Heritable Thrombophilia and Pregnancy Associated Thrombosis

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INTRODUCTION

Venous thromboembolism VTE is the major cause of morbidity and mortality in pregnant woman in industrialized countries. VTE is said to occur at the rate of about 1 per 1000 pregnancies[1,2]. It is important to note that the frequency of asymptomatic DVT is probably not negligible specially in multiparity women as shown by the results of the Sirius Study in which multiparity was found to be a risk factor for VTE[3]. A small number of studies have clearly shown that in women with heritable thrombophilia (antithrombin, protein C deficiency), the risk of VTE during pregnancy is significantly increased but these thrombophilias are rare[4-6]. The more recently discovered thrombophilias in particular the Factor V Leiden and the F II 20210A gene mutation are much more frequent. Their discovery has stimulated clinical investigation on this subject[7-10]. The most common inherited thrombophilia is heterozygosity for the F V Leiden since in control caucasian populations, its incidence is about 6%.

Moreover, among pregnant women with VTE, the search of thrombophilia is positive in about 50% of cases[2].

The existence of a physiological hypercoagulable state in every woman during pregnancy has been well documented. The frequently positive Dahlback test for the search of F Va resistance to activated protein C in women without associated F V Leiden thrombophilia is related to this hypercoagulable state.

The evaluation of the level of risk in different heritable thrombophilias is not an easy task. There are two main methods to evaluate the thrombotic risk associated with pregnancy in women with heritable thrombophilia. In the first one (method I), the frequency of pregnancy-associated VTE is determined prospectively or more often retrospectively in women with thrombophilia. This method is recommended in women with a rare variety of thrombophilia such as AT, PC or PS deficiency. In the second method (method II), women with VTE associated pregnancy are studied in order to determine the frequency of heritable thrombophilia. It could be more appropriate to perform this study in fa-

mily members rather than in propositi. This second method is recommended for thrombophilias such as F V Leiden and F II 20210A gene mutation which are more common than AT, PC or PS deficiency.

This evaluation is essential in order to determine the possible indication of a prophylactic treatment which should be adjusted to the level of risk[11,12]. Although the genotype of heritable thrombophilias is well defined, the phenotype, i.e. the clinical expression of the gene mutation is heterogeneous[13].

The Increasing Number of Heritable Thrombophilias

Since the discovery in 1965 of AT deficiency by Egeberg in Norway the number of thrombophilia has progressively increased (Table 1)[14]. Some are well documented while some genetic mutations are good candidates requiring further studies. The increase in F VIII seems an important acquired or congenital cause of predisposition to VTE[15,16]. We have analyzed carefully the whole literature in order to evaluate the most likely level of risk expressed, when available, in odds ratio (OR) or in relative risk (RR) for each category of thrombophilia (Tables 2,3).

An approximate estimation of the relative risk can be calculated by comparing the frequency of pregnancy-accociated VTE in thrombophilias with the generally accepted risk in the normal population (1 per 1000 pregnancies).

More recently, double or triple association of genetic mutations have been encountered, the more common being the combination of heterozygous F V Leiden and heterozygous F II 20210A. The calculated frequency of this double thrombophilia is about 1/1000 in a caucasian control population.

Once the respective ORs have been determined for the 2 different genetic mutations, one has to multiply these ORs to anticipate a global OR for the multigenic thrombophilia. Epidemiological studies are necessary to determine the additive or the multiplicative characteristic in different combined thrombophilias[21].

In some small groups of patients the OR is very high such as for combined F V Leiden and heterozygous AT deficiency type I. Gerhardt et al in pregnant women with F V and F II mutations has found an extremely elevated OR for VTE with a very wide 95% confidence interval[22].

Table 1. Risk factors for venous thromboembolism

Hereditary	Acquired	Mixed
	Permanents	
AT deficiency	Age	Hyperhomocysteinemia
Protein C deficiency	TE antecedents	F VIII increase
Protein S deficiency	Antiphospholipid antibodies	Activated protein C resistance without F V-Leiden mutation
F V Leiden mutation	Cancer	
Prothrombin gene 20210A	Myeloproliferative syndrom	
Blood group ABO	Obesity	F IX increase
Plasminogen deficiency	Transitory	F XI increase
Some dysfibrinogenemias	Surgery	
	Traumatism	
	Immobilization	
	Pregnancy	
	Delivery	
	Contraceptives	
	Estroprogestatives	
	Hormonal substitutive treatment	

Table 2. Risk of pregnancy complications associated with congenital thrombophilias adapted from Kupferminc et al[17]

Defect	OR	95% CI	P value
Factor V Leiden	3.7	1.5-9.0	0.003
MTHFR C677T	3.1	1.4-7.1	0.005
Prothrombin G20210A	3.9	1.1-14.6	0.03
Total	5.2	2.8-9.6	< 0.001

MTHFR: Methylenetetrahydrofolate reductase, OR: Odds ratio, CI: Confidence interval.

Table 3. Thromboembolic episods (TE) during pregnancy in patients with AT, or PC, or PS deficiency

	AT deficiency	PC deficiency	PS deficiency	Method	Patients
Conard 1990[4]					
TE	36%	20%	16%		
During APP	14%	4%	0%	I	P + FM
During PPP	28%	18%	17%		
De Stefano 1994[5]					
TE	39%	12%	14%		
During APP	12%	2%	0%	I	P + FM
During PPP	32%	11%	14%		
Pabinger 1996[6]					
TE	46%	15%	27%		
During APP	40%	10%	6%	I	P + FM
During PPP	11%	5%	22%		
Friederich 1996[18]					
TE, n	3%	1.7%	7%		
During APP, n	3%	1.7%	0%	I	FM
During PPP, n	0%	0%	7%		
Simioni, 1999[19]	The three types of deficiencies are mixed				
Pregnancies, n		169			
APP/PPP, n		169/169			
TE during APP/PPP		7 (4.1%)			
Mc Coll 1997[20]					
Pregnancies, n	72201	72201	72201		
TE, n	62	62	62		
				II	ND
% women carriers	Type I: 8%	2%	0%		
of the deficiency	Type II: 4%				

P: Propositus, FM: Family members, ND: Not done, APP: Antepartum period, PPP: postpartum period.

A common often raised question is who should be tested, when is it the more appropriate and how should patients be tested[13].

Who Should be Tested?

Every woman with a personal or a family history of VTE in first degree siblings planning to conceive should be tested.

The indication for testing should be extended to women with a history of abnormal outcome of a previous pregnancy, such as fetal loss, death in utero, stillbirth or severe in utero growth retardation IUGR, preeclampsia, placental abruption or repeated abortions at the first trimester of pregnancy. In these pregnant women it is indicated to search also an antiphospholipid syndrome which plays an important role in abnormal pregnancy outcome[23].

It is hypothetized that heritable thrombophilias are also associated with an increase of the rate of pathological pregnancies but the results of the literature are somewhat contradictory[24].

When Should Patients be Tested?

Hormonal treatments, pregnancy, inflammatory syndrome may induce a modification of the plasma levels of protein C and protein S. During pregnancy a small increase of protein C and moderate to important decrease in protein S are well documented. During pregnancy, a decrease in protein S could be misleading when trying to diagnose heritable thrombophilia. Oral anticoagulation treatment induces a decrease of the plasma concentration of proteins C and S, since their synthesis is vitamin K dependent. The inflammatory syndrome could modify the level of free protein S and that of factor VIII. The measurement of the C reactive protein and orosomucoid may be indicated in these patients to confirm or exclude a coexisting inflammatory reaction as a cause of plasma factor VIII increase.

The measurement of various proteins should be performed a few weeks after the thrombotic episode. It is essential to make a clear distinction between congenital and acquired blood alterations.

How Should Patients be Tested?

In young women a complete work-up seems unavoidable if the clinical investigation suggests an heritable thrombophilia.

A blood cells count, PT and aPTT are performed systematically. In a first stage AT, PC, PS dosage with a functional method are preferable to the measurement of the respective antigens. However, the measurement of active PS is difficult since the available methods are not very reliable, in contrast to the measurement of PS free antigen. Thus, many laboratories prefer to use the latter measurement.

F V Leiden mutation and F II 20210A gene mutation can be reliably determined and the preanalytical variables are less stringent than those required for AT, PC and PS activity or antigen measurement.

Hyperhomocysteinemia and the search of MTHFR homozygous mutations are omitted in a first stage since most pregnant women receive a supplementation of folic acid. It has to be emphasized that heterozygous MTHFR is not a risk factor for VTE while homozygous MTHFR is considered by some authors as a prothrombotic risk factor. Hyperhomocysteinemia is a weak predisposing factor to VTE but its addition to a heritable risk factor may increase significantly the global risk[25].

The cut-off for hyperhomocysteinemia may vary according to the method used: 12 or 15 to 18 nmol/L are the ones most commonly used to define elevations in pregnant women and a slightly higher value for nonpregnant women[25,26].

Prophylactic Treatment in Pregnant Women with Thrombophilia

It is still a very debated question. There are several recommendations in the 6th ACCP Consensus Conference published in the special supplement of Chest in January 2001, and in guidelines of the British Society of Haematology[12,27].

These recommendations have been discussed in our group taking into account our experience in this field[28]. There are also some clear recommendations proposed by the group of Greer et al from Glasgow (UK)[2]. Anyhow it is clear that no results of large randomized trials are available. Thus all recommendations have a low level of evidence (grade C). It is important to take into account at least two different parameters, the variety of thrombophilia and personal risk factors, to evaluate the global risk in order to propose to the pregnant women the apparently most appropriate stra-

tegy. It seems appropriate to classify these women into low, median or high risk group for VTE. The type of thrombophilia AT deficiency, plurigenic thrombophilia and homozygous patients with PC or PS deficiency are at the higher risk. Heterozygous PS deficiency, F V Leiden and F II 20210 gene mutations, hyperhomocysteinemia and/or homozygous MTHFR, are in general the less severe thrombophilias. Heterozygous protein C deficiency and homozygous F V Leiden or F II 20210A mutations could be classified between these two groups. The presence of a previous VTE episode associated or not with a previous pregnancy and its mechanism, idiopathic or associated with an exposing factor, are essential to determine the level of the predisposition. Table 4 shows the strategies followed in our group[27-29].

All experts make the same recommendations regarding the importance of postpartum prophylactic treatment during about 6 weeks (4 to 12 weeks). Not only the existence of thrombophilia, but also age over 35, obesity, multiparity (> 3 pregnancies), gemellarity, cesarean section and various comorbid conditions are well known risk factors for ante and/or postpartum thrombosis. However we should mention that the thrombotic risk after planned cesaean section is less than after urgent cesarean section. In each woman the physician has to take into account the different risk factors in order to determine the level of the risk for VTE.

The type of prophylactic treatment could differ for the antepartum period. Thus, it seems appropriate to classify women into low, medium or high risk.

Elastic stockings are always recommended and the

Table 4. Recommendations concerning prophylactic treatment of VTE in women with heritable thrombophilia (from 12, 27-29)

Prophylaxis during antepartum period
1. Heritable thrombophilia without a history of VTE before pregnancy
• Clinical surveillance and elastic stockings during pregnancy (F V, F II, PC and PS)
• LMWH prophylaxis should be considered from the very beginning of pregnancy in women with heterozygous AT, homozygous PC or PS deficiency or multigenic thrombophilia
• Family history and presence of other risk factors should be taken also into consideration
2. Heritable thrombophilia associated with a single VTE before pregnancy
It is important to know if the TE episode was idiopathic or if it was associated with a persistent or a transient risk factor
• Clinical surveillance, elastic stockings in every patient
• Prophylactic treatment with LMWH is indicated from the very beginning of pregnancy in women with AT deficiency or homozygous PC or PC deficiency or multigenic thrombophilia. The appropriate dosage is not established but several experts use a dose which is twice the prophylactic dose
• In F V or F II thrombophilia prophylactic treatment with LMWH is considered and the decision will be taken case by case. In patients with a transient risk factor associated with the previous VTE episode, pharmacologic prophylaxis may not be used systematicaly
3. Heritable thrombophilia and more than one previous VTE episode
• Usually these patients are under a long term oral anticoagulant treatment subcutaneous heparin or LMWH is indicated as soon as pregnancy starts.
• The dosage of LMWH is not well established. A dosage at least twice the prophylactic doses is often used.
Prophylaxis during postpartum
In every patient prophylaxis with heparin or oral anticoagulants is indicated during postpartum period during 4 to 8 weeks

most often used pharmacological treatment is subcutaneous unfractionated heparin (1 to 3 injections per day). However, the short half-life of unfractionated heparin (UFH) and the frequently observed resistance to heparin in pregnancy are serious drawbacks to the use of this medication.

Low molecular weight heparins (LMWHs) are being used more extensively because of their superior pharmacokinetics, their increased tolerance regarding the lower risk of heparin-induced thrombocytopenia (HIT) and of osteoporosis. The results obtained in two large series of pregnant women have been recently reported[30,31]. They demonstrate the safety of using LMWH prophylactic treatment. A recent work has compared the osteoporosis induced in two groups of pregnant women by UFH and LMWH[18]. Although the numbers of women are small, there is a significant difference in favor of LMWH.

Finally, the most difficult problem in some groups of pregnant women is the dosing of LMWH and its timing.

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