

# The Use of Heparin for Preventing Miscarriage

Jerome H. Check

Division of Reproductive Endocrinology & Infertility, Department of Obstetrics and Gynecology, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Camden, NJ, USA

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## Correspondence

Jerome H. Check, 7447 Old York Road,  
Melrose Park, PA 19027, USA.  
E-mail: laurie@ccivf.com

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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.<sup>1</sup> 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.<sup>2</sup>

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 hemostasis: 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.<sup>3</sup>

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

intercellular adhesion molecule I, and vascular cell adhesion molecule I expression.<sup>7</sup> Also aPL can increase the secretion of proinflammatory cytokines, for example, interleukin one beta and interleukin-6.<sup>7</sup>

Decreased endothelial cell prostacyclin (PGI<sub>2</sub>), the principal inhibitor of platelet aggregation, and increased thromboxane A<sub>2</sub> production by platelets may also predispose to thrombosis.<sup>8</sup> Arachidonic acid is required for PGI<sub>2</sub> production, and aPL inhibits arachidonic acid release.<sup>9</sup> Not only does PGI<sub>2</sub> inhibit thrombotic aggregation but it is a potent vasodilator. Thus, the combination of vasoconstriction from decreased PGI<sub>2</sub> and increased risk of thrombosis formation and platelet activation from both decreased PGI<sub>2</sub> and increased thromboxane A<sub>2</sub> 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.<sup>10</sup>

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.<sup>11</sup>

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.<sup>12</sup>

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.<sup>13</sup>

#### 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 heteroge-

**Table 1** The Antiphospholipid Antibodies

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

neous 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.<sup>1</sup> 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.<sup>1</sup>

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.<sup>14</sup> 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.<sup>15</sup> The committee recommend that only three antibodies contribute to the diagnosis of APS: the lupus anticoagulant, anti-beta two glycoprotein 1 (IgG and IgM).<sup>15</sup> 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.<sup>15</sup> The ACOG bulletin #118 refers to the study by Tebo et al.<sup>16</sup> 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%).<sup>17,18</sup>

### 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.<sup>19</sup> 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.<sup>20</sup> 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.<sup>21,22</sup>

### 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.<sup>23</sup> Of course, low-dose aspirin blocks the conversion of arachidonic acid to thromboxane A<sub>2</sub> that aggregates platelets and causes vasoconstriction.<sup>24</sup> 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.<sup>25</sup> 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.<sup>15</sup> 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.<sup>26</sup> 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.<sup>15,26</sup> 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.<sup>15,26</sup>

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'.<sup>15</sup> 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.<sup>27</sup>

Since that time, the authors have completed a more updated (2011) Cochrane review.<sup>28</sup> 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%).<sup>28</sup> 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.<sup>28</sup> However, the systematic review could not find any adequate studies comparing the efficacy of unfractionated heparin versus LMWH.<sup>28</sup> Importantly, this review found three studies that found no benefit of aspirin in reducing pregnancy loss.<sup>28</sup> It is interesting that in the ACOG Bulletin No. 118 (2011), they also refer to heparin, so it is unclear whether they simply mean unfractionated heparin only or is it a wider term that would include LMWH? Finally, the review by Empson et al.<sup>28</sup> 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.<sup>29-32</sup> However, prospective studies failed to find any association with factor V Leiden mutation nor with the prothrombin G20210A.<sup>33,34</sup>

One publication suggested that the one hereditary thrombophilia with the most evidence suggesting an association with early first-trimester losses is hyperhomocysteinemia.<sup>35</sup> Others state that factor V Leiden mutation is the thrombophilia most associated with second-trimester losses.<sup>36</sup> 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'.<sup>37</sup>

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.<sup>38</sup> 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.<sup>39</sup>

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.<sup>40</sup> 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 unfractionated 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.<sup>41</sup> 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.<sup>42</sup> 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 Immunopathology section in the manuscript deals with other potential mechanisms other than thrombosis where APS can potentially cause fetal harm.<sup>42-44</sup> Some data suggest that both unfractionated heparin and LMWH cause a decrease in antiphospholipid antibody activity.<sup>45</sup> The possibility exists that heparin binds to and interferes with beta 2 glycoprotein.<sup>46</sup> Thus, the beneficial effect may be its ability to prevent the interaction of anti-cardiolipin antibody with beta 2 glycoprotein 1.<sup>46</sup> 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.<sup>46</sup>

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.<sup>47-49</sup> 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 fondaparinux nor hirudin which are anticoagulants that do not inhibit complement activation inhibited murine fetal loss despite anticoagulation levels.<sup>50</sup> Heparin also initiated C3 deposition in deciduas of mice infused with antiphospholipid antibodies.<sup>50</sup> 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.<sup>50</sup> 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-

tial benefits of unfractionated heparin such as anti-inflammatory effects in women with three miscarriages or more with antiphospholipid antibodies. So far, there has been only one study with a reasonable number of patients enlisted comparing unfractionated heparin plus aspirin to only LMWH (plus aspirin) and found comparable miscarriage rates (20% versus 16% miscarriage rate).<sup>51</sup> However, adherence to the new standards of diagnosing APS according to the latest ACOG bulletin was not followed, and it could be that many did not actually have APS. There is still need to determine whether unfractionated heparin and LMWH are equally effective in achieving live deliveries in women with APS.

The most dreaded risk of unfractionated heparin was rare but potentially fetal thrombocytopenia. At one time, it was thought that using LMWH would markedly reduce the risk of thrombocytopenia.<sup>52</sup> However, more recently the risk of thrombocytopenia has been found to be the same with both agents.<sup>53</sup>

#### *Author's personal opinion*

I think that most recent ACOG guidelines are reasonable and emphasize evidence-based medicine though compromised by a paucity of prospectively designed studies. These guidelines will allow the greatest number of women given proper heparin without a huge number of women mistreated with a potentially dangerous and very expensive drug.

Nevertheless, one must realize that these are only guidelines. A physician has to consider the guidelines but must make decisions on a case by case basis and realize that there are exceptions to every rule.

For example, I would certainly treat a woman with heparin if she had aCL IgG >40 GPL who has had only two rather than three early miscarriages. Similarly, I would treat a woman with heparin who had a history of unexplained second-trimester losses but whose aCL GPL was 29 not >40.

Until I see more data, I will continue to also obtain measurements of antiphosphatidylserine and ethanolamine and consider heparin therapy if the titer was consistently over 40 especially IgG. I will still order serum homocysteine levels for unexplained first-trimester miscarriages and still consider heparin even without a history of thrombosis. Similarly for unexplained late first-trimester or second-trimester losses, I would consider heparin for factor V Leiden mutation, and thus, I would still obtain measurements for factor V Leiden mutation in the right clinical circumstance but not for recurrent first-trimester losses.

For APS, I would begin heparin immediately after ovulation to help implantation and placentation of the invading trophoblast for not only women with a history of first-trimester losses but also mid-trimester losses. For first-trimester miscarriage possibly related to hyperhomocysteinemia, I would begin heparin once pregnancy was established. For second-trimester losses, I would begin heparin after ultrasound confirmation of pregnancy to reduce the risk of fractures and osteoporosis and of course to save money. I would continue treatment 6 weeks postpartum for all these circumstances. Neither heparin nor warfarin accumulates in breast milk, so that I have no objection to switching to warfarin postpartum.<sup>54,55</sup>

My preference is to use unfractionated heparin given the recent realization that LMWH also risks thrombocytopenia. I choose unfractionated heparin because it may better prevent complement activation than LMWH, and I think the data suggest that complement activation may be the one of the major ways that antiphospholipid antibodies cause fetal damage. Also unfractionated heparin is much less expensive than enoxaparin. Furthermore, should emergency surgery or an epidural be needed, the time interval from stopping of the unfractionated versus LMWH to be safe from bleeding is much shorter with the former versus latter.

Finally based on our own studies and lack of other convincing evidence of benefit, I will treat with unfractionated heparin alone and not use aspirin either combined or alone for APS. I would not use aspirin either for inherited thrombophilias or unexplained recurrent miscarriages.

As far as inherited thrombophilias, I agree with the statement from the ACOG Practice Bulletin No. 124 (2011) that 'most of the available studies are small case controlled and cohort studies assembled in heterogeneous population, are frequently contradictory and display potential reporting biases'.<sup>56,57</sup> Thus, I would consider ordering an inherited thrombophilia panel for unexplained second-trimester losses or a woman with a history of thrombosis if an inherited thrombophilia was detected, but I would tend to dissuade treatment for first-trimester losses.

For unexplained miscarriage without APS or evidence of an inherited thrombophilia, my preference is not to treat with heparin or as stated aspirin because of lack of evidence of any benefit and risks of therapy. My preference is to empirically supplement the luteal phase with progesterone and continue through the first trimester. The reasons for this

therapy as a personal preference have been presented in an editorial.<sup>58</sup>

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