REVIEW ARTICLE

The Use of Heparin for Preventing Miscarriage

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Recommendations for the use of heparin for preventing miscarriage are recently rapidly changing based on evidenced based prospective studies. At present either heparin or low molecular weight heparin (LMWH) is recommended for the antiphospholipid syndrome (APS). However criteria for diagnosing APS have become much stricter. The exact timing of the heparin is still being evaluated since it is not clear if the main therapeutic effect is in inhibition of thrombosis when the heparin could be started at the time in the first trimester when the platelets become thrombophilic or does its main role in improving implantation in which it would be started shortly before or shortly after ovulation. Possibly heparin is superior to LMWH in improving the implantation process though more studies are needed to corroborate or refute this suggestion. At present inherited thrombophilias are not considered a cause of first trimester miscarriage and thus measuring these factors are not recommended. There is no evidence that heparin has any benefit in preventing miscarriage from unexplained causes. Heparin is effective alone and there does not appear to be any extra benefit from adding aspirin (or even aspirin may negate some of its benefits).

Introduction

The antiphospholipid syndrome (APS) was first described in 1983.[1] Antiphospholipid antibodies (aPL) are a group of autoimmune antibodies that bind to negatively charged phospholipids (predominantly B2-glycoprotein I), and they are associated with thrombotic events that could lead to pregnancy loss.[2]

Although they have been associated with a wide variety of clinical disorders and obstetric complications, the focus of this manuscript will be on the role of these autoantibodies in early ($\leq$10 weeks) and late (>10 weeks) miscarriages and the importance of heparin in the prevention of miscarriage related to APS.

Furthermore, the efficacy of heparin or low molecular heparin in preventing miscarriage for inherited thrombophilias or for unexplained recurrent miscarriage will be reviewed.

Immunopathology – antiphospholipid syndrome

Thrombosis and Placental Infarction

The principal manifestation for APS is thromboembolism. The underlying basis for the hypercoagulable state in APS is complex and involves altered activity of all three major components that govern hemostatis: platelets, fibrinolysis, and the coagulation cascade. These aPLs inhibit both protein C activation and the formation of activated protein C, thereby preventing the inactivation of factor V and VIII. This inhibition is conditional upon the presence of beta two glycoprotein I that is a prerequisite for the binding of aPL to protein C.[3]

Other prothrombotic activities may be involved including tissue factor an initiator of the extrinsic coagulation cascade.[4–6] Also aPL can further up-regulate adhesion molecules, for example, E-selection,

intercellular adhesion molecule I, and vascular cell adhesions molecule I expression.[7] Also aPL can increase the secretion of proinflammatory cytokines, for example, interleukin one beta and interleukin-6.[7]

Decreased endothelial cell prostacyclin (PGI2), the principal inhibitor of platelet aggregation, and increased thromboxane A2 production by platelets may also predispose to thrombosis.[8] Arachidonic acid is required for PGI2 production, and aPL inhibits arachidonic acid release.[9] Not only does PGI2 inhibit thrombotic aggregation but it is a potent vasodilator. Thus, the combination of vasoconstriction from decreased PGI2 and increased risk of thrombosis formation and platelet activation from both decreased PGI2 and increased thromboxane A2 leads to compromise of fetal blood supply and could lead to miscarriage.

Other Mechanisms of Fetal Loss Associated with aPL

The classic concept is that aPL leads to miscarriage related to their effect on negatively charged phospholipids leading to thrombosis with subsequent placental infarction. Although thrombosis is observed frequently in the deciduas and placentas of patients with APS, this observation is not seen in all such patients. Furthermore, it does not present in sufficient degree to adequately explain pregnancy loss with APS.[10]

Inflammation may be responsible for a significant part of the APS syndrome. Deciduas from women with APS showed more necrosis and acute inflammation compared to women with normal pregnancies.[11]

Some data suggest that APS cause pregnancy loss by binding to phospholipids expressed on the invading trophoblast that inhibits placental development and thus subsequent embryo implantation in early pregnancy.[12]

Some murine studies have shown that complement activation is a central mechanism of antiphospholipid antibody-induced pregnancy loss related especially to the cleavage product C5a of complement component C5.[13]

Types of Antiphospholipid Involved in the APS

The antiphospholipid syndrome refers to various pregnancy complications including early miscarriage, late first-trimester or mid-trimester miscarriage, pregnancy-induced hypertension, pre-eclampsia, and intrauterine growth retardation with or without other thromboembolic complications related to a heterogeneous group of autoantibodies directed against different antigens predominantly anionic phospholipids- or phospholipids-containing structures. The first study implicating that phospholipids antibodies could be an etiologic factor in miscarriage was published by Hughes in 1983, and it referred to the lupus anticoagulant.[1] The lupus anticoagulant is an antiphospholipid antibody that prolongs phospholipids-dependent clotting assays. The clotting defect is not corrected with normal plasma but with the addition of phospholipids.[1]

Table I The Antiphospholipid Antibodies

Lupus anticoagulant
Anticardiolipin
Antiphosphatidyl serine
Antiphosphatidyl ethanolamine
Antiphosphatidyl choline
Antiphosphatidyl glycerol
Antiphosphatidyl inositol
Antiphosphatidyl acid
Anti-beta 2 glycoprotein 1

There are aPLs that do not prolong phospholipid-dependent clotting assays, and they are usually measured by ELISA assay. These other aPLs are listed in Table I. There have been several published manuscripts ascribing various degree of importance to specific aPLs. For example, antiphosphatidylethanolamine (aPE) and antiphosphatidylserine (aPS) have been implicated as being associated with early first-trimester miscarriage.[14] Nevertheless, aPLs especially in low titers are frequently present in women without a history of miscarriage. American College of Obstetricians and Gynecologist (ACOG) has provided guidelines in Bulletin 118 to prevent women unlikely to have the APS from being treated with a potentially risky drug for example, heparin or low molecular weight heparin when the need for such treatment is low.[15] The committee recommend that only three antibodies contribute to the diagnosis of APS: the lupus anticoagulant, anti-beta two glycoprotein 1 (IgG and IgM).[15] They also recommend that the APS not be considered unless at least one of these tests is positive in a titer >40 GPL or MPL units for anticardiolipin antibody or standard IgG units, or SMU >99th percentile for a normal population for anti-beta two glycoprotein 1 12 weeks apart lupus anticoagulant is either positive or negative.[15] The ACOG bulletin #118 refers to the study by Tebo et al.[16] who stated 'some laboratories offer testing often in a panel of tests for other phospholipids anti-

Table II The Inborn (Hereditary) Thrombophilias

Protein S deficiency
Protein C deficiency
Antithrombin III deficiency
Factor V Leiden mutation
Factor II (prothrombin) G20210A variant
Hyperhomocysteinemia

Table III American College of Obstetricians and Gynecologist Practice Bulletin does not Recommend Screening all Women but Select Individuals

History of previous thrombosis
Unexplained fetal death >10 weeks (even one)
History premature birth <34 weeks (even one)
History of eclampsia or severe pre-eclampsia
History of 3 or more unexplained miscarriages before 10 weeks

bodies. Results from such assays do little to improve the accuracy of the diagnosis of PS, and testing of such antibodies is not recommended'.

Some studies suggest that when the more strict requirement of aPL titer >40 GPL or MPL was not followed, the pregnancy loss rate was more than twice as high if a woman was positive for aCL versus lupus anticoagulant (38% versus 16%).[17,18]

Immunopathology – inherited thrombophilias

The Hereditary Thrombophilia

A list of the inborn or hereditary thrombophilias is seen in Table II. These conditions have been associated with an increased risk of thromboembolic pathology.

As the initial assumption was that antiphospholipid antibodies that are also associated with thromboembolic pathology were similarly associated with pregnancy loss on a thrombosis/infarction basis (which actually may not be true), it was assumed that the hereditary thrombophilia may similarly be associated with placental thrombosis.[19] However, another study found a high frequency of placental infarcts (~50%) in women with thrombophilia and miscarriage but found a similar frequency in women without thrombophilia.[20] In fact, there is evidence that not only in hereditary thrombophilia but in APS, thrombosis has not been convincingly demonstrated in decidual vessels but, in fact, fetal thrombotic vasculopathy is found and may be related to pathology other than a tendency for thrombosis.[21,22]

Current clinical approach

Antiphospholipid Syndrome

According to ACOG Bulletin 118 not all women should be screened for APS but select individuals as listed in Table III.

Some data suggest that aspirin could protect the trophoblast from damage after placentation has been established.[23] Of course, low-dose aspirin blocks the conversion of arachidonic acid to thromboxane A2 that aggregates platelets and causes vasoconstriction.[24] As low-dose aspirin seems to be devoid of major side effects other than a slight risk of small vessel bleeding during surgical procedures, it has been included in most therapeutic paradigms since the discovery of the APS because the main concept at that time was that placental thrombosis was the most likely cause of fetal loss. Aspirin was considered a relatively harmless potential adjunctive therapeutic agent that could possibly help but would not hurt. In fact, in borderline cases of APS, it was empirically used by itself without addition of heparin. Though several studies have shown the combination of heparin and aspirin is superior to aspirin alone in enhancing live birth in women with recurrent pregnancy loss and the presence of antiphospholipid antibodies. There is a paucity of studies evaluating aspirin versus placebo in these circumstances.[25] Similarly, there is a paucity of studies comparing heparin versus heparin plus aspirin to determine whether aspirin adds any benefit or in fact could be detrimental in APS.

The current clinical approach for the treatment of women with a history of miscarriage and the presence of antiphospholipid antibodies has been provided by the American College of Obstetricians and Gynecologist (ACOG) No. 118.[15] The first thing emphasized is to properly identify women with true APS syndrome. For diagnosis of APS, they refer to the study of Miyakis et al.[26] They state that the term APS should refer to any women with recurrent miscarriage who have met the laboratory criteria as provided earlier in this manuscript and who have had either a history of vascular thrombosis (including arterial, venous, or small vessel thrombosis in any tissue or organ) or certain specific types of preg-

nancy morbidity. These morbidities include (i) one or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with normal fetal morphology documented either by sonography or by direct examination of the fetus, and (ii) three or more unexplained consecutive pregnancy losses before the 10th week of pregnancy of chromosomally normal fetuses without any maternal hormonal or anatomic explanation.[15,26] In addition, the ACOG committee will consider a woman as having APS if she has laboratory criteria and has had one or more premature births before 34 weeks of a morphologically normal neonate because of eclampsia, severe pre-eclampsia, or evidence of placental insufficiency.[15,26]

The ACOG Bulletin No. 118 mentions that patients enrolled in most published series besides heparin also received low-dose aspirin, but they stated 'the benefit of adding aspirin for this indication is unknown'.[15] They refer to the systematic review of Empson et al. published in 2002 that found that the combination of heparin and aspirin may reduce pregnancy loss rate by 50% when properly selected women with APS are treated.[27]

Since that time, the authors have completed a more updated (2011) Cochrane review.[28] They reviewed 13 studies with 849 participants, but they admit that the quality was not high related to different selection criteria and only 50% had clear evidence of allocation concealment. Only unfractionated heparin combined with aspirin was shown to reduce the incidence of pregnancy loss (by 54%).[28] Low molecular weight heparin (LMWH) combined with aspirin did not significantly reduce pregnancy loss through the point estimates were in the direction of benefit, suggesting LMWH probably has some benefit.[28] However, the systematic review could not find any adequate studies comparing the efficacy of unfractionated heparin versus LMWH.[28] Importantly, this review found three studies that found no benefit of aspirin in reducing pregnancy loss.[28] It is interesting that in the ACOG Bulletin No. 118 (2011), they also refer to heparin, so it is unclear whether they simply mean unfractioned heparin only or is it a wider term that would include LMWH? Finally, the review by Empson et al.[28] did not find any advantage of high versus lower dosage unfractionated heparin. Hopefully, future meta-analysis or prospective studies will follow the new ACOG guidelines for diagnosing APS, so that a more uniform data set can be evaluated. As mentioned, some of the conclusions of previous studies and the meta-analyses could be erroneous by including women who by present ACOG criteria would not be considered to have APS.

Inherited Thrombophilia

There had been some previous meta-analyses, one matched-controlled study, and a retrospective review that suggested that there was an association between inherited thrombophilias and first-trimester miscarriage.[29–32] However, prospective studies failed to find any association with factor V Leiden mutation nor with the prothrombin G20210A.[33,34]

One publication suggested that the one hereditary thrombophilia with the most evidence suggesting an association with early first-trimester losses is hyperhomocysteinemia.[35] Others state that factor V Leiden mutation is the thrombophilia most associated with second-trimester losses.[36] In reality, evidence linking inherited thrombophilia with miscarriage is weak which supports growing suspicion that thrombosis may not be the main reason for miscarriage with the APS.

Lockwood and Wendell in ACOG Bulletin 124 September 2011 concluded after critically reviewing all manuscripts related to miscarriage and inherited thrombophilia that 'whereas meta-analysis and a retrospective cohort study have revealed an association between inherited thrombophilia and first-trimester pregnancy loss, prospective cohort studies have found no association between thrombophilia and fetal loss'.[37]

Thus, it does not seem reasonable to order an inherited thrombophilia panel for unexplained first-trimester recurrent miscarriage (except possibly a homocysteine level). It is not unreasonable to obtain such a panel for unexplained second-trimester losses and consider therapy even without a history of thromboembolism as long as the patient is informed that there is no proof that the therapy is warranted.

Unexplained Recurrent Miscarriages

A previous study suggested that the low-dose aspirin could improve uterine blood flow and improve endometrial thickness.[38] As previously mentioned, diminished blood flow on the maternal side could explain thrombosis on the fetal side, and this could be theoretically how aspirin helps prevent miscarriage. However, other studies failed to corroborate

the beneficial effect of aspirin on uterine blood flow, and one study found, in fact, a significantly lower pregnancy rate following frozen embryo transfer in the group taking aspirin versus untreated (for thromboprophylaxis) controls.[39]

A multicenter randomized controlled trial of LMWH and low-dose aspirin plus intensive pregnancy surveillance resulted in a 22% miscarriage rate in women with unexplained recurrent miscarriage versus 20% in the group receiving intensive surveillance alone.[40] This study would thus suggest no basis for using LMWH or aspirin for unexplained recurrent miscarriage. Alternatively, the proponents for using heparin could argue that the aspirin negated the beneficial effect of the heparin, and the LMWH was started too late in the pregnancy, that is, it should have been started before implantation or with implantation, or unfractioned rather than LMWH is better for this category.

A Cochrane meta-analysis published prior to the SPIN study found only two studies that could be used in their review but found no evidence for benefit of heparin or aspirin compared with placebo. Based on the maternal risk (though still small) to the mother of bleeding, thrombocytopenia, osteoporosis, and bone fractures, the authors recommend not to use either agent for unexplained recurrent miscarriage.[41] Another prospective RCT published in 2010 similarly found no benefit of adding heparin to aspirin for unexplained recurrent miscarriage, and as previously mentioned, there are no data showing benefits of aspirin in this group.[42] Thus, in the present era of treating unexplained recurrent miscarriage, aspirin, heparin, or the combination of both is not indicated.

Potential clinical approach

Section B under the Immunolopathology section in the manuscript deals with other potential mechanisms other than thrombosis where APS can potentially cause fetal harm.[42–44] Some data suggest that both unfractionated heparin and LMWH cause a decrease in antiphospholipid antibody activity.[45] The possibility exists that heparin binds to and interferes with beta 2 glycoprotein.[46] Thus, the beneficial effect may be its ability to prevent the interaction of anticardiolipin antibody with beta 2 glycoprotein 1.[46] The same authors found that heparin in high dosages can interfere with antiphospholipid IgG binding to primary trophoblast cells and thus negate the adverse effect that antiphospholipid antibodies have on inhibiting placentation and thus trophoblast invasiveness and differentiation.[46]

As previously mentioned earlier in the chapter, complement split products, especially C5, are mediators of antiphospholipid antibody-induced fetal injury. Heparin has been shown to have anticomplementary effects by inhibiting complement activation at various points.[47–49] A murine study found that heparin and LMWH (enoxaparin) protected mice from fetal absorption from passive transfer of human IgG containing antiphospholipid antibodies, whereas neither fondaparinox nor hirodin which are anticoagulants that do not inhibit complement activation inhibited murine fetal loss despite anticoagulation levels.[50] Heparin also initiated C3 deposition in deciduas of mice infused with antiphospholipid antibodies.[50] Also heparin in such small dosages that it did not provide any anticoagulant effect but could still inhibit complement activation also still protected the mice.[50] Thus at least based on these murine studies, it seems that merely inhibiting coagulation is not sufficient to adequately protect fetal loss from antiphospholipid antibodies. This could explain why there is an association of the coagulopathy known as APS with miscarriage and why heparin or LMWH improves chances of live birth, whereas the hypercoagulable state related to inherited thrombophilia is not as obviously associated with fetal loss, and unfractionated LMWH is of dubious value in preventing fetal loss in the presence of inherited thrombophilia.

Some advocate the start of heparin as soon as a positive pregnancy test is achieved, and others suggest that it is sufficient to initiate with the first sign of ultrasound evidence of pregnancy. However, based on the suspicion that the main effect may be with implantation and placentation, the question arises as to whether heparin should be started immediately after ovulation or even before ovulation. Randomized controlled trials should be conducted to determine the best starting time of heparin. Also the history of the timing of miscarriage, that is, early first trimester versus late first or second trimester, may dictate the starting time of heparin, that is, are early losses more related to trophoblast invasion, implantation, and placentation issues, whereas are late losses more related to thrombosis or are late losses related to earlier events also?

Although it is clear that enoxaparin is equally as effective as an anticoagulant as unfractionated heparin, it is not clear that it is equally as potent in inhibiting complement activation or the other poten-