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Thrombophilias and adverse pregnancy outcome

In this issue of the journal, Facchinetti *et al.*[1] investigated the incidence of inherited thrombophilias, namely factor V Leiden and prothrombin A20210 mutation in women who presented with acute placental abruption. Not surprisingly, they show an increased incidence of both thrombophilias in women with abruptio placentae.

Pre-eclampsia, *abruptio placentae*, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) greatly contribute to maternal and fetal morbidity and mortality. Their causes are unknown, but all of them may be associated with abnormal placental vasculature and disturbances of hemostasis leading to inadequate maternal-fetal circulation.[2-8]

The subsequent vasculopathy and secondary

thrombosis from hypercoagulability may result in inadequate perfusion of the intervillous spaces, leading to pre-eclampsia, placental infarcts, IUGR, placental abruption and IUFD.[9]

Histopathology examinations of the placenta from women with adverse pregnancy outcome and thrombophilia and from women with pregnancy complications but without thrombophilia were compared.[10-13] Pathologic findings were noted in most women, and in a few studies,[10,13] there were also typical findings in the thrombophilia group such as villous infarcts, and fetal stem cells thrombosis which were not as prominent in the non-thrombophilia group.

The known thrombotic nature of the placental vascular lesions and the increased thrombotic risk associated with the existence of thrombophilias strongly suggest a cause-and-effect relationship between inherited and acquired thrombophilias and the above severe obstetric complications.

Indeed, in recent years investigators around the world have described an association between adverse pregnancy outcomes and thrombophilias. One of the earlier reports was by Dekker *et al.*,[14] who showed an increased incidence of thrombophilia in women who had severe early pre-eclampsia. Other investigators confirmed this finding.[15-17]

Severe pre-eclampsia is associated mainly with factor V Leiden,[18] hyperhomocysteinemia, and deficiencies of protein S, C and antithrombin III. It is not clear yet whether severe pre-eclampsia is associated with the prothrombin and methylenetetrahydrofolate reductase (MTHFR) mutations. Most studies have not revealed any association between thrombophilias and mild pre-eclampsia or pregnancy induced hypertension.

Martinelli *et al.*[19] and our group[20] found that late IUFD was associated with inherited thrombophilias. There is also an evidence that recurrent miscarriage is more prevalent in patients with thrombophilia.[21,22] Other studies have shown that there is an increased incidence of thrombophilias in women with pregnancy complications such as severe IUGR and abruptio placentae.

The diversity in the incidence of different thrombophilias in patients with pregnancy complications and the negative results some investigators reported may be partly attributed to the prevalence of the genes in different ethnic groups. For example, the FV Leiden mutation is highly prevalent among the Caucasian population, the prevalence ranging from 10-15% in Sweden, 4-8% in central Europe, and 2% in the south, and 5% in USA. The mutation is almost non-existent in Asia, Japan, Africa, South America and among African-Americans.

If this is all true, is it justified to offer a thrombophilia work-up to women with a previous severely adverse pregnancy outcome? Can a woman with thrombophilia be offered any treatment?

In answer to the first question we point out that a carrier of certain thrombophilias is at increased risk of thromboembolism in various situations, such as after surgery, during oral contraceptive use, and in a future pregnancy.[23] Some thrombophilias might also increase the risk of cardiovascular and cerebrovascular disease and the risk of these occurring at an earlier age. In our opinion, all this is sufficient to justify a thrombophilia work-up in women with a previous adverse pregnancy outcome (even in those who are not planning a future pregnancy).

The answer to the second question is much more complicated as it implies intervening in order to improve the outcome of a future pregnancy. The available data are so far very limited. One of the conditions which has been relatively well studied is antiphospholipid syndrome (APLS). In this thrombophilic condition there is an increased risk of recurrent abortions and other pregnancy complications. Based on controlled trials,[24] it is currently recommended that women with APLS and recurrent fetal loss are prescribed aspirin combined with heparin. Pregnancy outcome was improved when heparin was added to aspirin in this group of patients.

Are thrombophilic (other than APLS) pregnant women with a previous pregnancy complication and/or placental thrombosis candidates for antithrombotic therapy as certainly are those with venous and arterial thrombosis? If we consider a severe pregnancy complication as a thrombotic event (as evident in the placenta), one might argue that these women should be administered antithrombotic/anticoagulant treatment during the next pregnancy.

Unfortunately, so far, only very few studies[25,26] have addressed this clinical dilemma. These preliminary small studies suggest that low molecular weight heparin (LMWH) may have an additional favorable effect on the pregnancy outcome of women with a history of severe pre-eclampsia and/or IUGR and documented thrombophilia. This is obviously not sufficient evidence for the routine use of heparin or LMWH in these women.

We believe that, at the moment, use of these anticoagulant agents during pregnancy, in thrombophilic women with a prior history of a severe adverse pregnancy outcome, is justified only as part of controlled trials. Large randomized, well controlled studies are urgently needed.

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Inherited thrombophilia is unlikely to affect the outcome of assisted reproductive techniques

In recent years, Haematologica has published several papers on the subject of genetic thrombophilia.[1-10] More recently, Grandone *et al.*[11] reported data suggesting that maternal thrombophilia is significantly associated with fetal death, and that a family history of obstetric complications is significantly associated with the occurrence of fetal death. In this issue, Facchinetti and co-workers[12] report studies indicating that patients suffering from abruptio placentae need to be screened for thrombophilic disorders. The related editorial 13 discusses the relationship between obstetric complications and inherited thrombophilia.

The paper by Martinelli and co-workers[14] adds an important contribution to the role of inherited thrombophilia in women who fail to become pregnant after assisted reproductive techniques. In particular, the prevalence of thrombophilia due to factor V Leiden or prothrombin 20210GA in women with implantation failure after assisted reproductive procedures is similar to that found in the general population. Therefore, anticoagulant treatment is not warranted in women undergoing assisted reproductive procedures.

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