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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.

When appraising research, prospective cohort studies are considered to be less prone to bias than retrospective case–control studies. A comprehensive meta-analysis in the study of MTHFR and recurrent miscarriage concluded that no significant association existed. Eight studies with a total population of 1818 were included. This must not be confused with hyperhomocysteinaemia, in which a clear association with recurrent miscarriage has been documented.[10,39]

Homocysteine levels vary, depending on an individual's state when measured (intake of folic acid, vitamin B12); therefore, it is difficult to achieve representative results. In 2000, a meta-analysis concluded that hyperhomocysteinaemia was a risk factor for recurrent miscarriage.[40] More recently, Kumar et al.[41] examined the interactions between folate status and MTHFR mutation on the homocysteine concentration in 24 women experiencing unexplained consecutive recurrent pregnancy losses. High-dose folic acid (5 mg) and vitamin B12 (0.5 mg) once daily has been reported to reduce levels of homocysteine; however, a randomised-controlled trial (RCT) on the effect of variable doses of both vitamins on pregnancy has yet to be conducted.[41]

Acquired thrombophilia

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) was first described in the early 1980s as a unique form of autoantibody-induced thrombophilia and pregnancy complications. The antibodies involved promote activation of the endothelial cells, monocytes and platelets. As a consequence, tissue factor and thromboxane A2 are overproduced.[42] The most common obstetric manifestation is recurrent miscarriage; however, other features include pre-eclampsia and placental insufficiency prompting delivery.[43] A concise list of the varied clinical manifestations of APS is presented in Table 1.[44] It is estimated that APS is prevalent in 15% of women who have had recurrent miscarriages.[3]

Diagnosis can be complex and is usually a combination of clinical manifestation and presence of lupus anticoagulant, anti-cardiolipin antibodies, or both. The prevalence of anti-cardiolipin antibodies in obstetrics has been quoted to be between 2.7 and 7%. With a positive result, studies have shown a three- to nine-fold greater risk of a fetal loss.[44–46] The hypothesis behind APS and recurrent miscarriage is the encouragement of a prothrombotic environment. Microthrombi are common in the placental vasculature and decidua in pregnancy samples from women who have had recurrent miscarriages.[47] Antiphospholipid syndrome can cause pregnancy loss before the growth and development of the placental vasculature. Inflammation is a significant component of APS pathogenesis as demonstrated in recent mice studies, showing a pivotal role for complement activation in thrombosis and fetal loss induced by antiphospholipid antibodies.[48] In-vitro studies have reported that antiphospholipid antibodies can impair signal transduction mechanisms controlling endometrial cell decidualisation.[49] It has also been claimed that antiphospholipid antibody binding reduces the secretion of human chorionic gonadotropin, and may trigger an inflammatory response, resulting in trophoblastic damage.[50]

Acquired activated protein C resistance

Acquired APCR is associated with lupus anticoagulant and high concentrations of coagulation factor VIII. A large observational study conducted in a recurrent miscarriage clinic concluded that a stronger

Table 1
Clinical manifestations of antiphospholipid syndrome.[44]

Common (>20% cases)	Less frequent (10–20%) cases	Atypical (<10% cases)	Rare (<1% cases)
Venous thromboembolism	Pre-eclampsia and eclampsia	Pulmonary hypertension	Adrenal haemorrhage
Thrombocytopaenia	Premature delivery	Epilepsy	Transverse myelitis
Miscarriage	Haemolytic anaemia	Chorea	Budd–Chiari syndrome
Stroke	Coronary artery disease	Antiphospholipid syndrome nephropathy	
Migraine	Heart valve disease	Leg ulcers	

association exists with acquired APCR rather than FVL APCR.[51] Acquired APCR is a recognised risk factor for VTE as well as recurrent miscarriage[32,51,52]; however, the cause remains unknown.[53] The hypothesis of alternative polymorphisms on the factor V gene was explored by Dawood et al.[53] to elucidate the existence of acquired APCR. Fifty-one women who had experienced recurrent miscarriage and acquired APCR were recruited, and their factor V gene was intensely analysed to identity single-nucleotide polymorphisms (SNP). Samples were compared with carefully selected controls, and results showed a significantly increased number of particular SNP in the recurrent miscarriage cohort. This study also explored the theory of whether some SNP increase the risk of recurrent miscarriage in women with acquired APCR.[53]

Pregnancy and miscarriage

Pregnancy promotes an increase in particular coagulation factors and reduces levels of anticoagulant proteins and fibrinolysis. Factor VIII, von Willibrand Factor, ristocetin cofactor, Factor X and Factor XII increase during pregnancy.[54] The risk of suffering a VTE is four to five times higher than in women who are not pregnant.[55] Thrombophilia in combination with pregnancy further enhances this risk. The pathogenesis of VTE remains diversified with interaction of genetic predisposition and acquired risk factors for thrombosis. The principal clinical event (i.e. VTE) does not manifest in most cases.[56]

Miscarriage is defined as the spontaneous end of a pregnancy before fetal viability, and is the most common complication in the first trimester.[57] About 15% of all clinically recognised pregnancies result in miscarriage. The definition of recurrent miscarriage remains subject to debate. The European Society for Human Reproduction and Embryology defines recurrent miscarriage as three or more consecutive pregnancy losses occurring before 20 weeks amenorrhea.[58] Recurrent miscarriage effects 1% of couples and can be distressing for the family involved. Recurrent miscarriage is a clinical condition of heterogeneous cause. Classification of recurrent miscarriage is of fundamental importance in the investigation of any possible pathophysiological mechanisms. An in-depth history and established screening protocol[59] is recommended practice.[60] Recognised associations aside from thrombophilia consist of uterine abnormalities, endocrine disorders, chromosomal imbalances and infection. In most cases (60%), the cause of recurrent miscarriage remains unknown (idiopathic).[61] The existence of conflicting research findings and recommendations is not uncommon among women who have had recurrent miscarriages. Recent evidence has exposed the futility of unproven treatment regimens in the management of idiopathic recurrent miscarriage (e.g. heparin).[6,62] Such research endeavours to modify current practice of prescribing potentially harmful non-evidence-based treatments in pregnancy.

Diagnosing thrombophilia in women who have had recurrent miscarriages

When screening for thrombophilia, a discrepancy exists between recommended inclusion criteria and investigation protocols. Established guidelines and individual protocols are in practice[58,63]; however, debate surrounds laboratory disparity in specific tests for APS and also inconsistencies when screening for heritable thrombophilia. Even after a pregnancy loss, inherited thrombophilia has apparently no effect on the outcome of the next pregnancy.[21] Analysis leads to an increasing number of positive results, which could prompt a request for genetic counselling. In 2008, data from early pregnancy units across the country were collected from routine heritable thrombophilia investigations in women who had experienced recurrent miscarriages. Testing was diverse, and positive results frequently lead to the use of antithrombotic medication.[64] Currently, most services carry out routine investigation for heritable thrombophilia among women who have had recurrent miscarriages. Patient demand is a factor, and investigation can also be part of providing an explanation for a previous pregnancy loss.

In contrast, the causal link between APS and recurrent miscarriage has been established. The classification criteria was originally released in 1998 from Japan[65] and updated in 2006. Laboratory and clinical standards are shown in Tables 2 and 3.[66] Lupus anticoagulant is the most powerful predictor of thrombosis, and is strongly associated with recurrent miscarriage. To a lesser extent, immunoglobulin G and immunoglobulin M anticardiolipin antibodies (ACA) are known to increase the risk of miscarriage.[67] Inter-laboratory variation exists in the context of testing for APS. Standardisation in

Table 2
Clinical classification criteria for antiphospholipid syndrome.[66]

Pregnancy morbidity	Vascular thrombosis
One or more unexplained deaths of a morphologically healthy fetus documented on ultrasound or examination aged 10 weeks or over.	One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ.
One or more premature births of a morphologically healthy baby aged less than 34 weeks due to eclampsia or pre-eclampsia according to standards of recognised features of placental failure.	Thrombosis should be supported by objective validated criteria (i.e. unequivocal findings of appropriate imaging studies or histopathology). For histopathological support, thrombosis should be present without substantial evidence of inflammation in the vessel wall.
Three or more consecutive spontaneous miscarriages up to 10 weeks, with maternal anatomical or hormonal abnormalities and paternal and maternal chromosomal causes excluded.	

preparation and cut off ranges is lacking. Anti- β2-glycoprotein-1 antibodies are not associated with recurrent miscarriage in isolation; however, in combination with positive results for lupus anticogulant and ACA, there is a high risk of obstetric complications.[42]

Annexin A5 slows down the effect of phospholipids on the coagulation system. A recent study has shown that antiphospholipid antibodies may produce a resistance to annexin A5. Hence accelerating the coagulation process. Annexin A5 resistance may be a mechanism in a subset of women with APS for pregnancy losses and thrombosis. The elucidation of APS mechanisms in recurrent miscarriage may open new paths towards addressing this disorder with targeted treatments and mechanistic assays.[68]

Treatments for thrombophilia in recurrent miscarriage

Research on recurrent miscarriage and treatments for thrombophilia has been diverse. A variety of treatments have been tried in isolation or in combination. These include the following: low-dose aspirin (75 mg); low-dose low-molecular-weight heparin (LMWH); unfractionated heparin (UFH); corticosteroids; and intravenous immunoglobulin (IVIG).

Anticoagulant treatment for inherited thrombophilia and recurrent miscarriage

Debate over the treatment for inherited thrombophilia is ongoing. Given that the prevalence of abnormal results in the obstetric population is 20%,[69] the question arises whether screening for inheritable thrombophilia among women who have had recurrent miscarriages is advantageous. The treatment decision has, in part, been extrapolated from the treatment of APS, where low-dose aspirin and heparin are frequently prescribed.

Support for the use of antithrombotic prophylaxis was first published by Brenner et al.[71] The investigators described 61 pregnancies in 50 women with recurrent miscarriage and thrombophilia. Enoxaparin (LMWH) was prescribed throughout the pregnancy and 4-6 weeks into the postpartum period. Forty-six of the 61 pregnancies (75%) resulted in live births compared with a success rate of 20% in previous pregnancies without antithrombotic therapy.[70] The investigators subsequently published

Table 3
Laboratory classification criteria for antiphospholipid syndrome.[66]

Lupus anticoagulant present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society of Thrombosis and Haemostasis.
Anticardiolipin antibody of IgG or IgM, immunoglobulin M isotype, or both, in serum or plasma present in medium or high titres (i.e. greater than 40 GPL or MPL, or greater than the 99th percentile) on two or more occasions, at least 12 weeks apart, measured by a standardised enzyme-linked immunosorbent assay.
Anti-β-glycoprotein 1 antibody of IgG or IgM isotype, or both, in serum or plasma (in titres greater than the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardised enzyme-linked immunosorbent assay, according to recommended procedures.

IgG, immunoglobulin G; IgM, immunoglobulin M.; GPL, Immunoglobulin G phospholipid; MPL, Immunoglobulin M phospholipid.

a RCT, the LIVE-ENOX study,[71] comparing varying doses of enoxaparin. Results showed an increase in live birth rates and a decrease in the incidence of complications in thrombophilic women who have had recurrent miscarriages. Doses of 40 mg day^{-1} and 80 mg day^{-1} led to similar clinical results. Data were omitted data on a number of women positive with APS who received additional aspirin. Carp et al.[72] treated selected women with heritable thrombophilia and women who had experienced recurrent miscarriages with enoxaparin; results showed a higher live birth rate (26/37 [70.2%]) compared with 21 out of 48 (43.8%) in untreated patients.[72]

Supporters in favour of a low-dose aspirin and heparin regimen tend to acquire results from small observational studies.[73] Not all studies use a randomisation technique, and therefore present the problem of confounding variables. The strength of association between subgroups of inherited thrombophilia (i.e. antithrombin III, FVL) and recurrent miscarriage does fluctuate. A large dedicated recurrent miscarriage clinic co-ordinated a prospective study comparing pregnancy outcome in 25 women whose screening blood tests were positive for the heterozygous form of FVL with a control group. Participants in the control group had also suffered at least three consecutive miscarriages. The live birth rate was lower in women positive for FVL (38%) compared with the control group (49%). The investigators suggested the use of thromboprophylaxis in future pregnancies.[74]

A prospective observational study analysed 37 women positive for antithrombin, protein C deficiency or protein S deficiency, and were followed through the index pregnancy. Thromboprophylactic treatment included LMWH, UFH and vitamin K antagonists. Twenty-six women (70%) received treatment and no fetal losses occurred. This compares with a 45% fetal loss rate (five out of 11) in women with no treatment intervention. When comparing fetal loss rates in women without thromboprophylaxis, antithrombin was the highest (63%) followed by protein C deficiency (50%). The investigators state that thromboprophylaxis reduces the fetal loss rate in women with such inherited thrombophilia by 15%.[22] The small number of participants is a limitation in this study. Women, however, were identified and recruited with reference to a large family cohort study and not because of previous recurrent miscarriages. In addition, 21 out of 26 (81%) women receiving thromboprophylaxis in pregnancy had suffered a previous thromboembolic event.

Sabadell et al.,[11] in a descriptive, retrospective study, assessed the pregnancy outcomes for nine women diagnosed with antithrombin. Out of a total of 18 pregnant women, 12 (67%) received LMWH, as antithrombin had not been diagnosed in the other participants at the time. Miscarriage occurred in two women (11%) of women; one case of pre-eclampsia was diagnosed, and two women suffered a still birth. Three episodes of VTE occurred in women without thromboprophylaxis. A significant observation was that none of the women miscarried.[11]

Well-designed trials are the solid basis for evidence-based practice. The description of a 'before and after' study design, used in publications to assess the evidence for inherited thrombophilia and recurrent miscarriage[75] has been explored. A population-based prospective cohort study of 2480 women to assess the pregnancy outcome of women with FVL mutation with previous fetal loss showed a substantial 'regression towards the mean,' as those with previous low birth weight consequently increased to a high live birth rate.[52] Those with no treatment intervention had in fact the highest current birth rate in the study. Evidence such as this supports the argument that antithrombotic prophylaxis is not required for inheritable thrombophilia among women who have experienced recurrent miscarriages. No pharmacological therapy, especially in pregnancy, should be allowed before robust evidence from comprehensive clinical trials. LMWH administration can be laborious with daily subcuticular injections, often associated with bruising and skin reactions.

An alternative cohort study from Denmark reviewed pregnancy outcomes in 35 women with either FVL or prothrombin gene mutation compared with a control group.[9] Every participant had suffered a minimum of three pregnancy losses and no anticoagulation therapy was prescribed. The adjusted odds ratio for live birth in FVL and prothrombin gene mutation was 0.48 (95% CI = 0.23 to 1.01); $P = 0.05$, and therefore results did not reach a statistical significance. Treatment did occur in the form of IVIG as part of an RCT performed by Christiansen et al.[76] Of those women with recurrent miscarriage who tested positive for FVL or prothrombin gene mutation, 9(25.7%) and 107 (32.6%) women in the idiopathic cohort were allocated to receive IVIG intervention. IVIG can cause thromboembolic complications[77] and, even though no adverse effects were reported in the trial, this risk factor needs to be recognised.

In conclusion, the role of anticoagulation therapy in the treatment of women who have had recurrent miscarriages with hereditary thrombophilia remains to be accurately assessed. Historical study design and small participant numbers limits the effect found in published data. Recruitment criteria varies significantly even in RCTs, and so conclusions cannot be assumed to represent women who have had recurrent miscarriages. Limited numbers of studies incorporate women with at least three consecutive miscarriages, as their inclusion criteria and therefore results have to be treated with caution. A dearth of well-structured placebo-controlled trials have been published. Women should be counselled and reassured that there is a good prognosis for subsequent pregnancy; however, if appropriate, they could potentially be included in high-quality research to ascertain a more reliable evidence base for recurrent miscarriage and inherited thrombophilia.

Anticoagulant treatment for antiphospholipid syndrome and recurrent miscarriage

Antiphospholipid syndrome is now recognised to be the most important treatable cause of recurrent miscarriage.[78] The pregnancy outcome for untreated women with APS is significantly poor, as described in a prospective, highly selected observational study.[79] The miscarriage rate of women positive for APS was 90% with no pharmacological intervention compared with 40% in a control group. Guidelines are in place for the treatment of positively diagnosed APS with thromboprophylactic treatment.[58,66,69,80] Regular surveillance is recommended throughout the whole pregnancy. Close observation for maternal hypertension and proteinuria in addition to appropriate fetal surveillance by ultrasound is advised in the second and third trimester. Doppler assessments are widely used in Europe to assess for pre-eclampsia, placental insufficiency and fetal growth restriction.[42]

Aspirin versus placebo

It is believed that aspirin improves vasodilation, prostacyclin production and reduces levels of thromboxane A_2.[81] Aspirin is commonly used to treat women with thrombophilia who have had recurrent miscarriages, who are also deemed idiopathic. Two RCTs compared aspirin with placebo or supportive care in women with APS.[81,82] No significant difference was found in the defined outcomes. These results were further supported as part of a meta-analysis conducted in 2005.[83]

Aspirin alone versus aspirin with heparin

Recent studies have challenged the efficacy of low-dose aspirin and heparin in women positive for APS who have had recurrent miscarriages.[5] The hepASA trial[5] included an RCT of 88 pregnant women positive for APS over 4 years. Participants were randomised to treatment with aspirin and LMWH or aspirin alone. Live birth rates were achieved in 35 out of 45 women (78%) and 34 out of 43 (79%), respectively. The trial was stopped prematurely, as no difference was found in primary outcome. Also, women with two consecutive miscarriages rather than three were part of the trial. These findings concur with an RCT conducted by Farquharson et al.[84] in 2002. The live-birth rate in 98 women diagnosed with APS was 72% in the aspirin alone cohort compared with 78% in the aspirin and LMWH cohort (odds ratio 1.39, 95% confidence interval 0.55, 3.47). This study has been criticised for including women with low positive titres for ACA. By contrast, the actual ACA levels in this study were numerically higher than previous published RCTs. The debate, however, on the clinical implications of different antithrombin antibodies and appropriate cut-off levels is still open.

A large Cochrane review of 13 studies looked at the treatment of APS among women who had experienced recurrent miscarriages.[4] A total of 849 women were involved, although the quality of the included studies was not high; 50% had clear evidence of allocation concealment. The authors concluded that combined UFH and aspirin may reduce pregnancy loss by 54%, yet RCTs with adequate allocation concealment are needed to explore potential differences between UFH and LMWH.

Unfractionated heparin versus low-molecular-weight heparin

Low-molecular-weight heparin is favoured clinically because of its once-daily injection regimen. Currently, no RCT has compared UFH and LMWH for APS in women who have had recurrent miscarriages. Stephenson et al.[85] conducted a pilot trial with women diagnosed with APS and were treated with dalteparin (LMWH) or UFH. A successful pregnancy occurred in nine out of 13 women (69%) prescribed dalteparin compared with four out of 13 (31%) prescribed UFH.

In 2005, a US study assigned women positive for APS to LMWH and aspirin or UFH and aspirin.[86] Twenty one out of 25 (84%) in the LMWH group had a live birth compared with 20 out of 25 (80%) in the UFH group. Results were not statistically significant. Three RCTs, part of an up-to-date systematic review with a total of 212 participants, assessed the effect of UFH combined with aspirin compared with aspirin alone.[7] Ultimately, outcome improved with UFH in women with a history of early pregnancy loss. Treatment with UFH and aspirin instead of aspirin alone was the superior treatment, as trials with LMWH and aspirin compared with aspirin alone showed no benefit. Despite particular study design weaknesses within the review it is suggested that aspirin (81 mg/d) started before conception, and the addition of UFH (5000–10,000 units every 12 h) after a positive pregnancy test leads to a higher number of live births.[7]

Adverse effects associated with aspirin and heparin

Aspirin in frequently prescribed to women who have had recurrent miscarriages; however, caution is advocated, as side-effects (maternal and fetal bleeding) can occur, albeit rare. Cases of major congenital abnormalities including gastroschisis have been linked with the use of aspirin during pregnancy. A 22-study meta-analysis quoted a two- to three-fold increase in gastroschisis if aspirin was taken in the first trimester.[87]

Heparin has been a cause of concern when assessing its effect on bone mineral density and the development of osteoporosis. No cases of osteoporosis or fractures as a consequence of heparin during pregnancy have been reported. A multi-centre RCT studying LMWH prophylaxis on pregnancy outcomes in women with thrombophilia claimed that no evidence of a significant decrease in bone mineral density was found.[88] A specific recurrent miscarriage clinic designed a prospective, observational study of bone mineral density commencing pre-conceptually, compared the effects of LMWH in pregnancy with an untreated control group. Bone loss associated with the use of long-term LMWH was found to be not significantly different from physiological losses during pregnancy.[89] LMWH is a more popular choice because of its longer half life and fewer side-effects. Both types are heparins do not cross the placenta and they are not known to be teratogenic.[90]

Antiphospholipid syndrome and corticosteroids

Moderate-to-high doses of prednisolone were initially prescribed for APS purely as an autoimmune disorder, manifesting as recurrent fetal loss. In the early 1990s, two small trials in women positive for APS demonstrated no benefit with the treatment of prednisolone in pregnancy.[91,92] Laskin et al.[93] studied the efficacy of prednisone and aspirin in women with APS who had experienced previous miscarriages, looking specifically at maternal morbidity and fetal survival. This study was part of a prominent Cochrane review.[94] Among the women who had experienced recurrent miscarriages who were positive for APS, prednisone and aspirin were no more effective than placebo in preventing fetal loss. Gestational diabetes and hypertension were important maternal side-effects.

Antiphospholipid syndrome and intravenous immunoglobulin treatment

The theory of immunologic aberrations in association with recurrent miscarriages has been extensively considered. Defects in cytokines and growth factors at a trophoblastic level have been postulated; however, experimental models of miscarriage have shown that pregnancy survival depends on the inhibition of local inflammatory mediators.[95] IVIG is a fractionated blood product made from human plasma. It is expensive and limited in quantity. Side-effects include anaphylaxis, fever,

muscle pains, nausea and headache. A number of studies have been conducted; however, no evidence has been found to suggest that IVIG improves pregnancy outcome of women who have had recurrent miscarriages and APS. Triolo et al.[95] conducted an RCT comparing LMWH and aspirin with IVIG in women with APS who have had recurrent miscarriages. A higher miscarriage rate was found with IVIG. Those women who progressed in the pregnancy had a two fold risk of premature delivery. Recent systematic reviews have reached the same conclusion that IVIG has no benefit for women with APS and should only be used in controlled trials.[83,96]

Conclusion

Much research has been invested into the role of thrombophilia in recurrent miscarriage. It is acknowledged that APS is the only thrombophilia known to have a direct influence on pregnancy loss. When treated, the prognosis of a subsequent pregnancy is good. A retrospective cohort study involving 693 women who had had recurrent miscarriages found that the live birth rate for women with APS was comparable to those deemed idiopathic (69% and 63%, respectively). The live birth rate was 79% (53/67) for those women treated with aspirin and LMWH compared with 62% (64/104) treated with aspirin alone.[97] As current research and guidelines stand, certain aspects of heritable thrombophilia may not need any therapeutic intervention. The use of LMWH within this cohort is experimental, and sufficient clinical evidence is required. Recent trials have questioned the efficacy of heparin in APS; however, current guidelines recommend its use among women who have had recurrent miscarriages in combination with aspirin (75 mg).[42,53,58,70]

The cause of recurrent miscarriage is multifactorial. It is a continuing challenge to find an effective treatment when a direct cause fails to be identified. Laboratory tests should be standardised for results to be representative. Couples ultimately require supportive dedicated care. They express the need to intervene with medication to reduce feelings of unease and guilt. There is scope to collaborate with a number of research centres in order to avoid small participant numbers, poor study design with the aim of producing strong evidence-based medicine in the future. The appearance of enhanced genetic tools, for example, comparative genomic hybridisation, to detect underlying lethal chromosomal anomalies in failed pregnancy should be used by future RCTs as a set standard.

Practice points

- Recurrent miscarriage is a clinical condition of heterogeneous cause.
- APS is the most significant treatable cause of recurrent miscarriage.
- Pregnancy outcome for women with heritable thrombophilia is generally good without therapeutic intervention.
- The combined therapeutic use of aspirin and heparin to treat APS is still contentious .
- Postpartum thromboprophylaxis is recommended in women who have evidence of heritable thrombophilia and APS.

Research agenda

- Multi-centre collaboration to maximise study numbers.
- Standardise diagnostic criteria and laboratory values in study cohorts.
- Use of comparative genomic hybridisation to exclude chromosome abnormality in failed pregnancy in RCTs.

Conflict of interest statement

None declared.

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