Royal College of
Obstetricians and Gynaecologists

Bringing to life the best in women's health care

Scientific Advisory Committee
Opinion Paper 26

June 2011

The Use of Antithrombotics in the Prevention of Recurrent Pregnancy Loss

The Use of Antithrombotics in the Prevention of Recurrent Pregnancy Loss

1. Purpose and scope

Over the last 5 years, there has been a large increase in the use of aspirin and low-molecular-weight heparin (LMWH) to attempt to prevent pregnancy loss. Until recently, robust clinical evidence to examine this practice was lacking. In 2009, a Cochrane review of anticoagulants for non-antiphospholipid recurrent pregnancy loss indentified only two studies of 189 women. Neither study showed a benefit of one treatment over another. The Cochrane review concluded that there was no evidence for this practice and identified the urgent need for further trials.[1] Furthermore, even in the case of antiphospholipid syndrome (APS)-associated pregnancy loss, no benefit was found in an analysis of three trials of aspirin compared with placebo.[2] The purpose of this opinion paper is to discuss the rationale behind the use of antithrombotics in women with recurrent pregnancy loss.

2. Background and introduction

Recurrent pregnancy loss has several definitions. In this paper the definition used is 'the occurrence of three or more consecutive pregnancies that end in miscarriage of the fetus before 20 weeks of gestation'. Recurrent pregnancy loss affects about 0.34% of women who become pregnant. Approximately 15% of all clinically recognisable pregnancies end in pregnancy loss,[3] with three or more losses affecting 1–2% of women of reproductive age and two or more losses affecting around 5%.[4] Despite extensive investigation of women with three or more miscarriages,[5] the cause of recurrent pregnancy loss remains unknown in the majority of women.[5]

Up to 15–20% of women with recurrent pregnancy loss have antiphospholipid antibodies (aPL). A significant difference in pregnancy outcomes was reported by Rai et al. in 1997 in a cohort of women with aPL when treated with low-dose aspirin and unfractionated heparin compared with low-dose aspirin alone in those with pregnancy losses before 13 weeks of gestation.[6] Interestingly, no difference was noted in pregnancies that advanced beyond 13 weeks of gestation. However, a similar study by Farquharson et al. of 98 women treated with LMWH instead of unfractionated heparin showed no statistically significant improvement in pregnancy outcome with the addition of LMWH.[7] Neither the study by Rai et al. nor that of Farquharson et al. included a no-treatment arm.[6,7] In 2005, Empson led a systematic Cochrane review which concluded that the quality of studies in women with recurrent pregnancy loss and aPL was not high; in particular, there was no allocation concealment.[2] The authors' conclusion that there may be a 54% absolute risk reduction in pregnancy loss in women treated with unfractionated heparin and aspirin was not based on the Farquharson et al. trial that used LMWH.[2] In addition, the authors concluded that aspirin alone, compared with placebo, did not improve live birth rates.[2]

3. Pathophysiology of recurrent pregnancy loss

3.1 Antiphospholipid antibodies

The concept of using antithrombotics for managing recurrent pregnancy loss stems from the data around APS. One of the many targets of aPL is the placenta. The major histopathological findings in the placenta of aPL-positive women are thrombosis, acute atherosis, a decreased number of synctiovascular membranes, increased numbers of syncytial knots and obliterative arteriopathy.[8] These findings are not specific to APS and do not always correlate with fetal outcome.

The mechanism by which aPL causes damage to the placenta has not been clarified. Originally, it was attributed to a direct effect on haemostasis. However, in vitro studies have shown that aPL have a direct effect on trophoblast cell function, specifically differentiation, apoptosis, invasion and migration.[9–12]

An elegant mouse model of obstetric APS has suggested that complement activation mediates the effect of aPL. Moreover, in this model, heparin (which is known to have an anticomplement effect in both mice and humans) blocked activation of complement and prevented pregnancy loss.[13] As yet, there are no data from human studies to address whether these intriguing findings are applicable to humans.

The clinical phenotype of APS varies widely, suggesting that different women have different types and quantities of aPL. The best predictor of pregnancy outcome in women with aPL is past obstetric history. Current practice is to individualise treatment depending on mode of presentation, previous pregnancy outcomes and history of venous or arterial thrombotic events.

3.2 Inherited thrombophilia

Publications suggesting that heparin and aspirin reduced pregnancy loss in women with aPL led others to hypothesise that women with inherited thrombophilia may also be subject to recurrent pregnancy loss. The European Prospective Cohort on Thrombophilia identified a group of 1384 women positive for thrombophilia who showed an increased risk of miscarriage (defined as loss up to 28 weeks of gestation) (OR 1.35, 95% CI 1.01–1.82) and a greater increased risk of stillbirth (defined as loss after 28 weeks of gestation) (OR 3.6, 95% CI 1.4–94).[14] Subsequent studies have confirmed the relationship with second- and third-trimester losses, and a slightly increased risk of first-trimester losses for some of the thrombophilias.[15,16] The presumption is that the inherited thrombophilias, like aPL, predispose to placental vasculopathy. However, how they might cause increased first-trimester loss through a thrombotic mechanism is uncertain.

It is recognised that a thrombophilia screen is positive in only approximately 60% of those patients with both personal and family history of venous thromboembolism, suggesting that there remain unidentified inherited thrombophilias. One group has used thromboelastography and showed that a group with a history of miscarriage had a more prothrombotic trace than those without.[17] Does this study suggest that there might be other as yet unidentified thrombophilias related to pregnancy loss? More studies are required to confirm the association before a conclusion can be reached.

It seems that a practice of routinely giving LMWH and aspirin to these women has developed as a consequence of these studies, the weak association between thrombophilia and pregnancy loss and the lack of any other treatment to offer women with recurrent pregnancy loss,.

4. Recent randomised controlled trials in recurrent pregnancy loss

The publication of four well conducted randomised controlled trials in the UK,[18] the Netherlands,[19] Finland[20] and Canada[21] has provided valuable new data. Two of the studies recruited women with a history of only two or more idiopathic pregnancy losses at enrolment (SPIN[18] and ALIFE[19]); in the SPIN study, women subsequently found to have a thrombophilia were not excluded.[18] The SPIN study compared LMWH (enoxaparin), low-dose aspirin and intensive surveillance with intensive surveillance alone in 294 women who were recruited at less than 7 weeks of gestation.[18] There was no reduction in pregnancy losses with antithrombotic intervention. Kaandorp et al. randomised 364 women who were attempting to conceive into three groups: low-dose aspirin and LMWH (nadroparin), low-dose aspirin alone or placebo.[19] Pregnancy was achieved in 299 women and 197 women had a live birth (65.9% of those who became pregnant). The live birth rate did not differ statistically between the three study groups. In addition, the live birth rate in the placebo group (67%) was higher than that in the low-dose aspirin group (62%); however, this potentially deleterious effect of aspirin in causing miscarriage (absolute risk difference 5.2, 95% CI 1.8–7.8) did not reach statistical significance.[19]

The HABENOX trial was a randomised double-blind multicentre trial on 207 women with three or more consecutive first-trimester miscarriages (at less than 13 weeks of gestation), two or more second-trimester miscarriages (at 13–24 weeks of gestation) or one third-trimester fetal loss combined with one first-trimester miscarriage.[20] The live birth rate was 71% (RR 1.17, 95% CI 0.92–1.48) for enoxaparin and placebo and 65% (RR 1.08, 95% CI 0.83–1.39) for enoxaparin and aspirin compared with aspirin

alone (61%).[20] However this trial was ended prematurely because of slow recruitment.[20] Thus, there are now three placebo-controlled trials in women with idiopathic recurrent pregnancy loss that show no benefit from antithrombotic treatment.

Thrombophilias have been associated with recurrent pregnancy loss, although the incidences in the control, general and recurrent pregnancy loss populations vary hugely. There is a lack of data for pregnancy outcomes with individual coagulation abnormalities and as a result treatment varies widely. In women with previous thromboembolic disease, LMWH is often used in pregnancy to prevent maternal thrombosis. In women who have had a previous pregnancy loss, aspirin and LMWH are increasingly used with the aim of preventing both pregnancy loss and maternal thrombosis. The HepASA trial recruited women with a history of two or more pregnancy losses and at least one of the following: aPL, an inherited thrombophilia and/or antinuclear antibody.[21] Out of the 859 women who were screened, 88 became pregnant and were randomised to receive low-dose aspirin and LMWH (dalteparin) or low-dose aspirin alone. There were no differences in the live birth rate between the two groups (77.8% versus 79.1%).[21] The HepASA trial did not have a no-therapeutic treatment arm, as was present in both the SPIN[18] and Netherlands[19] trials. The SPIN, ALIFE and HABENOX trials also included women with inherited thrombophilias, and the subset analyses of these found no benefit from either low-dose aspirin or low-dose aspirin and LMWH above absence of pharmaceutical treatment in these women.[19,20]

5. Therapeutic effects of heparin

In vitro studies of the effect of heparin on trophoblast function have demonstrated varying results: heparin reversed the in vitro effect of aPL in supra-therapeutic doses;[10] supra-therapeutic doses of unfractionated heparin inhibited trophoblast apoptosis;[22] at therapeutic doses, unfractionated heparin promoted but LMWH inhibited trophoblast differentiation;[23] and both unfractionated heparin and LMWH inhibited trophoblast invasion.[24] Hence, in vitro studies do not support a role for heparin in improving trophoblast development in the absence of APS.

In normally developing pregnancies, intervillous blood flow starts only between 8 and 12 weeks of gestation and is consistently present only from 12 weeks of gestation.[25] Hence, the end of the first trimester is characterised by a progressive increase in blood flow, oxygenation and oxidative stress.[26] First-trimester miscarriage has been characterised by early and excessive placental blood flow.[26] Thus, in this biological framework it is unlikely that thrombosis leading to a reduction in blood loss is a contributory factor in early pregnancy loss and that prevention of thrombosis will prevent early pregnancy loss.

A key issue for clinical studies is that most studies include losses up to 20 weeks of gestation, although the definition of fetal loss varies. This means that studies may contain women with losses attributable to two different mechanisms. Before 10–12 weeks of gestation there is no intervillous blood flow; until then, respiration and nutrition are by passive transfer across tissues. Some might argue that such distinctions ignore the reality that embryo–fetal development is truly a continuum. However, contrary to the continuum paradigm, there are clear milestones in development, and the 10–12-week mark is one of these. Thus, 'thrombosis of the placenta' as a cause of fetal loss can be ascribed only to losses after the initiation of blood flow at 10–12 weeks of gestation. Moreover, as the majority of trials of recurrent pregnancy loss contain women with pregnancy losses before 12 weeks of gestation, the effect of heparin and aspirin is not being properly assessed in those with losses after 12 weeks of gestation; that is, in the second trimester. There is evidence from two pilot trials of LMWH that the use of antithrombotics may be effective in preventing placental thrombosis after 12 weeks of gestation.[27,28] In support of the concept of a gestation-specific effect of antithrombotic treatment on pregnancy loss is the finding that low-dose aspirin has a moderate effect at preventing pre-eclampsia in the second and third trimesters.[29]

6. Opinion

Four recent randomised controlled trials including women with two or more pregnancy losses have failed to demonstrate any improvement in pregnancy outcome in women with idiopathic recurrent pregnancy loss with low-dose aspirin with or without LMWH. The trials are underpowered to confirm or refute an effect in women with three or more losses or those with thrombophilia, although in all trials post hoc subgroup analyses for these factors showed no trend in terms of benefit. These findings are important, as they indicate that the empirical administration of heparin and aspirin in recurrent pregnancy loss should discontinue. The only place for heparin and aspirin in the prevention of pregnancy loss in the absence of APS is in well conducted randomised controlled trials of high-risk women. However, in the case of APS and recurrent pregnancy loss, aspirin and heparin are still recommended.

The use of antithrombotic therapy in women with recurrent pregnancy loss in the second trimester is biologically plausible. Future clinical trials should test this by separate analysis and/or recruitment to either recurrent first-trimester loss or second-trimester loss trials in view of the probable different mechanisms by which these losses occur.

The other broader implication of these recent trials is that non-thrombotic mechanisms for treatment of recurrent first-trimester pregnancy loss should be sought.

References

1. 1. Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin or anticoagulants for treating recurrent miscarriage in women without antiphospholipid syndrome. *Cochrane Database Syst Rev* 2009;(1):CD004734.
2. Empson MB, Lassere M, Craig JC, Scott JR. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev* 2005;(2):CD002859.
3. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. *N Engl J Med* 1988;319:189–94.
4. Younis JS, Ohel G, Brenner B, Ben-Ami M. Familial thrombophilia: the scientific rationale for thromboprophylaxis in recurrent pregnancy loss? *Hum Reprod* 1997;12:1389–90.
5. Royal College of Obstetricians and Gynaecologists. *The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage*. Green-top Guideline No. 17. London: RCOG; 2011.
6. Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997;314:253–7.
7. Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol* 2002;100:408–13. Erratum in: *Obstet Gynecol* 2002;100:1361.
8. Levy RA, Avvad E, Oliveira J, Porto LC. Placental pathology in antiphospholipid syndrome. *Lupus* 1998;7 Suppl 2:S81–5.
9. Chamley LW, Duncalf AM, Mitchell MD, Johnson PM. Action of anticardiolipin and antibodies to beta2-glycoprotein-I on trophoblast proliferation as a mechanism for fetal death. *Lancet* 1998;352:1037–8.
10. Bose P, Black S, Kadyrov M, Bartz C, Shlebak A, Regan L, et al. Adverse effects of lupus anticoagulant positive blood sera on placental viability can be prevented by heparin in vitro. *Am J Obstet Gynecol* 2004;191:2125–31.
11. Quenby S, Mountfield S, Cartwright JE, Whitley GS, Chamley L, Vince G. Antiphospholipid antibodies prevent extravillous trophoblast differentiation. *Fertil Steril* 2005;83:691–8.
12. Mulla MJ, Myrtolli K, Brosens JJ, Chamley LW, Kwak-Kim JY, Paidas MJ, et al. Antiphospholipid antibodies limit trophoblast migration by reducing IL-6 production and STAT3 activity. *Am J Reprod Immunol* 2010;63:339–48.

13. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. *Nature Med* 2004;10:1222–6.
14. Preston FE, Rosendaal FR, Walker ID, Briët E, Berntorp E, Conard J, et al. Increased fetal loss in women with heritable thrombophilia. *Lancet* 1996;348:913–6.
15. Alfirevic Z, Roberts D, Martlew V. How strong is the association between maternal thrombophilia and adverse pregnancy outcome? A systematic review. *Eur J Obstet Gynecol Reprod Biol* 2002;101:6–14.
16. Rey E, Kahn SR, David M, Shrier I. Thrombophilic disorders and fetal loss: a meta-analysis. *Lancet* 2003;361:901–8.
17. Rai R, Tuddenham E, Backos M, Jivraj S, El'Gaddal S, Choy S, et al. Thromboelastography, whole-blood haemostasis and recurrent miscarriage. *Hum Reprod* 2003;18:2540–3.
18. Clark P, Walker ID, Langhorne P, Crichton L, Thomson A, Greaves M, et al.; Scottish Pregnancy Intervention Study (SPIN) Collaborators. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood* 2010;115:4162–7.
19. Kaandorp SP, Goddijn M, van der Post JA, Hutten BA, Verhoeve HR, Hamulyák K, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med* 2010;362:1586–96.
20. Visser J, Ulander VM, Helmerhorst FM, Lampinen K, Morin-Papunen L, Bloemenkamp KW, et al. Thromboprophylaxis for recurrent miscarriage in women with or without thrombophilia. HABENOX: a randomised multicentre trial. *Thromb Haemost* 2011;105:205–301.
21. Laskin CA, Spitzer KA, Clark CA, Crowther MR, Ginsberg JS, Hawker GA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA trial. *J Rheumatol* 2009;36:279–87.
22. Bose P, Black S, Kadyrov M, Weissenborn U, Neulen J, Regan L, et al. Heparin and aspirin attenuate placental apoptosis in vitro: implications for early pregnancy failure. *Am J Obstet Gynecol* 2005;192:23–30.
23. Quenby S, Mountfield S, Cartwright JE, Whitley GS, Vince G. Effects of low-molecular-weight and unfractionated heparin on trophoblast function. *Obstet Gynecol* 2004;104:354–61.
24. Ganapathy R, Whitley GS, Cartwright JE, Dash PR, Thilaganathan B. Effect of heparin and fractionated heparin on trophoblast invasion. *Hum Reprod* 2007;22:2523–7.
25. Jauniaux E, Hempstock J, Greenwold N, Burton GJ. Trophoblastic oxidative stress in relation to temporal and regional differences in maternal placental blood flow in normal and abnormal early pregnancies. *Am J Pathol* 2003;162:115–25.
26. Burton GJ. Oxygen, the Janus gas; its effects on human placental development and function. *J Anat* 2009:215:27–35.
27. Gris JC, Chauleur C, Faillie JL, Baer G, Marès P, Fabbro-Peray P, et al. Enoxaparin for the secondary prevention of placental vascular complications in women with abruptio placentae. The pilot randomised controlled NOH-AP trial. *Thromb Haemost* 2010;104:771–9.
28. Rey E, Garneau P, David M, Gauthier R, Leduc L, Michon N, et al. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. *J Thromb Haemost* 2009;7:58–64.
29. Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2007;(2):CD004659.

APPENDIX 1

Glossary/definitions used in this report

Antiphospholipid antibodies (aPL)

The persisting presence of either a lupus anticoagulant and/or anticardiolipin antibody and/or antibodies to beta-2 glycoprotein I on separate occasions more than 8–12 weeks apart.

Antiphospholipid syndrome (APS)

The association of arterial and/or venous thrombosis and/or specific pregnancy-related morbidity with antiphospholipid antibodies. The specific obstetric morbidity includes:

- unexplained recurrent first-trimester loss
- second- or third-trimester loss with no other explanation
- evidence of placental dysfunction: pre-eclampsia and placental abruption before 34 weeks of gestation, fetal growth restriction.

The term obstetric APS is often used for those with previous obstetric problems as described above and persisting aPL. The term thrombotic APS is used for those with previous thrombosis and persisting aPL.

Recurrent pregnancy loss

Habitual abortion, recurrent miscarriage or recurrent pregnancy loss is the occurrence of repeated (three or more consecutive) pregnancies that end in miscarriage of the fetus before 20 weeks of gestation.

This opinion paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:
Professor S M Quenby FRCOG, Warwick; Professor B J Hunt FRCP FRCPath MD, Guy's and St Thomas' NHS Foundation Trust, London; and Dr HJ Maybury MRCOG

and peer reviewed by:
Professor J G Thornton FRCOG, Nottingham; Dr S Middeldorp, The Netherlands; Professor I Greer FRCOG, Liverpool; RCOG Consumers' Forum; The Miscarriage Association.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The review process will commence in 2014 unless otherwise indicated.

