thrombophilia on adverse outcomes of pregnancy is debated. There are numerous adverse pregnancy outcomes related to thrombophilia, preeclampsia, placenta abruption, intrauterine growth retardation and miscarriage. Etiopathogenesis of obstetric complications in thrombophilia is not clearly defined yet, which is probably one of the reasons for the occasional failure of anticoagulant drugs given for antithrombotic prophylaxis to pregnant women at risk. For example, in pregnancies with hereditary thrombophilia the oxidative stress responses had been also involved in pathogenesis of some important complications (e.g., preeclampsia) and antithrombotic medications does not influence these biological pathways. Previously conducted studies have attempted to deal with this issue, but it still remains unclear due to lack of wide agreements within medical community about true clinical significance of thrombophilia for fetal loss (1). The researchers analyzed data from 5000 pregnant women and found that there was indeed 10.9 higher risk for stillbirth for factor V Leiden carriers (15). However, link with early miscarriage was not established in the same study, and mutation of the prothrombin gene was not related with increased risk for adverse pregnancy outcomes.

Another study, included 100 pregnant women and concluded that there was relationship between factor V Leiden and stillbirth, as well as mutations of the prothrombin gene (16). However, with these mutations was only associated with the late not with the early fetal loss (up to 12th gestational week) loss (1). In the NOHA study, of total 32,000 patients included, in 18% of patients who experienced miscarriage, significant association with heterozygosity for factor V Leiden and prothrombin gene mutations with odds ratios 3.19 (95% CI 2.37-4.30, $p< 0.001$), was noticed (17). The miscarriages recorded generally happen after two month, with no association has been identified in early gestation. According to the results of previously mentioned and other similar studies, the absolute risk for stillbirth in women who had factor V Leiden had been estimated on 4.2% which is considered to be of small magnitude (18). Two meta-analyzes reported the evidence that an higher exposure of miscarriage in the 1. or 2. trimester, as well as repeated miscarriages were related with prothrombin G20210A or factor V Leiden mutation presence (19, 20).

The role of other thrombophilia disorders remains incompletely clear. The systematic evidence confirmed significant associations between miscarriages impedance to protein C activation and protein S deficiency. G20210A prothrombin mutation, factor V Leiden and protein S deficiency are related with late and repeated early miscarriage, but their influence on other pregnancy complications is contradictory. Between protein C deficiency, antithrombin and adverse pregnancy outcomes any association was not found, mostly due to their low prevalence (13). Between maternal thrombophilia and early miscarriage there was no association in Rock's cohort study conducted on over 491 patients (21). Heterozygous G20210A prothrombin gene, homozygous and heterozygous factor V Leiden mutation, activated protein C resistance, homocysteinaemia, or anti-cardiolipin IgG antibodies were more often associated with placental abruption (13).

Among several observational studies there is a general agreement that possible risk factors for placenta-mediated diseases, like spontaneous abortion, pre-eclampsia and placental abruption can be due to deficiency of folate, hyperhomocysteinaemia and homozygosity for the methylenetetrahydrofolate reductase thermolabile variant. One of the less well defined as an important factor was vitamin B12 deficiency (22, 23). The association between preeclampsia and thrombophilia is also controversial. The researchers estimated that total of 40% women with preeclampsia had thrombophilia. However, data are still inconsistent about other negative pregnancy outcomes because of the very common presence of other comorbidities in pregnant women which could confound the effects of thrombophilia such us HELP syndrome (hypertension, elevated liver enzymes and thrombocytopenia). Moreover, factor V Leiden was related with 2,5 higher risks for preeclampsia and severe hypertension during pregnancy.

Risk of preeclampsia can be 12,7 times increased with protein S deficiency and 21,5 times with protein C deficiency (24). Many authors have addressed the role of thrombophilia on intrauterine stagnation in fetal growth, that is, babies with

low birth weight. Previous study that examined the roles of prothrombin mutation genes and factor V Leiden, MTHFR homozygote and intrauterine growth retardation risk, have not detected any significant connection (16).

THROMBOPHILIA AND ANTICOAGULATION IN PREGNANCY

The low molecular weight heparin (LMVH), aspirin, unfractionated heparin (UFH), corticosteroids and intravenous immunoglobulin have been used in the treatment of thrombophilia during the gestation. Anticoagulant therapy of choice during pregnancy is low molecular weight heparin (LMVH), whereby standard doses of unfractionated heparin (UFH) can be used. There are significant preferences of low molecular weight heparin due to prolonged half-life, better bioavailability, simply use, reduced bone mass loss incidence and occurrence of HIT syndrome compared with unfractionated heparin. LMVHs are usually indicated during the first trimester and treatment continues into the 36th week of pregnancy (14). After that period, the change to unfractionated heparin is recommended in order to decrease the risk of complications of epidural anesthesia that may occur more frequently with LMWH due to their longer half-life. In randomized controlled trials, optimal prophylactic heparin or LMVH dose has not been established in pregnancy and therefore, the prescription was primarily empirically-based (14). It was suggested that pregnant women need higher doses of LMVH to achieve both therapeutic and prophylactic efficacy on treatment outcomes. The therapeutic dose of LMVH needs dose modification throughout gestation as the body mass of the women increases during this period. The highest anti-Xa activity in pregnant women is still lower than the activity of anti-Xa in women after childbirth. In women with higher possibility of recurrent VTE, in pregnancy, use of UFH or LMVH intermediate dose is recommended strategy for the VTE prophylaxis and it is supported by authoritative professional societies recommendations (e.g. ACCP- American College of Chest Physicians Evidence-Based Clinical Practice Guidelines) (8).

Table 1. The doses and route of administration of parenteral anticoagulants in pregnancy

Drug	Prophylactic dose, low risk	Prophylactic dose, moderate to high risk	Therapeutic dose
Unfractionated Heparin	5000 IU/12 hours	10000 IU/12 hours	
Enoxaparin (Clexane®)	40 mg daily	40 mg/12 hours or 1 mg/kg daily	1 mg/kg/12 hours
Dalteparin (Fragmin®)	5000 IU daily	5000 IU/12 hours	100 IU/kg/12 hours
Nadroparin (Fraxiparine®)	3800 IU daily	3800 IU every 12 hours	100 IU/kg/12 hours

*for deep-venous thrombosis (DVT) and venous thromboembolism (VTE); prophylactic doses for moderate to high risk pregnant women are also referred as intermediate dosing regimen

The mechanisms of action of heparins include the interaction with antithrombin (also referred to as antithrombin III or, more recently, serpin family C member 1). Binding of indirect thrombin inhibitors, such as heparins, increases the catalytic antithrombin activity up to thousand fold. Therefore, heparin and LMWHs in fact have no intrinsic anticoagulant action but increase the activity of antithrombin on its inhibition of different coagulation factors. UH acts on factor Xa and thrombin inhibition to a similar extent but LMWH, due to shorter molecules, primarily inhibit factor Xa activity and in lesser extent the activity of thrombin (depending on the preparation). Heparins can be administered for prophylaxis purposes or as therapeutic doses. Therapeutic doses are recommended for acute thromboembolic events in pregnancy and in expectant mother with prosthetic heart valves (8, 11). Prophylactic doses (with regular monitoring) are recommended for pregnant women with idiopathic thrombosis in medical history, transient risk factors and with low or high risk of thrombophilia without occurrence of more than two thromboembolisms in medical history (8). For women with diagnosis of antiphospholipid syndrome, the use of prophylactic doses of low molecular weight or unfractionated heparin is recommended. Prophylactic dose of LMVH has a target of 0.1–0.3 units/mL for anti-Xa level, 4 hours after application. Intermediate-intensity anticoagulation therapy is recommended for patients with moderate to high VTE relapse risk (severe thrombophilia and previous DVT). Moreover, the intermediate dose of enoxaparin may consist of 40 mg/12 hours or enoxaparin applied in dose of 1 mg/kg once daily. Patients who require a therapeutic dose, enoxaparin can be used a 1 mg/kg/12 hours or 100 IU/kg/12 hours of dalteparin, with a 0.6–1.0 units/mL as a target factor Xa level,

4 hours after administration. According to PTT value, unfractionated heparin dose can be adjusted to reach a PTT between 1.5 and 2.5 times more than control parameters (8). In pregnancy, women with AFS and/or those with increased flow resistance in uterine arteries can require the addition of aspirin to basal heparin treatment which could be sometimes considered in clinical practice based on the results of some clinical trials. The studies reported that in expectant mother with positive antiphospholipid antibodies and recurrent miscarriage combination of aspirin and heparin in comparison with aspirin alone achieved 71% and 42% of live births, respectively (8).

The recommendations about risk stratification and indication for treatment of thromboembolism and prophylaxis in pregnant women with thrombophilia and/or previous thrombotic events (VTE) (8) are given by several professional societies and the guidelines of ACOG (American Association of Obstetricians and Gynecologists) are summarized in essential issues as follows:

A. Pregnant women with thrombophilia

1. Low risk: mutation heterozygous form mutation factor II G20210A, factor V Leiden, protein S and protein C deficiency

a. without prior VTE

- monitoring during pregnancy, without maintenance anticoagulant therapy
- LMWH or UH only prenatally
- anticoagulant therapy should be included prepartally only if there are additional risks (e.g. multiple trauma, fracture of the pelvis, hip or long bones, prolonged immobility after surgery)

b. with one previous episode of VTE not on long-term therapy

- antepartal treatment involves prophylactic or intermediate dose of LMVH or monitoring without therapy.
- postpartum anticoagulant treatment with intermediate doses of LMWH or UH

2. High-risk: antithrombin deficiency, an existing double heterozygous mutation for factor V Leiden and factor II G20210A, homozygous factor V Leiden and homozygote for mutation factor II G20210A.

a. without previous VTE

- prophylactic administration of LMWH or UH, antepartal and post-partum.

b. with a prior episode of VTE

- anticoagulant therapy during gestation and childbirth with therapeutic doses of LMVH or UH
- It is necessary postpartum for the patient to receive LMVH for six weeks with therapy higher or at the values of prepartum therapy.

B. Pregnant women without thrombophilia

1. Previous episode of VTE related with individual transitory risk that has not been present for a long time (excluding pregnancy or other estrogen-induced risk factor)

- monitoring without anticoagulant drugs pre- and postpartum.
- women with one VTE without thrombophilia, are required to receive prophylactic dose of LMVH prepartum and postpartum

2.Women who had one episode of VTE, paired with pregnancy or estrogen dependent factor without additional risk factors and who did not receive long-term anticoagulant therapy

- need to receive prophylactic dose prepartum and postpartum

3. Women who had two or more VTE

a. long-lasting anticoagulant drugs not used

- is required to receive prophylactic or therapeutic dose of LMWH antepartum and anticoagulant therapy postpartum (8)

b. therapeutic dose of LMVH or UH used

- anticoagulant therapy to be continued prepartum and postpartum

Intermediate dose indicates a dose adjustment of therapy due to weight gain in pregnancy, so it is recommended that you take 40 mg Enoxaparin twice daily or 1mg / kg Enoxaparin once daily. This intermediate dose should be started after the 20th week of gestation. Prophylactic or intermediate doses are used in pregnancy without thrombophilia, at moderate or high risk of developing venous thromboembolism (single thromboembolism, pregnancy-related or increased estrogen levels, and multiple thromboembolisms).

CONCLUSION

The changes occur in the woman's body during pregnancy that lead to the appearance or increase of all elements of Virchow's triad contributing to thrombosis: endothelial damage, hypercoagulability and the venous stasis. Given the severity of the possible complications, withholding administration anticoagulants for prophylactic or therapeutic purposes when they are indicated represents serious professional mistake. Women with hereditary thrombophilia in their

anamnesis should be informed that expert recommendations regarding the indication for anticoagulant prescribing are not uniformly agreed and they may vary depending on the country and/or health-care settings. In addition, further research is needed in order to clarify definitively the link between the uses of anticoagulation drugs to successful pregnancy outcomes. More likely is that women with acquired thrombophilia will have benefit from anticoagulation therapy and they should be treated with personalized treatment approach, depending on risk stratification criteria and previous VTE episode experiences. Because there is a powerful connection between venous thromboembolism and hereditary thrombophilia, reasonable prevention is the timely detection of gene mutations. However, association between uteroplacental thrombosis and hereditary thrombophilia that leads fetal loss, preeclampsia, and intrauterine growth arrest fetal and placental abruption is still insufficiently understood issue, requiring further research.

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