Low molecular weight heparin: the answer to adverse outcomes in obstetrics?

Obstetricians like all of us are a mixed group. Some are early adopters, picking up on trends and anecdotes and adapting them to their practice, with or without appropriate evidence. Others are more considered, awaiting high-quality evidence or endorsed Guidelines and Recommendations before changing their practice.

One of the areas of obstetrics where this pattern has been most obvious is the area of thrombophilias and pregnancy outcome. From the first publications linking antiphospholipid syndrome and recurrent miscarriage, a burgeoning literature has evolved associating congenital and acquired thrombophilic disorders and the late pregnancy clinical sequelae of pre-eclampsia, fetal growth restriction and placental abruption. The putative common mechanism is placental ischaemia and infarction although other mechanisms may also occur. In response to this association, obstetricians started to adopt antithrombotic prophylaxis in women considered at risk of events because of any history of late pregnancy complications.¹ This was driven by a lack of alternative therapies and the hope that evidence would emerge showing benefit similar to those demonstrated for antithrombotic interventions in women with antiphospholipid syndrome.

Medicine based on hope rather than evidence is not optimal for practice

The premature adoption of interventions raises not only hope but also risks adverse outcomes, and can delay or prevent appropriate clinical trials through an assumption of efficacy, and reluctance of patients to be randomized when obstetricians are already using the intervention.

Two recent trials have recently reported their findings regarding the use of low molecular weight heparin for the prevention of these late, placenta-mediated pregnancy complications in women, one including those with a recognized heritable thrombophilia.^{1,2} Conducting such trials is no easy matter in pregnancy and takes considerable time. These investigators should be commended for not only developing the trials, but also for persevering with recruitment over many years to achieve an outcome. At almost the same time as these two trials were published, the American College of Chest Physicians published their updated guidelines and specified:

For women with inherited thrombophilia and a history of pregnancy complications, we suggest not to use antithrombotic prophylaxis (Grade 2C). For women with two or more miscarriages but without APLA or thrombophilia, we recommend against antithrombotic prophylaxis (Grade 1B).³

So do these trials impact on this recommendation? The HAPPY trial by Martinelli *et al.*¹ was the first large, well designed, prospective, randomized trial to examine the use of Heparin in pregnant women with Adverse Pregnancy outcome to

improve the rate of successful Pregnancy. They compared the incidence of recurrent events in 135 women considered at increased risk because of previous late pregnancy complications such as pre-eclampsia. The women were randomized to treatment with low molecular weight heparin (LMWH) or to medical surveillance alone. The HAPPY trial was stopped by reason of futility after three years. Only 50% of the planned patients had been recruited. Overall, 21% of women randomized to active treatment developed a combined end point compared with 18% of controls, a difference that was not significant (event risk difference of 2.2 [95% CI: 11.6 to 16.0]). The distribution of the individual components of the composite end point namely pre-eclampsia, eclampsia, HELLP syndrome, fetal growth restriction, intrauterine fetal death and abortion did not differ between the groups. The women in the study were not selected on the presence of a heritable thrombophilia; therefore, this trial would not have influenced the ACCP recommendation, but clearly showed no benefit in women selected on the basis of clinical outcome in their previous pregnancies.

The FRUIT study (FRactionated heparin in pregnant women with a history of Utero-placental Insufficiency and Thrombophilia) was a randomized, multicentre trial examining the addition of LMWH to aspirin at less than 12 weeks gestation on recurrence of hypertensive diseases (HD) in women with documented thrombophilia (excluding antiphospholipid syndrome).² HD included early-onset (delivery prior to 34 weeks) pre-eclampsia, HELLP syndrome, eclampsia and/or delivery of a small for gestational age (SGA) (<10th centile) baby. All the women were selected on the basis of heritable thrombophilia (protein C deficiency, protein S deficiency, activated protein C resistance, factor V Leiden heterozygosity and/or prothrombin gene G20210A mutation heterozygosity).

One hundred and thirty-nine women were included. They were randomized to daily LMWH with low-dose aspirin (LDA) or LDA alone. The primary outcomes were recurrent HD onset (i) <34 weeks gestation and (ii) irrespective of gestational age. The secondary outcomes were recurrent SGA baby, preterm birth, maternal/neonatal hospitalization, spontaneous miscarriage and individual HD. Analysis was by intention-to-treat. LMWH with aspirin reduced recurrent HD onset <34 weeks gestation (risk difference [RD] 8.7%: confidence interval CI of RD 1.9–15.5%; $P = 0.012$) but recurrent HD irrespective of gestational age was not different between the arms. However, other than the reduced use of steroids the clinical benefit of this is uncertain as all other clinical outcomes were not different between the groups. In designing the trial, the risk of recurrent events in the women was overestimated (albeit based on previous experience) and the actual event rate was much lower than anticipated and similar to that seen in the HAPPY trial. In addition, unlike the HAPPY trial, a one-sided statistical analysis was performed assuming that the intervention could not result in a worse outcome, so reducing the necessary sample size. The appropriateness of this assumption is debatable. Further, a large systematic review of thrombophilia and adverse pregnancy outcome did not show clear associations with HD or SGA for all the thrombophilias used as inclusion criteria.⁴ Therefore the FRUIT trial reports a modest effect on reduction in early onset HD in women with

previous adverse outcomes and heritable thrombophilia, without any additional clinical benefit other than reduced steroid use.

Thus while encouraging that such intervention may be effective, essentially these data can only be regarded as preliminary in terms of clinical benefit. There is an urgent need for further evidence of genuine clinical benefit, and the results of the TIPPS trial⁵ remains important. Until such further evidence emerges, the ACCP recommendation remains appropriate.

Ian Greer

Faculty of Health & Life Sciences, University of Liverpool, Liverpool, UK
Email: Ian.Greer@liverpool.ac.uk
DOI: 10.1258/om.2012.12E007

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(Accepted 28 September 2012)