

# Thrombophilia and obstetrics



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**The 1990s and the new millennium brought an explosion of new studies introducing the topic of thrombophilias to the field of obstetrics. With it arrived the promise of a way to identify women at risk of having pregnancy complications such as preeclampsia, recurrent miscarriage, placental abruption and small-for-gestational age (SGA) pregnancies.**

Not only would we be able to identify these women, but the tests would tell us which women would need treatment to improve the outcome in their next pregnancy. Thousands of women were tested – some reassured that their test results were negative, others alarmed that a positive result meant a bad outcome in their next pregnancy. Moreover, many

obstetricians experienced a sinking feeling when they realised that they couldn't escape from the clutches of the coagulation cascade. Haematologists, albeit briefly, felt smug, until the challenge of helping someone else understand the complexities of physiological thrombosis and its control became evident. What was touted as having the potential to shed light on managing women with complex pregnancy complications became ever more murky and obscure. Now that we are approaching the second decade of the 21st century, does the place of thrombophilias in obstetrics look any clearer? The answer, I'm afraid, is no.

## What is a thrombophilia?

Thrombophilia is a term that describes a predisposition to developing blood clots and is derived from the Greek *thrombos*, 'a clot of blood', and *philia*, 'friendship'. Thrombophilias can either be inherited or acquired (see Table 1). Interest in thrombophilias first arose in the 1960s and 1970s when studies of families with a high rate of venous thromboembolism (VTE) led to the discovery of the rare thrombophilias, therefore, antithrombin, protein C and protein S deficiency present in around one in 2000 to one in 5000 of the general population, but in about three to five per cent of patients with VTE. Following the discovery of Factor V Leiden (FVL) and the prothrombin G20210A mutation (PT20210) in the 1990s, haematologists could identify clotting tendencies in around 50 per cent of patients with VTE. Factor V Leiden (FVL) and PT20210 are less prothrombotic than the previously discovered thrombophilias, but their high prevalence, five per cent and three per cent respectively, in the general (European) population increases their clinical impact.

**Table 1.**

Acquired thrombophilias	Inherited thrombophilias
Lupus anticoagulant	Antithrombin deficiency
Anticardiolipin antibodies	Protein C deficiency
β2-glycoprotein 1	Protein S deficiency
Plasma homocysteine	Factor V Leiden
	Prothrombin G20210A mutation

## Why should inherited thrombophilias play a role in pregnancy complications?

The presence of clots and infarction in the placenta of women who have had placental mediated complications such as preeclampsia, SGA pregnancies and fetal loss prompted renewed interest in the possible association of thrombophilias and these adverse pregnancy outcomes. Kupferminc's paper<sup>1</sup> in the *New England Journal of Medicine* showed that one of three thrombophilias (FVL, the prothrombin gene mutation and the methylentetrahydrofolate reductase polymorphism) were present in 52 per cent of 110 women with obstetric complications compared to only 17 per cent of 110 women with uncomplicated pregnancies [OR 5.2 (95%CI 2.8-9.6)]. This opened the floodgates for a deluge of case-control studies examining the prevalence of numerous thrombophilias in women with placental-mediated pregnancy complications. Most review articles<sup>2,3</sup> of case-control studies have confirmed a slight increase in the prevalence of thrombophilias in women with these pregnancy complications compared to women who have normal pregnancies, but in general, the odds ratio suggests a two to three-fold increase in prevalence at most. These odds ratios have been interpreted by many clinicians to indicate that women with FVL, for example, have a 2.19-fold increased risk of developing preeclampsia or a 3.26-fold increased risk of having a late fetal loss. However, this does not necessarily follow – an odds ratio of 2.3 does not necessarily equate to a relative risk of 2.3. Odds ratios derived from case-control studies suggest an association between the abnormality and the disease, but an association itself does not confirm causation.

Two prospective studies have not confirmed an increased risk of preeclampsia in women with thrombophilias. A nested case-control study from Canada<sup>4</sup> showed no increase in the prevalence of FVL, PT20210 and the MTHFR polymorphism in women with preeclampsia (n=113) compared to women (n=443) with uncomplicated pregnancies [OR 1.2 (95%CI 0.3-4.1); OR 1.1 (95%CI 0.1-8.8); OR 0.2 (95%CI 0.2 (0.1-1.0)), respectively. A large prospective cohort study<sup>5</sup> revealed similar rates of preeclampsia in women (n=134) who were heterozygous for FVL (n=5, 3.7%) compared to women (n=4751) without the mutation (n=141, 3%), [OR 1.3 (95% 0.4-2.8)]. Similarly, studies have failed to demonstrate that women with FVL or PT20210 are at increased risk of fetal loss.<sup>6</sup>

## So why the difference between the case-control and the prospective studies?

It may be that the case-control studies have confounding factors that exaggerate any potential association – most are retrospective raising the possibility that some women with milder disease may

have been missed. It has also been suggested that the relatively low rates of preeclampsia in the large cohort studies (three per cent and 2.2 per cent) means that they were underpowered to detect an association between the individual thrombophilias and preeclampsia, especially severe preeclampsia.

It seems likely, however, that the association between the inherited thrombophilias and placental-mediated pregnancy complications is, at most, weak. This should not be surprising given the complexity of these disorders. What should make us think we are going to find one pathological trigger to diseases with such variable manifestations?

## Thrombophilias and pregnancy complications: biologically plausible?

Given the possible weak association, does it make biological sense that the thrombophilias could play a pathophysiological role in development of placental-mediated pregnancy complications? Given that the thrombophilias play a role in the development of thrombosis in the venous circulation, it makes sense that the increased levels of thrombin found in patients with thrombophilias could further tip the balance in the already prothrombotic environment of pregnancy. In addition, it is becoming increasingly clear that there is interplay between coagulation and inflammation and the increased levels of thrombin could enhance the inflammatory response seen in pregnancy and in preeclampsia, predisposing to development of these conditions.<sup>7</sup>

## Do thrombophilias modify the risk of recurrent adverse pregnancy outcome?

In contrast to the data confirming an increased risk of recurrent miscarriage in women with the antiphospholipid syndrome, there are precious little data that investigate this question when dealing with inherited thrombophilias and adverse pregnancy outcomes. One small study<sup>8</sup> has shown an increase in the rate of recurrent preeclampsia in women with a thrombophilia compared to women with no thrombophilia. However, in this study the women with thrombophilia were also more likely than women without thrombophilia to have had severe or early onset preeclampsia in the first pregnancy – by themselves risk factors for recurrent preeclampsia, so it is unclear from this paper whether the presence of a thrombophilia was an independent risk factor.

As a corollary, although the inherited thrombophilias, FVL and the prothrombin gene mutation play a clear role in development of venous thrombosis, they have not been shown in large studies to be an independent risk factor for recurrent VTE (strange but true!). Even in the world of thrombosis and haemostasis, there is great debate about whether patients with VTE should be tested for inherited thrombophilias.<sup>9</sup> It is argued that if the test result is not helpful in predicting who is at increased risk of recurrence, nor does it provide information to guide duration of anticoagulation in patients with VTE and given that the tests cause major anxiety in patients and their families, why order the test in the first place?

Given that there is less information relating to the clinical significance of the inherited thrombophilias and placental-mediated pregnancy complications, there is even less reason to test women for these disorders.

So it seems both unreasonable and unscientific to consider modifying management of women with adverse pregnancy outcomes such as preeclampsia, miscarriage or stillbirth, on the basis of a thrombophilia result until there is proof that this test result modifies the risk of recurrence.

There also seems to be a move to decide on management in a subsequent pregnancy depending on the result of the thrombophilia test, with women with positive tests often being counselled to take low molecular weight heparin (LMWH) in addition low dose aspirin. While there is no doubt of the evidence that supports the use of low dose aspirin in women with previous preeclampsia or a small-for-gestational age baby, there is no evidence from adequately powered randomised clinical trials that investigate whether the addition of LMWH further reduces the risk of recurrence. Also, unless the inherited thrombophilias are demonstrated to be independent risk factors for recurrence, there is no reason to modify management depending on whether they are present or not. Similar arguments can be made for not testing for thrombophilias in women with recurrent pregnancy loss.

The arguments about thrombophilias and adverse pregnancy outcome appear to be clearer for the acquired thrombophilias that comprise of the antiphospholipid syndrome, therefore, lupus anticoagulant, anticardiolipin antibodies and anti  $\beta$ 2-glycoprotein 1. Small studies suggest improved outcome in women with these abnormalities who have a history of recurrent miscarriage. It is generally accepted that women with early onset preeclampsia, severe growth restriction or stillbirth, who have one of the acquired thrombophilias should receive LMWH and aspirin in the next pregnancy (no randomised clinical trials have been done for these pregnancy complications however).

So where does that leave us? This is my 'Top Ten' of the current state of knowledge with regards to the inherited thrombophilias and the placental-mediated pregnancy complications (preeclampsia, SGA pregnancies, stillbirth and fetal loss):

1. There is no indication to screen asymptomatic women for inherited thrombophilias: it does not help predict who will be at risk from pregnancy complications.
2. If there is an association between these placental-mediated pregnancy complications and the inherited thrombophilias, at most, the association is likely to be weak.
3. It is biologically plausible that the inherited thrombophilias could play a role in the pathophysiology of placental-mediated pregnancy complications, but these disorders are multifactorial and the thrombophilias are likely to play only a small contributory role – but they may be the straw that breaks the camel's back!
4. There are no data confirming that the inherited thrombophilias are an independent risk factor that predict recurrence of the placental-mediated pregnancy complications.
5. There are no data that suggest that women who have had a placental-mediated pregnancy complication, who have an inherited thrombophilia, should be managed any differently from women with the same history who do not have one.
6. Thrombophilia testing creates alarm in women and their families and usually leads to testing within the extended family – 50 per cent of the results will be positive and the clinical implications of the results are not known – counselling all the affected people takes time, money and effort.
7. Thrombophilia tests cost money – around NZ\$250 for gene tests (Factor V Leiden and prothrombin gene tests alone!).
8. Until more data are available, given the lack of data relating clinical utility and the potential for harm, at present, women with placental-mediated pregnancy complications should not be tested for inherited thrombophilias, except in the context of a clinical trial.

9. Some women will have these tests done, so health professionals will need to know what to tell women who come to them with such a pregnancy history and a positive thrombophilia result.
10. You will need to 'watch this space' and you can't forget about the coagulation cascade yet.

Also, look out for the results of the SPIN study – a randomised study of enoxaparin with low dose aspirin in women with recurrent pregnancy loss (results expected late 2009).

In Auckland in 2010, we plan to start the EPPI trial (enoxaparin in prevention of preeclampsia and intrauterine growth restriction), a randomised double blind placebo controlled study assessing the effect of enoxaparin in addition to standard care in women with previous early onset preeclampsia or severe SGA pregnancies ([www.eppi.org.nz](http://www.eppi.org.nz)).

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