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Thrombophilia and early pregnancy loss

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Early pregnancy loss is the most common pregnancy complication. About 15% of pregnancies result in pregnancy loss and 1% of women experience recurrent miscarriage (more than three consecutive miscarriages). The influence of thrombophilia in pregnancy is a popular research topic in recurrent miscarriage. Both acquired and inherited thrombophilia are associated with a risk of pregnancy failure. Antiphospholipid syndrome is the only thrombophilia known to have a direct adverse effect on pregnancy. Historically, clinical research studying thrombophilia treatment in recurrent miscarriage has been of limited value owing to small participant numbers, poor study design and heterogeneity. The debate on the efficacy of aspirin and heparin has advanced with recently published randomised-controlled trials. Multi-centre collaboration is required to ascertain the effect of thrombophilia on early pregnancy loss and to establish an evidence-based treatment protocol.

Thrombophilia and early pregnancy loss

Thrombophilia are a diverse group of coagulation disorders associated with a predisposition for thrombotic events (e.g. deep vein thrombosis and pulmonary embolism).[1] Inherited factors associated with thrombophilia include Factor V Leiden (FVL), prothrombin G20210A gene mutation, deficiencies

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in protein C and protein S as well, as antithrombin. The most established acquired thrombophilia in early pregnancy loss is antiphospholipid syndrome (APS). Antiphospholipid syndrome is a non-inflammatory auto-immune disease characterised by thrombosis or pregnancy complications in the presence of antiphospholipid antibodies.[2] Recognised obstetric complications include fetal loss, recurrent miscarriage, intrauterine growth restriction, pre-eclampsia and preterm labour.[3]

Pregnancy loss is associated with acquired and inherited thrombophilia. The efficacy of various treatment regimens has been much contested.[4–9] In this chapter, we attempt to clarify the effect of a hypercoagulable state on early pregnancy loss and to provide an overview of current evidence on therapeutic management.

Inherited thrombophilia

Inherited thrombophilia can interfere with the natural coagulation system or alter levels of certain coagulation factors. Factor V Leiden mutation results from a replacement of adenine by guanine at the 1691 gene position. As a consequence, factor V becomes resistant to the action of activated protein C. The 677C → T mutation of the MTHFR gene results in an alanine to valine substitution. This in turn reduces the conversion of homocysteine to methionine. Hyperhomocysteinaemia impairs endothelial cell function and promotes thrombosis.[10] Antithrombin is an anticoagulant synthesised in the liver and endothelial cells. It has an inhibitory effect on thrombin, clotting factors X, IX, XI, XII and tissue factor bound VIIa protein.[11] Antithrombin, protein C and protein S deficiency are heterogeneous in their genetic aetiology and are not as prevalent as FVL and prothrombin mutation among women who have experienced recurrent miscarriages.

The existence of a causal role for heritable thrombophilia and pregnancy failure is controversial.[12] Support for a relationship has been extensively published.[5,9,11,13–23] Previous research suggests that blood coagulation defects are responsible for 55–62% of recurrent miscarriages, whereas 90% of first-time miscarriages are caused by chromosomal defects.[24] The pathophysiology is uncertain, but is thought to involve thrombosis in the uteroplacental circulation leading to inflammation and placental insufficiency.[25]

Antithrombin deficiency was the first inherited thrombophilia identified, and is the most thrombogenic. In the general population, the prevalence is thought to be 1:600–1000.[26] Initial research established an increased risk of miscarriage in women with antithrombin deficiency[25]; however, subsequent publications have challenged this.[19,22,27,28] A Spanish retrospective study found that 10 out of 18 (56%)women with antithrombin deficiency had an adverse pregnancy outcome.[11] Two women suffered a spontaneous miscarriage; however, no cases of recurrent miscarriage were observed. The small population number is a stark limitation in this review, and a larger study would be desirable.

Resistance to activated protein C is almost always caused by a single point mutation in the factor V gene. Heterogeneity for FVL is prevalent in 4% of the general population. A large meta-analysis conducted in 2003 discovered an association between recurrent miscarriage and FVL when other potential underlying factors were excluded. Research into activated protein C resistance (APCR) in recurrent miscarriage has suggested no correlation[29–31]; however, this claim has been disputed.[32] An animal study on thrombo-modulin deficient mice, lacking the anticoagulant protein C pathway, experienced pregnancy demise before 9 weeks.[33]

Protein S deficiency and recurrent miscarriage has been rarely studied in isolation. In a case–control study, 52 consecutive women who had experienced recurrent miscarriage were tested for inherited thrombophilia. The incidence of protein S deficiency was twice as high in the recurrent miscarriage cohort compared with the control group. This, however, was deemed statistically insignificant.[34]

The prothrombin mutation affects 2–3% of Europeans, and is present in 17% of pregnant women who have suffered a venous thromboembolism.[35] Two European case–control studies found no correlation between prothrombin mutation and recurrent miscarriage.[36,37] This conclusion was supported by a recent prospective cohort study of more than 4000 women.[38]

A systematic review conducted by Robertson et al.[12] found an odds ratio of 2.70 (95% confidence interval 1.37 to 5.34) for recurrent miscarriage with women who were positive for prothrombin mutation compared with those without. This is discordant with previous research. Factors such as small study numbers, varied definitions of recurrent miscarriage and co-morbidities can implicate bias.