Antithrombotic therapy to prevent miscarriages

Since the original publications on the relation between thrombophilias and adverse pregnancy outcome in the mid-1990s, more and more obstetricians and gynaecologists started to use heparin and/or low-molecular weight heparin (LMWH) empirically for secondary prevention of late pregnancy complications and the prevention of miscarriages in couples presenting with recurrent pregnancy loss.

In the absence of good evidence, it is not surprising to see ongoing, often heated, debates between 'believers' and 'sceptics'. With regard to the use of LMWH in patients with recurrent spontaneous miscarriages (RSM), the two recent publications by Kaandorp *et al.* (*N Engl J Med* 2010) and Clark *et al.* (*Blood* 2010) have at least filled one gap in our evidence base to manage couples presenting with RSM patients.

Aspirin plus heparin or aspirin alone in women with recurrent miscarriage

Kaandorp *et al.*

N Engl J Med 2010;**362**:1586–96

In the multicentre Dutch trial (ALIFE study), the investigators enrolled 364 women with a history of unexplained recurrent spontaneous miscarriage (RSM), excluding women with antiphospholipid syndrome. Patients were randomly assigned to receive daily 80 mg of aspirin plus open-label subcutaneous nadroparin (at a dose of 2850 IU, starting as soon as a viable pregnancy was demonstrated), 80 mg of aspirin alone or placebo. In this study, 299 patients did conceive, leaving about 90 patients per treatment arm. The results of this study show that neither aspirin combined with nadroparin nor aspirin alone improved the live-birth rate, as compared with placebo, among women with unexplained recurrent miscarriage.

In itself this is a very important trial, since it clearly shows that clinicians should not use low-molecular weight heparin (LMWH) or aspirin (or the combination) as a panacea in couples presenting with unexplained RSM. Although this trial advances our understanding, some 'sceptics' have advocated this as the definitive proof against the use of LMWH for *any* couple presenting with RSM. Comparing this study for instance with the previous trial by Gris *et al.*,¹ a number of differences are apparent. In the Gris study, 138 of the 160 patients were younger than 30, while the average age in the Dutch study was about 34 years with greater than 30% of patients being older than 36. This is a very important difference in the study groups since it is now clear that many (>70%) of women aged greater than 34 years presenting with RSM already have major drops in their anti-Müllerian hormone levels reflecting poor oocyte quality (abstracts McCormack *et al.*, COGI, 2008, Paris and RANZCOG ASM, 2010, Adelaide).

It should also be noted that only 35–40 patients per arm had a history of a prior late miscarriage, but it is not specified how many of this subgroup actually conceived. This is of major importance since miscarriages occurring <10 weeks gestation

in the absence of antiphospholipid antibodies are probably unrelated to pathological activation of the clotting cascade, since the intervillous space is absent prior to 9–10 weeks gestation. These miscarriages are mostly linked to aneuploidy, and pregnancy outcome in these cases will not be influenced by any known treatment.

It should also be noted that in this particular study the actual number of patients with thrombophilia was (surprisingly) low – with a more 'normal' prevalence of 9.2 % for Factor V Leiden in the placebo group versus a very low prevalence of 4.8% in the aspirin + Nadroparin group. Of note, antithrombin deficiency, known to be extremely rare, was diagnosed in 1.9% in the aspirin plus Nadroparin group and 3% in the aspirin only group! Again, this very low prevalence of thrombophilias in the ALIFE study fits with the concept that in a majority of these RSM couples, the main problem had nothing to do with pathological degrees of thrombosis. Furthermore, the authors used a homocysteine level of <16 µmol/L as normal, a cut-off that is too high for women in their reproductive years. In our own experience a homocysteine of 9.5 µmol/L represents the 90th centile.

Although the investigators do provide the pregnancy outcome in these small subgroups, they appropriately identify the need for adequately powered randomized controlled trials in patients with pregnancy loss >10 weeks gestation with a thrombophilia. Overall, this is an excellent study, but it provides only limited guidance for management of these women. The study confirms that one should not use antithrombotic therapy as a panacea in women in their mid-30s presenting because of unexplained RSM.

SPIN: the Scottish Pregnancy Intervention Study: a multicenter randomized controlled trial of low molecular weight heparin and low dose aspirin in women with recurrent miscarriage

Clark *et al.*

Blood 2010;**115**:4162–7

In this Scottish trial, 294 patients less than seven weeks gestation, with a history of two or more consecutive previous pregnancy losses at 24 or fewer weeks gestation and no evidence of anatomic, endocrine, chromosomal or immunologic abnormality (antiphospholipid patients excluded) were studied. They were randomly assigned to receive either enoxaparin 40 mg subcutaneously and 75 mg of aspirin orally once daily along with intense pregnancy surveillance or intense pregnancy surveillance alone from assignment until 36 weeks gestation. The primary outcome measure was pregnancy loss rate. Of the 147 participants receiving pharmacological intervention, 32 (22%) pregnancy losses occurred, compared with 29 losses (20%) in the 147 subjects receiving intensive surveillance alone, giving an odds ratio of 0.91 (95% confidence interval, 0.52–1.59) of having a successful pregnancy with pharmacological intervention.

The main issue with this study is that no data are provided with regard to the gestational age of prior pregnancy losses. By default one has to assume that most of these losses were

early – i.e. <10 weeks gestation – so one could really not expect any beneficial effect from antithrombotic therapy.

In addition, this trial has only 10 patients with a thrombophilia (8 factor V Leiden, 2 with prothrombin gene); hence like the the ALIFE study, this study does not provide any data with regard to how to manage patients with miscarriages >10 weeks gestation in the presence of a documented thrombophilia.

What these studies show us:

Both trials provide more or less the same limited message for clinicians, i.e. don't use antithrombotic therapy empirically in patients with unexplained miscarriages, particularly if they are aged in their mid to late 30s and have experienced primarily early miscarriages. It is important to emphasize, once more, that we still lack evidence to guide us in the management of the smaller group of often younger patients presenting with

pregnancy losses >10 weeks gestation and a documented thrombophilia. The limited evidence that does exist suggests that these are the patients who might benefit from antithrombotic therapy.

REFERENCE

- 1 Gris JC, Mercier E, Quéré I, *et al.* Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. *Blood* 2004;103:3695–9

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