

# Is 17 $\alpha$ -hydroxyprogesterone caproate contraindicated in twin gestations?

R Romero,<sup>a,b,c</sup> A Conde-Agudelo<sup>a</sup>

<sup>a</sup>Perinatology Research Branch, Program for Perinatal Research and Obstetrics, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD and Detroit, MI, USA <sup>b</sup>Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA <sup>c</sup>Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA

Correspondence: R Romero, Perinatology Research Branch, NICHD, NIH, DHHS, 3990 John R, Box 4, Detroit, MI 48201, USA.  
Email: romeror@mail.nih.gov

Accepted 25 July 2014. Published Online 3 October 2014.

Please cite this paper as: Romero R, Conde-Agudelo A. Is 17 $\alpha$ -hydroxyprogesterone caproate contraindicated in twin gestations? BJOG 2015;122:6–7.

In this issue of *BJOG*, Schuit et al.<sup>1</sup> report the results of an important individual patient data (IPD) meta-analysis on the efficacy of progestogens for the prevention of preterm birth and neonatal morbidity in twin gestations. IPD meta-analyses are based on the raw data from each patient and are considered the ‘gold standard’ for summarising evidence across clinical studies.

The primary outcome of the IPD meta-analysis was a composite of perinatal mortality and serious neonatal morbidity. Secondary outcomes included the individual events of the composite endpoint and fetal death or preterm birth at several gestational ages. The investigators performed subgroup analyses to explore the effect of progestogens on these outcomes according to chorionicity, sonographic cervical length at randomisation (and at <24 weeks of gestation), and a previous spontaneous preterm birth (<37 weeks of gestation). Two progestogens were studied: 17 $\alpha$ -hydroxyprogesterone caproate (17-OHPC) and vaginal progesterone.<sup>2</sup>

The authors found that 17-OHPC did not reduce the risk of adverse perinatal outcomes in unselected women with a twin gestation. However, there was a trend towards an increase in the risk for the majority of adverse perinatal outcomes among women treated with 17-OHPC. In addition, the administration of 17-OHPC in women with a cervical length >25 mm at randomisation and before 24 weeks of gestation was associated with a significantly increased risk of the composite perinatal outcome (relative risk [RR] 2.1, 95% confidence interval [95% CI] 1.9–2.2 at randomisation and RR 1.4, 95% CI 1.26–1.5 before 24 weeks). Given that 86%<sup>3</sup> to 99%<sup>4</sup> of women with a twin gestation have a cervical length >25 mm at mid-gestation and that

17-OHPC had no beneficial effects in those with a cervical length  $\leq$ 25 mm, we strongly agree with the authors of this IPD meta-analysis that 17-OHPC is contraindicated in twin gestations. These findings support a ‘call for caution’ when using 17-OHPC. A significant increased risk of perinatal mortality associated with 17-OHPC use was reported in one<sup>5</sup> of two randomised controlled trials in which triplet gestations were allocated to receive 17-OHPC or placebo.<sup>5,6</sup> Moreover, the American Congress of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommended that women be counselled about the potential risks when receiving 17-OHPC (Letter to Members; Friday, 29 April 2011).

Schuit et al. report that vaginal progesterone did not reduce the rate of the composite perinatal outcome in unselected twins. Nevertheless, subgroup analyses showed that there was a significant ~44% reduction in the risk of the primary composite outcome measure in women with a short cervix at randomisation (26.8% versus 36.7%; RR 0.57, 95% CI 0.47–0.70; four studies) or before 24 weeks of gestation (26.9% versus 37.5%; RR 0.56, 95% CI 0.42–0.75; four studies). Similar findings were reported by our group, indicating that the administration of vaginal progesterone to women with twin gestations and a short cervix ( $\leq$ 25 mm) may reduce the rate of preterm birth at <33 weeks of gestation by 30% (RR 0.70; 95% CI 0.34–1.44), and nearly halved the rate of a composite neonatal morbidity and mortality outcome (RR 0.52; 95% CI 0.29–0.93).<sup>7</sup> Although both IPD meta-analyses found that vaginal progesterone had an effect in a similar direction and magnitude, the results should be considered ‘hypothesis-generating’, rather than ‘hypothesis-testing’.<sup>8</sup> We agree

with the recommendation that randomised clinical trials are required to determine whether vaginal progesterone reduces the rate of preterm birth and adverse perinatal outcome in twin gestations with a short cervix. A rationale for such a trial, as well as issues referring to study design, have been the subject of commentary in *BJOG*.<sup>9</sup> This trial proposes to enroll women with dichorionic–diamniotic twin gestations and a short cervix (sonographic cervical length between 10 and 25 mm) at 20–24 weeks of gestation (Romero R., pers. commun.). Such studies are important to elucidate whether progesterone can reduce the rate of preterm birth and improve neonatal outcome in twin gestations.

### Disclosure of interests

The authors report no conflicts of interest. ■

### References

- Schuit E, Stock S, Rode L, Rouse DJ, Lim AC, Norman JE, et al. Effectiveness of progestogens to improve perinatal outcome in twin pregnancies: an individual participant data meta-analysis. *BJOG* 2014; DOI: 10.1111/1471-0528.13032 [Epub ahead of print].
- Romero R, Stanczyk FZ. Progesterone is not the same as 17 $\alpha$ -hydroxyprogesterone caproate: implications for obstetrical practice. *Am J Obstet Gynecol* 2013;208:421–6.
- To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH. Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. *Am J Obstet Gynecol* 2006;194:1360–5.
- Liem S, Schuit E, Hegeman M, Bais J, de Boer K, Bloemenkamp K, et al. Cervical pessaries for prevention of preterm birth in women with a multiple pregnancy (ProTWIN): a multicentre, open-label randomised controlled trial. *Lancet* 2013;382:1341–9.
- Combs CA, Garite T, Maurel K, Das A, Porto M. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. *Am J Obstet Gynecol* 2010;203:248.e1–9.
- Caritis SN, Rouse DJ, Peaceman AM, Sciscione A, Momirova V, Spong CY, et al. Prevention of preterm birth in triplets using 17 $\alpha$ -hydroxyprogesterone caproate: a randomized controlled trial. *Obstet Gynecol* 2009;113:285–92.
- Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol* 2012;206:124.e1–19.
- Klebanoff MA. Subgroup analysis in obstetrics clinical trials. *Am J Obstet Gynecol* 2007;197:119–22.
- Romero R. Progesterone to prevent preterm birth in twin gestations: what is the next step forward? *BJOG* 2013;120:1–4.