AGAINST: A call for a measured response to the OPPTIMUM trial

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With the concluding words of her plenary talk at the 2016 Society for Maternal–Fetal Medicine Annual Meeting – 'I wouldn't advise my daughter take vaginal progesterone' – had Jane Norman and the OPPTIMUM team placed a proverbial nail in the coffin of the only class of medication routinely used for the prevention of preterm birth (PTB)? For practitioners in a field with tragically few effective interventions, it is imperative that we cast a critical eye on even the most robust randomised controlled trial (RCT).

First, although OPPTIMUM studied 1197 women, the inclusion criteria were remarkably broad. This is curious, as the clinical efficacy of progestogens differs not only by formulation (e.g. natural vaginal versus synthetic intramuscular), but also by indication (e.g. prior PTB or short cervix). The OPPTIMUM study design almost immediately forced us to think about subgroup analyses. Though asymptomatic cervical shortening remains the primary indication for vaginal progesterone (ACOG Practice Bulletin 130, October 2012), in OPPTIMUM the subgroup with a cervical length of <25 mm was limited to only 256 women. In comparison, the American Congress of Obstetricians and Gynecologists (ACOG) based its recommendations on two RCTs of women with short cervix length: both studies randomised >410 women (Hassan et al. *Ultrasound Obstet Gynecol* 2011;38:18–31; Fonseca et al. *N Engl J Med* 2007;357:462–9).

Second, women were randomised at 22–24 weeks of gestation, so women delivering at 18–22 weeks of gestation as a result of PTB (arguably, those at highest risk) would not have been eligible for randomisation. Still others identified to be at highest risk <22 weeks of gestation – particularly those with a very short cervix – may have pursued active treatment in lieu of waiting several weeks to be randomised. Furthermore, given that progesterone is hypothesized to work through anti-inflammatory mechanisms, do irreversible (and potentially modifiable) changes occur <22 weeks of gestation among women destined to deliver preterm? Studies of intramuscular progesterone demonstrate increased efficacy with earlier initiation of treatment (Markham et al. *Obstet Gynecol* 2014;123:34–9). As several OPPTIMUM point estimates favour progesterone, we can't help but wonder if the right treatment was administered but just started too late to be efficacious.

Finally, the trial has been broadly described as a negative one. Although no significant reduction in the composite primary outcomes was identified, vaginal progesterone was associated with a significant reduction in neonatal death (odds ratio, OR 0.17; 95% confidence interval, 95% CI 0.06–0.49) and neonatal brain injury (OR 0.50; 95% CI 0.31–0.84). Perhaps on this point alone our opinions and the opinions of our patients diverge regarding the significance of the results? Or, as the Patient-Centered Outcomes Research Institute (PCORI) literature challenges us, who is best positioned to select the outcomes around which our studies should be powered?

Progestogens are estimated to prevent nearly 20 000 PTBs in the US annually (Schoen et al. *AJOG* 2015;213(2):175–180). Despite this, many others cannot be prevented. This work is a tremendous contribution, yet does not warrant practice change. As perinatologists we echo the authors' call for a 're-doubling of efforts to find alternative strategies to prevent preterm birth in women at risk'. Until that time, however, we will continue to prescribe the only class of medication with proven efficacy and safety for PTB prevention; progestogens. Our patients, and our daughters, deserve no less.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.