Medicine

THROMBOPHILIAS – PREGNANCY RELATED RISK CATEGORIES

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ABSTRACT

THROMBOPHILIA REPERESENT A GROUP OF PROTHROMBOTIC CONDITIONS, EITHER AQUIRED OR INHERITED, WHICH PREDISPOSE TO THROMBOEMBOLISM. IT IS CHARACTERISED BY A HYPERCOAGULABLE STATE, A TENDENCY OFTEN REPETEAD OVER AN EXTENDED PERIOD OF TIME, WHICH CAN LEAD TO VENOUS THROMBOEMBOLISM AND/OR OBSTETRICAL SEVERE ADVERSE OUTCOMES. RECENTLY HAS BEEN SHOWN THAT THROMBOPHILIA IS ASSOCIATED WITH SEVERE PREECLAMPSIA, STILLBIRTH, ABRUPTIO PLACENTAE, RECURRENT FETAL LOSS AND INTRAUTERINE GROUTH RETARDATION. THIS REVIEW AIMS TO PROVIDE AN OVERVIEW OF THE DIFFERENT THROMBOPHILIAS, ACCORDING TO THEIR ETHIOGENY, CLINICAL EFFECTS AND PREGANCY RELATED RISK CATEGORY. THE LATEST THERAPEUTIC STRATEGIES ARE ALSO TAKEN INTO ACCOUNT.

***KEY WORDS** : THROMBOPHILIA, PREGNANCY, INHERITED, AQUIRED*

The thrombophilic disorders appear to be associated with some pregnancy related pathologies. These include recurrent embryonic loss, fetal loss, intrauterine growth restriction, preeclampsia and/or eclampsia, even HELLP syndrome, placental abruption and stillbirth [1].

Thrombophilias can be divided in two large categories, depending on the thrombogenic risk they determine. The low risk thromophilic profile include: heterozygous factor V Leiden mutation, heterozygous G20210A prothrombin gene mutation, protein S and protein C deficiency. The high risk thrombophilic profile include: antithrombin III deficiency, the association between both heterozygous factor V Leiden and G20210A prothrombin gene mutations, homozygous factor V Leiden mutation or homozygous G20210A prothrombin mutation.

There are also some additional risk factors which modify the individual global thrombogenic risk. These are called environmental factors. They include a first degree relative with a thrombotic event which occured before the age of 50 years, obesity, or smoking. Other additional factors are estrogen containing medications, such as oral combined contraception or hormonal replacement therapy. Furthermore, some other transient conditions are implied in the occurance of a prothrombotic state: pregnancy and the postpartum first six

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weeks period, surgery (especially orthopedic and pelvic ones), fractures, long time strict immobilization, or cancer [5].

According to their ethiogeny, thrombophilias are diveded in two main groups: aquired and inherited. The aquired thrombophilias are associated with a great variety of deseases, such as the anitpspholipid anitbodies syndrome, hyperhomocysteinemia, pregnancy and the first 6 weeks of the postpartum period, neoplasia, estrogen therapies, heparin induced thrombocytopenia, Behçet desease, inflammatory bowel diseases (ie Crohn's disease or ulcerative colitis, during their active stages).

The most important aquired thrombophilia is antipospholipid antibody syndrome. These antibodies occur at a rate of 1 to 5% in healthy patients, but their frequency is much higher in patients who are disgnosed with autoimmune deseases, such as systemic lupus erythematosus. The antiphospholipid antibodies are lupus anticoagulant and anticardiolipin antibodies. Patients with this syndrome have an increased risk of venous thrombosis. In pregnant patients, the antiphospholipid antibodies increase the risk of recurrent pregnancy loss, usually during the first 6 weeks of gestation [11]. Studies couldn't agree on the exact mechanism of thrombosis induced by this type of antibodies. The accepted mechanisms include modulation of the expression of the phospholipid binding proteins involved in the clotting cascade regulation, disfunctions of the endothelial cells, injury of the vascular endothelium mediated in an oxidative manner [8].

Hyperhomocysteinemia can result either from genetic factors, such as a mutation of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene or from environmental factors that affect its circulating level [7]. Theses include reduced intake of folate or vitamins B12 or B6, increased methyonine intake (from eggs, nut and seeds – especially sesame seeds, Brazil nuts, fish, meats, fast foods and cereal grains), smoking, high amounts of coffee intake, thyroid deficiency, renal impairment, drugs (such as methotrexate, anticonvulsivants, cyclosporine, steroids).

The inherited thrombophilias include genetic conditions. There is a strong interconnection between this category of thrombophilias and the environmental additional risk factors discribed before.

Most thrombophilias play an important role in the occurance of the venous thrombi, rather than the arterial ones. In the latter localization, the main role is played by the endothelial defect caused by atherosclerotic damages and the activated platelets. The arterial site of thrombosis is found in patients with antiphspholipid antibody syndrome and hyperhomocysteinemia. The venous thrombosis in usually associated with the inherited, genetic thrombophilias, in which case the activated platelets only play a minor role.

It has been noticed that a rare adverse outcome associated to a specific form of thrombophilia usually occurs in a population that has a high prevalence of a given inherited thrombophilia. Judging upon the different prevalence of the yet known genetic mutations implied in thrombophilias in different geographic areas, it can be assumed that a certain adverse outcome is more likely to be found in that specific region where the prevalence of the associated mutation is the highest.

In fact, many patients who have a form of thrombophilia never experience a complication during their entire life. The environmental factors seem to play no role in this scenario. We cannot approximate the exact risk of a serious adverse outcome in patients with aquired or inherited forms of thrombophilia. Nevertheless we can dived these patients in two large risk categories: high and low. Caution should be used in interpreting case-control studies among patients of a certain race, known for their high prevalence of thrombophilia, such as Caucasians.

In the past thrombophilia used to be asssociated with patients who had an unusual manifestation of venous thrombosis. This was the case of young age at the onset of the

desease, an insolite site of thrombosis (ie mesenteric or cerebral sinus veins), recurrent episodes of venous thrombosis or a significant family history. Presently, it is known that the risk of any venous thrombosis is incresead by the thrombophilia. Most of the patients who carry a thrombophilic mutation register their first episode of venous thrombosis in conjunction with a prothrombotic state, either aquired or transient.

The mean age at the time of the onset of the first thrombotic episode in this kind of patients is usually ten yers lower than in the general population. Thrombosis at a young onset age is considered a criterion of inclusion in the thrombophilic condition. The intrinsec prothrombotic state found in patients diagnosed with thrombophilia is not sufficient per se to determine a thrombotic event. It may otherwise determine the onset of thrombosis when other risk factors arise. These factors also include age, so that thrombosis in the older patients may lean on the thrombophilic disorders as well.

The most common inherited form of thrombophilia is the factor V Leiden mutation. It has a prevalence of about 5% in the general Caucasian population, while in the venous thrombotic group it raises to about 21% of the cases. It is transmited in a co-dominant autosomal way and it is the most frequent cause of hereditary thrombophilia in Caucasian population. This mutation is found in 10 to 20% of the patients who experience their first venous thrombotic event. It is also found în 40% of the patients under the age of 50 years at their fist venous thrombosis and in 60% of the pregnant patients with a venous thrombosis [9]. The risk of a thrombotic event depends on the mutation form, either homozygous or heterozygous.

The mutation responsible for this disorder makes activated factor V resistant to inactivation by the activated protein C. This is known as activated protein C resistance or APCR. The punctiform mutation takes place on the 1q23 chromosome, thus replacing the aminoacid arginine by glutamine in the position 506 of the proteic clotting factor V - the cleavage site for activated protein C. This mutation leads to a 10 fold slower inactivation of the factor V Leiden than normal, as well as a longer persistence of the modified clotting factor in the blood stream, with consecutive higher amounts of thrombin and eventually hypercoagulability. This mutation is held responsible for 85 to 90% of the cases with resistence to activated protein C. The individual risk of thrombosis increases 4 to 8 fold in heterozygous than in wild factor V genotype, while in homozygous the risk is 80 to 100 times higher. The risk is exponentially higher in patients who have other thrombotic risk factors, such as pregnancy, estrogen therapies or other coexisting genetic defects. The latter group includes protein S, protein C or antithrombin III deficiency, homozygous C677T mutation of MTHFR gene with conssecutive hyperhomocysteinemia. When diagnosed in pregnant patients, factor V Leiden may lead to high risk of recurrent pregnancy loss, especially during the second or third trimester [12]. The same goes for G20210A prothrombin gene mutation and homozygous C677T mutation of MTHFR gene. Screening for factor V Leiden can be usefull in patients who plan to get pregnant or to get oral contraception, in cases with family history of recurrent thrombosis with onset under the age of 50 years.

The prothrombin G20210A mutation, also called factor II mutation, is mostly exclusively present in Caucasians, in which the prevalence of the heterozygous form is about 2-3%. In the venous thrombosis group, it comprises about 7% of the patients, confering a 2 to 3 fold higher risk of VTE [6]. This is a point mutation in the non-coding region of the prothrombin gene, where guanine is replaced with adenine, specifically in the 3' untranslated region nucleotide 20210. This mutation is responsible for higher levels of the inactive form of prothrombin than it is to be found in the wild genotipe, a form that is otherwise normal in structure [3]. Hyperprothrombinemia is one of the most common risk factors for VTE, apart from factor V Leiden mutation and the non-O blood types.

The physiologic inhibitors of the coagulation cascade known today are protein S, protein C and antithrombin III. Any deficiencies in these natural anticoagulants generate a prothrombotic state, through the increased amount of thrombin. These disorders are found in about 1% of the general population, while in the venous thrombotic group they are found in 7% of the patients. The risk of VTE is 5 to 10 fold higher than in general population.

There are two forms of protein S found in the blood stream. About 40 to 50 percent of it is the active, free protein S. The rest of it is bound to a certain protein of the complement – C4b binding protein. This explains the tree different types of protein S deficiency, depending on the amount of antigen and its activity. The type I deficiency is characterised by reduced antigen level and activity; type II has a normal amount of antigen, with reduced activity; while type III is found in patients with total antigen level within normal range, but reduced level and activity of the free antigen. The different types of deficiencies are generated by many mutations which are only partially studied until now, and whom clinical significance is yet unknown. Antithrombin III deficiency is a very thrombogenic condition, though its frequency is lower than protein S or protein C deficiencies. There are over 250 mutations that can lead to reduced gene transcription, thus producing either a decrease of the antigen quantity and activity, or alteration of the structure and function, which is translated in normal antigen level, but with lower activity. The frequency of antithrombin III deficiency is approximately 1/2500 patients. In non-pregnant patients, the venous thromboembolism risk is 25 fold higher. In pregnant patients, this risk is substantially elevated, because of the prothrombotic state induced by pregnancy alone. Without a personal or family positive history, the risk is considerably reduced.

Elevated levels of the antihemophilic globulin, also known as clotting factor VIII:C, is also known to be a risk factor for venous thrombosis. This condition is found to respect a family clustering and is persistent over time. This shows at least partial genetic determinism, since the exact ethyologic mechanism remains yet unknown [16]. It is notewothy that the prevalence of the increased levels of factor VIII:C in the general population is the highest of all the inhertited thrombophilias taken under consideration, reaching about 11%. In the venous thrombosis group, the prevalence of this condition is also the highest one, about a quarter of these patients being diagosed with it.

Methylenetetrahydrofolate reductase (MTHFR) catalyses the reduction of 5,10-methylene-tetrahydrofolate to 5-methylenetetrahydrofolate, which is a cofactor implied in the remetilation of homocysteine to methionine. A point mutation in the MTHFR gene, C677T, gives rise to a thermolabile variant of the reductase, which in turn is 20% less efficient in metabolising the homocysteine. This hyeprhomocysteinemia usually occurs especially in patients with preexistent folate deficit. About 10% of the patients that experience a venous thrombotic event are diagnosed with hyperhomocysteinemia, while the prevalence in the general population is of 5% [20]. The homozygous C677T mutation is to be found in about 11% of the Caucasians. These patients have greater risk of obstetrical adverse outcomes such as chromosomial defects, fetal malformations, recurrent fetal loss, abruptio placentae and severe preeclampsia [13]. The risk of venous thromboembolism with late onset during pregnancy or during the first six weeks of the postpartum period is also increased in these patients. The heterozygous form of the C677T mutation implies no greater risk of hyperhomocysteinemia or thrombotic episodes. There is another possible mutation in MTHFR gene, known as A1298C. Neither its homozygous, nor its heterozygous forms induce hyperhomocysteinemia. On the other hand, the association between both heterozygous forms of each mutation, C677T and A1298C, may lead to similar severe outcomes as the homozygous C677T mutation of the MTHFR gene. This particular association is also held responssible for neural tube defects. Patients who carry the heterozygous form of MTHFR gene mutation have a 2 to 3 fold higher risk for spina bifida or anencephaly. The exact

mechanism of action of the MTHFR gene mutations is not sufficiently known. It is yet accepted that the associated hyperhomocysteinemia affects the vascular endothelial cells, thus causing venous thromboembolism and placental insufficiency.

A series of other thrombophilias have been taken under consideration. These include alternative factor V gene mutations, a promoting PAI-1 gene mutation, protein Z deficiency as well as mutations that lead to increased activity of other clotting factors genes. Despite their independent venous thrombosis risk which is rather low, when associated to the above mentioned mutations the thrombotic risk increases considerably.

Many studies have been conducted in the last decade in order to establish the determinism of inherited thrombophilias over different adverse obstetrical outcomes. Their results are often contradictory and demonstrate potential preferential reporting.

Prospective cohort studies found no association between inherited thrombophilias and recurrent pregnancy loss, although meta-analysis and retrospective cohort studies showed a possible association between first trimester pregnancy loss and genetic thrombophilias [19]. There is insufficient evidence to support the association between hereditary thrombophilias and an increased preeclampsia incidence [14]. Many case-control and cohort studies have been conducted to determine whether there is significant association between factor V Leiden and intrauterine growth restriction (IUGR). Their results were inconclusive [15]. There is a similiar lack of significant association between G20210A prothrombin gene mutation and MTHFR gene mutations on the one hand, and IUGR on the other hand. Placental abruption incidence has been found to be higher in patients with hyperhomocysteinemia, with a titer that rises over 15 μmol/L. These data are extracted from the Hordaland Homocysteine Study, which was a population-based study conducted in Western Norway on more than 18,000 men and women, during 1992-1999. It has also concluded that there is a slight association between the homozygous MTHFR C677T polymorphism and abruptio placentae.

Screening for thrombophilia is quite controversial. It can be useful if the results have an influence upon the clinical behavior. If the appropriate treatment is already indicated for other risk factors, the screening becomes useless. There are some clinical situations where screening has proven to be useful. These include personal history of venous thromboembolism, associated to incidental risk factors, such as bone fractures, surgery, long term immobilization [18]. The recurrence risk among pregnant patients with sych personal history is 16%. Another clinical situation when screening needs to be undergone is represented by patients with a fisrt degree relative who have personal history of venous thromboembolism with onset below the age of 50 years, without any other risk factors. Testing for thrombophilia is not routinely recommended in any other circumstances.

Testing for inherited thrombophilia in patients with recurrent pregnancy loss or placental abruption is not indicated. Although a possible clinical association has been demonstrated by some authors, there is insufficient data to support the conclusion that antepartum prophylaxis with heparine or low mollecular weight heparine would prevent a possible relapse in these patients. Nevertheless, screening for antiphospholipid antibodies might be suitable for patients with recurrent feal loss history.

There is insufficient data to sustain an association between inherited thrombophilia and intrauterine growth restriction or preeclampsia [17]. Therefore, screening or prophylaxis of these poor pregnancy outcomes is not recommended. Because of the lack of association between MTHFR mutations and obstetric pathologies, screening for homcysteine and MTHFR gene mutations are not indicated [10].

The therapeutic decision for the initiation of thromboembolism prophylaxis during pregnancy and postpartum period is influenced by the personal venous thromboembolism history, the severity of the patient's form of thrombophilia and the presence of any additional

risk factors. Every patient with a genetic form of thrombophilia should be assesed from the individual risk point of view, which can influence a great deal on the final therapeutic decision [4]. This decision should take into account some other major risk factors, such as the potential cesarian section, long term immobilization, obesity, family history positive for thrombophilia or venous thrombosis events.

Patients with low risk thrombophilias without a personal history of venous thrombosis or with a family history of VTE should only get antepartum surveillance, without anticoagulant prophylaxis. The same approach is recommended in patients without thrombophilia, having a previous single episode of VTE associated with a transient risk factor, whict is no longer present, other than pregnancy or estrogen therapy. In patients with low risk thrombophilia with a single previous VTE event, as well as in high risk thrombophilia without previous VTE episode, either clinical surveillance or prophylactic dose of low mollecular weight heparine (LMWH) should be used antepartum [2]. In patients with high risk thrombophilia not receiving any long term anticoagulation therapy, who have a history of a single episode of VTE or an affected first degree relative, with onset age below 50 years, prophylactic or adjusted dose regimen of LMWH should be used [2]. In patients with no form of known thrombophilia, with a previous single episode of VTE associated with a transient risk factor, either pregnancy or estrogen therapy, as well as patients whitout an associated risk factor, not receiving log term anticoagulation therapy, prophylactic doses of LMWH are recommended during antepartum period. The same prophylaxis should be done in patients with or without a positive diagnosis of thrombophilia, who have at least two episodes of VTE, but who are not receiving any anticoagulation therapy [2]. A therapeutic dose of LMWH is only indicated for patients who are already receiving long term anticoagulation therapy, either diagnosed with thrombophilia or not, but who have a personal history of two or more episodes of VTE [2].

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