# Low-molecular-weight heparins have no place in recurrent miscarriage: Debate - For the motion

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# Low-molecular-weight heparins Have No Place In Recurrent miscarriage: Debate – *For the motion*".

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Pregnancy failure is extremely distressing for couples who desire to have children. Pre-eclampsia and HELLP syndrome (hemolysis, elevated liver enzymes, low platelet counts) are leading causes of maternal and perinatal mortality as well as extensive morbidity. Besides venous or arterial thromboembolic manifestations, pregnancy failure and pregnancy complications are clinical criteria for the diagnosis of antiphospholipid syndrome.(1) Analogous to this acquired thrombophilic syndrome, in the nineties of the last century, the association between inherited thrombophilic disorders and miscarriage was first detected in family studies of probands, who were identified because of their history of venous thromboembolism.(2-4) Since then, many studies have confirmed the relationship between inherited thrombophilia and pregnancy failure and complications.(5;6) The potential association with thrombophilia has increased the number of investigations in couples with recurrent miscarriage and other pregnancy complications. Moreover, hematologists and thrombosis specialists are increasingly being consulted by women who have some form of thrombophilia and who were tested by gynaecologists in the context of pregnancy complications.(7) Also, a presumed benefit of antithrombotic therapy, in the absence of perceived harms, has led many clinicians to prescribe low-molecular-weight heparin, aspirin, or both to women with placenta-mediated pregnancy complications including recurrent miscarriage. Here, I debate that with the currently available best evidence, there is no role for low-molecular-weight heparin in women with recurrent miscarriage.

Definitions of several forms of pregnancy failure have not been used consistently. Recently, a revision of the nomenclature of early pregnancy events was proposed that applies ultrasound for accurate clinical assessment and diagnosis.(8) Fetal loss is defined

as the previous identification of crown-rump length and fetal heart activity followed by loss of heart activity. Recurrent miscarriage is defined as 3 early consecutive losses or 2 late pregnancy losses. Early miscarriage comprises the ultrasound definition of intra-uterine pregnancy with reproducible evidence of lost fetal heart activity, and/or failure of increased crown-rump length over one week, or persisting presence of empty sac, at less than 12 weeks gestation. From here it follows logically that late fetal loss is defined as loss after 12 weeks gestational age, where fetal measurement was followed by loss of fetal heart activity. It is of note that most studies have used other than the abovementioned definitions.

It is unlikely that hypercoagulability with thrombosis of placental vasculature is the main pathophysiological substrate for the association between acquired and inherited thrombophilia, in particular for early miscarriage in the context of antiphospholipid syndrome.(9) *In vitro* experiments have shown that antiphospholipid antibodies inhibit extravillous trophoblast differentiation and subsequent placentation.(10) This "non-prothrombotic theory" is supported by the observation that both heparin and aspirin attenuate trophoblast apoptosis *in vitro*.(11) The fact that it is not biologically plausible that an assumed thrombotic component in women with inherited thrombophilia plays a role until 10 to 12 weeks of gestation, when the placental vasculature has been developed, leaves unexplained why the vast majority of women with recurrent miscarriage have early losses. For the common forms of inherited thrombophilia, experimental models to study trophoblast differentiation and early placentation are lacking. However, thrombomodulin-deficient mice, which lack the important natural anticoagulant protein C pathway, are unable to carry their fetuses beyond 8.5 weeks gestational age, and dead

fetuses are usually resorbed within 24 hours.(12) Elegant experiments have shown that fetal demise is caused by tissue factor-dependent activation of blood coagulation at the feto-maternal interface. Activated coagulation factors were found to induce cell death and inhibit growth of trophoblast cells. Administration of heparin or aspirin to the mice delayed absorption of their embryos but was unable to restore trophoblast differentiation and overcome the growth defect of these thrombomodulin deficient embryos.
From the above it can be concluded that mere hypercoagubility is unlikely to be the sole mechanism by which thrombophilia increases the risk for pregnancy failure, most notably early losses, whereas effects on trophoblast differention and early placentation may be involved through yet unknown mechanisms. Interestingly, both aspirin and heparin appear to affect these early trophoblast and placentation mechanisms *in vitro* and in a hypercoagulability mouse model.

***Evaluating effectiveness of interventions: observational research and randomized experiments***

Observational research is a valid method to establish an association or causal relationship between thrombophilia and pregnancy complications.(13;14) Obviously, in interpreting results from association studies it is necessary to take into account whether potential bias and confounders have been sufficiently addressed in the design and execution of the study, or the analysis of the data. For clinicians the consistency and strengths of associations, the biological plausibility in terms of potential mechanisms and, crucially, whether these should lead to targeted therapy are likely to be most relevant.

Contrary to investigations on associations, a randomized experimental approach is absolutely necessary for establishing whether therapy is beneficial in women with thrombophilia and pregnancy complications, in order to avoid the problem of confounding by indication. When judging a randomized controlled trial for its validity, internal and external validity should be considered. Of course, the intervention under study should have a valid comparator, i.e. current standard of care or, most preferable, placebo. Concealment of allocation, which means that the physician that enters a patient into a trial cannot predict the treatment the patient will receive, is the key quality component in the randomization process.(15) In fact, inadequate concealment overestimates effects of interventions in controlled trials by about 30%.(16;17) Furthermore, other quality parameters are blinding of patient and doctor, blinded outcome assessment, minimal loss to follow-up, intention-to-treat analysis and provision of similar care in both interventions arms. External validity items include the possibility to generalize findings in the study population to the patient population of interest.

***Evidence from interventional studies of (low-molecular-weight) heparin in women with recurrent miscarriage***

The Table lists the currently available evidence from randomized trials that investigated the effect of any type of heparin on pregnancy loss, compared to no heparin, in women with a history of recurrent miscarriage, stratified for women with antiphospholipid syndrome and type of heparin and women with unexplained recurrent miscarriage (low-molecular-weight heparin only). Pregnancy loss was chosen as an outcome in this Table,

because not all trials have reported live birth rates. Generally, the number of women that have been studied by this adequate study design is remarkably low.

*Recurrent miscarriage in women with antiphospholipid syndrome*

In women with recurrent miscarriage based on the antiphospholipid syndrome, a well-performed randomized controlled trial showed an absolute increase of live birth rate from 41% to 72% with the use of a combination of low-dose unfractionated heparin and low-dose aspirin, compared to aspirin alone.(18) Two other trials also showed a benefit of a combination of unfractionated heparin and aspirin compared to aspirin alone (Table).(19;20) However, two randomized controlled trials in which low-molecular-weight heparin was added to aspirin did not demonstrate benefit of this combination therapy.(21;22) Whether these differences can be explained by heterogeneous patients (i.e. with regard to the diagnostic criteria of antiphospholipid antibodies), cross-over between groups, timing of start of the intervention, or the agent, remains uncertain. Small studies in which unfractionated heparin was compared directly to low-molecular-weight heparin did not suggest a beneficial effect of unfractionated heparin over low-molecular-weight heparin.(23;24) It is remarkable that there are hardly any placebo-controlled trials to assess the efficacy of aspirin alone in women with antiphospholipid syndrome.(25) The ACCP guideline recommends treating women with antiphospholipid syndrome and recurrent miscarriage with a combination of low-dose aspirin and a low dose of either unfractionated or low-molecular-weight heparin (26). The grade 1B level of recommendation (i.e. a strong recommendation based on moderate quality evidence) from this guideline is not shared by another evidence-based guideline that categorizes this

strategy into “treatment requiring an international collaborative randomized controlled trial before it is used systematically in routine clinical practice”.(27)

*Recurrent miscarriage in women with inherited thrombophilia*

The usefulness of anticoagulant treatment of women with inherited thrombophilia and recurrent miscarriage and other pregnancy complications is heavily debated.(13;14;28-31) Those in favor of heparin base their beliefs mainly on observational research, in which generally a woman's poor obstetric history was taken as the comparator. Since the prognosis of women with recurrent miscarriage has been reported to be as high as 75%,(32) such a way of analyzing data results in a severe bias toward positive outcome of any investigational treatment in the studied next pregnancy. Some other observational studies did not use a randomized design, which introduces the problem of confounding by indication (15;33;34)

Two doses of enoxaparin (40 and 80 mg) were compared in women with inherited thrombophilia and recurrent miscarriage. (35) There was no difference between both treatment arms with live birth rates of 84 and 78%. A conclusion about the efficacy of enoxaparin cannot be drawn from this trial due to the lack of a control arm without treatment.(31;36)

The effect of low-molecular-weight heparin on pregnancy loss in women with inherited thrombophilia in the absence of a history of recurrent miscarriage has been discussed elsewhere, and is not the focus of this debate.(13;37)

*Unexplained recurrent miscarriage*

Recently, randomized controlled trials that investigated the efficacy of low-molecular-weight heparin in women with unexplained recurrent miscarriage have been published, and are listed in the Table.(38-42) One trial compared low-molecular-weight heparin to aspirin, and found no difference in live birth rate or miscarriage between both treatment arms.(38) Of the other four trials, two reported strong and statistically significant beneficial effects of low-molecular-weight heparin as compared to no pharmacological treatment or placebo on pregnancy outcome.(39;40) Both studies appear to have methodological limitations that include unclear randomization (concealment of allocation), blinding and placebo procedures, inconsistencies in the reporting of study outcomes in the paper, and the lack of prospective trial registration. The most recently published trials, i.e. the SPIN study and the ALIFE study, failed to demonstrate a beneficial effect of a combination of low-molecular-weight heparin and aspirin, as compared to no treatment (41) or to aspirin alone or placebo.(42) The interventions in the SPIN study and the ALIFE study differ from the trials finding an effect. Those trials investigated the effect of low-molecular-weight heparin alone, and therefore, a deleterious effect of aspirin on pregnancy outcome cannot be entirely excluded. In the ALIFE study, 16% of women had inherited thrombophilia. Although the study was clearly underpowered for subgroup analyses, an a priori planned analysis in women with inherited thrombophilia showed a relative risk for live birth of 1.31 (95%CI: 0.74 to 2.33) for the combined intervention compared to placebo, and 1.22 (95%CI: 0.69 to 2.16) for aspirin, with corresponding absolute difference in live birth rates of 16.3% (95%CI: −18.2 to 50.8) and 11.8% (95%CI: −21.1 to 44.6) respectively. The possibility that one or

both of these interventions might be beneficial in such women warrants further study in adequately powered, controlled trials.

## Conclusions

For women with APS, unfractionated heparin combined with aspirin has been shown to be superior to aspirin alone, and there is very limited evidence of the effect of aspirin alone in this study population. This effect has not been confirmed in two studies trials that investigated the use of low-molecular-weight heparin in addition to aspirin. For women with inherited thrombophilia and recurrent miscarriage, no evidence from randomized controlled trials is currently available to justify this therapy. Although two recent studies have reported a beneficial effect of low-molecular-weight heparin compared to no pharmacological intervention in women with unexplained recurrent miscarriage, two high-quality randomized controlled trials were unable to demonstrate benefit of low-molecular-weight heparin combined with aspirin in women with unexplained recurrent miscarriage.

**Table: Available evidence from randomized controlled trials investigating heparin compared to no heparin in women with a history of recurrent miscarriage; effect on pregnancy loss.**

| Author, year (reference) | Population | Number of randomized patients | Intervention Pregnancy loss, n/N (%) | Comparator Pregnancy loss, n/N (%) | Effect size (95%CI) | Remarks |
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| ***Antiphospholipid syndrome, unfractionated heparin*** | | | | | | |
| Kutteh, 1996 (19) | Pregnant women with APLA and 3 or more consecutive miscarriages. Women with lupus excluded. | 50 | Unfractionated heparin 5000 U SC bid adjusted to attain 6 hour post injection aPTT at 1.2-1.5 times baseline and Aspirin 81 mg daily<br><br>5/25 (20.0%) | Aspirin 81 mg daily<br><br>14/25 (56.0%) | RR 0.36 (0.15-0.84) | Methodological limitation: Quasi-randomized, i.e. inadequate concealment of allocation. |
| Rai, 1997 (18) | Pregnant women with APLA and 3 or more consecutive miscarriage. Women with | 90 | Unfractionated heparin 5000U SC bid and Aspirin 75 mg daily | Aspirin 75 mg daily<br><br>26/45 (57.8%) | RR 0.50 (0.30-0.84) | |

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| | prior thrombosis or lupus excluded. | | 13/45 (28.9%) | | | |
| Goel, 2006 (20) | Pregnant women with APLA (IgG anticardiolipin) with 2 or more first or second trimester miscarriages. | 72 | Unfractionated heparin 5000 IU SC twice daily and Aspirin 80 mg daily<br><br>5/33 (15.2%) | Aspirin 80 mg daily<br><br>15/39= (38.5%) | RR 0.39 (0.16-0.97) | |
| ***Antiphospholipid syndrome, low-molecular-weight heparin*** | | | | | | |
| Farquhason, 2002 (21) | Pregnant women with APLA and at least 3 consecutive losses or 2 losses with fetal death after 10 weeks | 98 | Low-molecular-weight heparin (dalteparin) 5000U/day SC and Aspirin 75 mg daily<br><br>11/51 (21.6%) | Aspirin 75mg daily<br>13/47 (27.6%) | RR 0.78 (0.39- 1.57) | |
| Laskin, 2009 (22) | Pregnant women with APLA or inherited thrombophilia or ANA with 2 or more unexplained | 88 | Low-molecular-weight heparin (dalteparin 5000 IU/day SC) and Aspirin 81 mg daily | Aspirin 81 mg daily<br>9/43 (20.9%) | RR 1.06 (0.48-2.36) | |

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| | consecutive pregnancy losses prior to 32 weeks | | 10/45 (22.2%) | | | |
| ***Unexplained recurrent miscarriage**** | | | | | | |
| Dolitzky, 2006 (38) | Pregnant women without acquired or inherited thrombophilia and at least 3 first trimester or at least 2 second trimester pregnancy losses | 107 | Low-molecular-weight heparin (enoxaparin 40 mg sc) daily<br><br>10/54 (18.5%) | Aspirin 100 mg daily<br><br>8/50 (16.0%) | RR 1.16 (0.50-2.70) | 3 patients lost to follow-up |
| Badawy, 2008 (39) | Pregnant women without acquired or inherited thrombophilia and at least 3 pregnancy losses prior to 12 weeks | 350 | Low-molecular-weight heparin (enoxaparin 20 mg sc) daily<br><br>9/170 (5.3%) | No pharmacological treatment<br><br>19/170 (11.2%) | RR 0.47 (0.22-1.02) | 10 patients lost to follow-up. Methodological limitation: randomisation through envelopes, i.e. unclear concealment of allocation. Inconsistencies of reporting outcomes in the paper. |
| Fawzy, 2008 | Pregnant women | 109 | Low-molecular- | Placebo | RR 0.37 | Methodological |

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| (40) | without acquired or inherited thrombophilia and at least 3 pregnancy losses prior to 24 weeks | | weight heparin (enoxaparin 20 mg sc) daily<br><br>11/57 (19.3%) | 26/50 (52.0%) | (0.21-0.67) | limitations: unclear blinding and placebo procedure; 2 patients lost to follow-up. Third intervention arm with prednisone and progesterone (n=61) excluded. |
| Clark, 2010 (41) | Pregnant women with at least 2 consecutive pregnancy losses at or before 24 weeks' gestation who were not known with APLA or thrombophilia at time of enrollment | 294 | Low-molecular-weight heparin (enoxaparin 40 mg sc) daily and aspirin 75 mg daily<br><br>32/143 (22.4%) | No pharmacological treatment<br><br>29/140 (20.7%) | RR 1.08 (0.69-1.69) | 11 patients lost to follow-up. |
| Kaandorp, 2010 (42) | Women who were attempting to conceive or were less than 6 weeks pregnant and at least 2 recurrent miscarriages | 364; 299 became pregnant (used as the denominator in this table) | Low-molecular-weight heparin (nadroparin 2850 IU sc) daily and aspirin 80 mg daily<br><br>27/97 (27.8%) | Aspirin 80 mg daily or oral placebo (for aspirin)<br><br>Aspirin: 37/99 (37.4%)<br>Placebo: 31/103 | RR (compared to placebo) 0.92 (0.60-1.43) | 16% of women had inherited thrombophilia. 2 patients lost to follow-up. The trial was stopped after an interim analysis based on |

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| | prior to 20 weeks | | | (30.1%) | | futility at a time when 22 women were still in follow-up |

APLA: antiphospholipid antibodies
* Various definitions

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