BJOG Mini-commentary by Andrew D. Weeks

2015-OG-15305- Raghavan et al.

Misoprostol for primary versus secondary prevention of postpartum haemorrhage: a cluster-randomised non-inferiority community trial

**1. The concept of ‘secondary prevention’**

The study by Raghavan et al examines a new concept in PPH management – that of ‘secondary prevention’. I know of no previous randomised trial in which that concept has been explicitly stated. The concept is that it may be more cost-effective and acceptable to women for PPH to be treated at an early stage (350mls) rather than the usually quoted level of 500mls. In truth, in many previous studies of PPH prophylaxis, actual blood loss was not measured and so the level at which they really treated blood loss is not know. But an individual patient data analysis of several large randomized trials shows that the individuals who receive treatment for PPH frequently have blood loss of much less than 500mls (N. Aflaifel, PhD Thesis, University of Liverpool), and this fits with data from simulation studies. Clinicians commonly start to treat PPH as soon as they consider it ‘more than normal’ and so often don’t wait for the woman to bleed 500mls. If this is true in previous studies then many of the previous ‘oxytocin’ versus ‘physiological’ management studies might have been very similar to this one. Intriguingly, the halving of PPH rates seen in this study is also very similar to the results of those previous active management studies (Begley et al. *Active versus expectant management for women in the third stage of labour.* Cochrane Database Syst Rev 2011;9:CD007412).

This study moves the understanding of PPH care forward considerably. Not because it provides any definitive answers, but because it dares ask the question ‘is physiological management cost-effective and safe in low risk women in low and middle income countries?’ This question would have been very ‘alternative’ and seen as being potentially dangerous talk just 10 years ago. And yet it is a very important question to ask and the research team should be congratulated for taking it on. The study opens up the whole field of PPH care and deserves to be replicated.

**2. Use of appropriate outcomes**

There is a noticeable difference between the results of the PPH outcomes (rate of measured blood loss >500, transfer for PPH and mean blood loss) and that of the postpartum levels of anaemia. It would appear that there are no recruitment haemoglobin levels done and this is a shame. In this study there were so few PPHs that any effect on the postpartum haemoglobin levels would be lost in the noise of background postpartum anaemia for other causes. Assuming that the only cause of a peripartum fall in haemoglobin is excessive blood loss (which was a rare problem), the antepartum anaemia rates are likely to have been far higher than expected.

The appropriate conclusion from the comparable rates of PN anaemia is not that the two strategies are equally effective, but that the rate of PPH is so low and background rates of anaemia so high, that postnatal anaemia is an inappropriate indicator of success in this population. So whilst on the stated primary outcome this study shows non-inferiority, the results provide considerable evidence that in this population the use of postnatal anaemia as the primary outcome was not the correct choice, especially when there was no baseline level to demonstrate that there was initial parity between the groups. And given the very low rates of PPH, this study was underpowered to detect a treatment effect.

But why was the PPH rate so low? This is likely to be because only low risk women in normal labour were included. This group has low rates of PPH and relatively good outcomes when they do get PPH. Therefore they may not be the women most at risk of PPH deaths (AD Weeks & JP Neilson. Rethinking our approach to postpartum haemorrhage and uterotonics. BMJ 2015). If we are to make inroads into the huge death toll form PPH, future studies need to concentrate on those at the highest risk: those with placenta praevia, abruption, emergency CS, intrapartum haemorrhage and prolonged labour.