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Recurrent pregnancy loss and thrombophilia

Antiphospholipid syndrome (APS) remains the commonest treatable cause of recurrent miscarriage. The association between maternal antiphospholipid antibodies (aPL) and RM was noted in the 1970s, and recognised as a treatable cause in the 1980s [1]. In a large, single centre study carried out among 500 women with recurrent miscarriage, antiphospholipid antibodies (aPL) were shown to be present in 15% [2] compared to only 1-5% in the general population [3]. The diagnosis of APS is challenging and is based on strict clinical and laboratory criteria [4]. It can occur in isolation or secondary to other autoimmune disorders such as systemic lupus erythematosus (SLE). The prevalence of primary APS in the general population is around 0.5% [5]. It is recommended that all women with recurrent first trimester miscarriage or one or more second trimester pregnancy losses should be screened for the presence of antiphospholipid antibodies. Thrombosis within the placental circulation was initially thought to be the primary cause of pregnancy loss in APS. Subsequent animal studies demonstrated the ability of aPL antibodies to bind directly to trophoblastic cells and cause cellular injury, defective tissue invasion and a local inflammatory response triggered by classical and alternative complement pathways, all of which could contribute to an adverse pregnancy outcome [6].

Inherited thrombophilias also cause recurrent miscarriage, and these include Factor V leiden, prothrombin gene mutation, antithrombin deficiency and deficiencies in protein C and S [7]. The prevalence of inherited thrombophilias among caucasians is as high as 15% [6]. Evidence of an association between inherited thrombophilia and RM came to light following the publication of the European Prospective Cohort on Thrombophilia (EPCOT) study in 1996 [8]. This study demonstrated an increased risk of pregnancy loss among 571 women with inherited thrombophilia. An interesting observation of this study was the strong association of inherited thrombophilias with late pregnancy loss; the association with early miscarriage was non-conclusive [9]. However, a meta-analysis carried out by Rey *et al* in 2003 was able to demonstrate a positive correlation with early recurrent pregnancy loss and factor V leiden mutation, activated protein C resistance, prothrombin G20210A mutation and protein S deficiency; it failed to show an association with methylenetetrahydrofolate mutation, protein C, and antithrombin deficiencies [10]. Similar studies among the Asian population are sparse. A study done in Sri Lanka which attempted to investigate the association between gene mutations associated with inherited thrombophilia and recurrent pregnancy loss failed to demonstrate any positive correlations [11].

Investigating for haematological causes of recurrent miscarriage

Thrombophilia screening with aPL antibodies is recommended in the presence of a history suggestive of antiphospholipid syndrome. The place of screening for inherited thrombophilic defects is not convincing because of conflicting scientific evidence. However, screening for the presence of factor V Leiden, prothrombin G20210A mutation and protein S deficiency may be prudent if a woman has experienced late pregnancy loss. There is emerging evidence that treating women with inherited thrombophilia with low molecular weight heparin (LMWH) may be beneficial in the presence of a history of placenta mediated adverse pregnancy outcomes [12].

Disparities exist not only in the diagnostic workup but also in standards of laboratory methods used to investigate acquired and inherited thrombophilia [13]. Laboratories that undertake such testing should be subjected to strict internal and external validation protocols and clinicians should be aware of limitations when interpreting results issued by laboratories that have not conformed to these standards.

Treatment of recurrent miscarriage in thrombophilia

APS is not only associated with RM but also with other obstetric complications such as pre-eclampsia, foetal growth retardation, intrapartum foetal distress and foetal demise [14]. It is hypothesized that these are the end results of thrombosis of the uteroplacental circulation. This hypothesis is supported by the observation of intervillous thrombosis, extensive villous fibrosis and marked infarctions noted in placentae of some women with APS [14]. This was the basis for antithrombotic agents being proposed as a mode of treatment. Previous studies, as well as a recent Cochrane meta-analysis which included 13 studies with over 840 women with recurrent pregnancy loss associated with APS, have confirmed the superiority of combined unfractionated heparin and aspirin compared to aspirin alone in reducing pregnancy loss [15,16]. A similar effect was not observed with other treatment regimes such as aspirin and prednisolone, or the addition of immunoglobulins to aspirin and LMWH.

Certain clinical presentations of APS are known to occur in the absence of elevated aPL levels. In a small retrospective study, Mekinian *et al* studied the benefits of treatment in a subgroup of women with APS like obstetric events but with low aPL levels. It showed that conventional APS treatment reduced adverse pregnancy outcomes, including recurrent pregnancy loss in a subsequent pregnancy, in this subgroup [17]. This observation demonstrates the wide spectrum of APS and the need for further studies to evaluate benefits of treating subgroups of women with clinical manifestations of APS in the absence of laboratory criteria.

Current evidence does not support the use of LMWH in women with RM and inherited thrombophilia or

unexplained recurrent pregnancy loss [18,19]. Two recent multicentre, randomised, controlled trials have studied the outcome of anticoagulation in women with unexplained recurrent miscarriage. The Anticoagulants for Living Fetuses (ALIFE) study conducted in several centres in the Netherlands, compared the outcome of aspirin combined with nadroparin versus aspirin alone and placebo [20], while the Scottish Pregnancy Intervention (SPIN) study, compared treatment with enoxaparin and low dose aspirin versus intensive pregnancy surveillance alone [21]. Both these studies failed to demonstrate a favourable outcome in the treatment groups. A higher proportion of adverse events, such as, bleeding were observed in the treatment group, though no difference in the incidence of serious adverse events such as ante- or postpartum haemorrhage were noted. Studies on pregnancy outcome in women treated with LMWH for inherited thrombophilia – the Thrombophilia in Pregnancy prophylaxis (TIPP) trial [18] and the ALIFE2 study are underway and their results are eagerly awaited [22]. There is currently no evidence of benefit of empirical treatments such as progesterone in either unexplained or RM associated with thrombophilia, and such practices should be questioned. The effect of progesterone on pregnancy outcome in women with RM is being investigated in a large multicentre trial which is nearing completion – the Progesterone in recurrent Miscarriage trial (PROMISE).

Placenta mediated adverse pregnancy events such as foetal demise, growth restriction and severe pre-eclampsia are thought to bear a close relationship to RM due to thrombophilia, as both conditions are considered to be end results of thromboembolic disease of the placenta. However, a recent trial, Heparin in Pregnant women with adverse Pregnancy outcome to improve the rate of successful pregnancy (HAPPY trial), failed to show any benefit of LMWH in preventing these adverse events, including pregnancy loss [23]. Subsequent studies have, however, shown that treatment with LMWH appeared beneficial in preventing the more severe forms of these adverse events in a subgroup of women with thrombophilia.

Conclusions

Thrombophilia is a heterogenous disease entity, which is associated with recurrent pregnancy loss and other adverse pregnancy events. The role of inherited thrombophilia in RM has not been clearly established and clinicians should inform patients of the knowledge gaps and limitations prior to embarking on investigations and treatment. The therapeutic benefit of antithrombotic treatment with aspirin and LMWH has been proven to be beneficial only in APS, and such treatments outside this indication should be undertaken only in research settings with strict laboratory standards and diagnostic criteria. There are several well powered randomised controlled trials underway that will hopefully give us answers and improve our knowledge on this important area of women's health.

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