Role of progestogens in women at risk for spontaneous preterm birth: the final word?

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Preterm birth is defined by WHO as delivery before 37 weeks of gestation.[1] It is one of the most common pregnancy complications, with an estimated global rate of 10·6% in 2014, equating to an estimated 14·84 million live preterm births.[2] Preterm birth considerably increases risk of neonatal morbidity and mortality, including long-term sequelae, and can result in long-term health and financial implications for families.[3]

Supplemental therapy with progesterone was thought to be an effective strategy in preventing spontaneous preterm birth in women at high risk (typically either women with a short cervical length on ultrasonography, or with a history of spontaneous preterm birth). Traditionally, two types of progesterone therapy have been used for the prevention of spontaneous preterm birth: weekly intramuscular 17-alpha hydroxyprogesterone caproate (17-OHPC) or daily vaginal progesterone (either as a vaginal suppository or natural micronised progesterone vaginal gel). Less frequently used is oral progesterone. In 2003, Meis and colleagues[4] and Da Fonseca and colleagues[5] reported a decrease in recurrent spontaneous preterm birth in women with a history of spontaneous preterm birth after treatment with 17-OHPC[4] or vaginal progesterone. Hassan and colleagues[6] reported that administration of vaginal progesterone gel to women with a mid-trimester short cervical length is associated with a 45% reduction in the rate of spontaneous preterm birth before 33 weeks, with improved neonatal outcomes. In 2013, a meta-analysis evaluating both 17-OHPC and vaginal progesterone[7] reported that

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progestogens prolonged pregnancy and were associated with a statistically significant reduction in the risks of perinatal morbidity and mortality and spontaneous preterm birth before 34 week and before 37 weeks. Despite these findings, other trials8, 9 prompted debate regarding which progestogen to use in different at-risk populations, and questioned the benefit of progestogens in the prevention of spontaneous preterm birth. The OPPTIMUM study[8] and the PROLONG trial[9] failed to confirm earlier study findings and found no statistically significant differences in spontaneous preterm birth or neonatal morbidity and mortality following treatment with vaginal progesterone[8] or 17-OHPC.[9]

In *The Lancet*, The EPPPIC study group[10] report results of an individual participant data meta-analysis (EPPPIC), in which they pooled harmonised data from 31 trials (including 11 644 women and 16 185 offspring) to determine the efficacy of progestogens in reducing spontaneous preterm birth and associated neonatal complications in high-risk pregnancies. They included trials of both singleton and multifetal pregnancies at risk of spontaneous preterm birth comparing vaginal progesterone, 17-OHPC, and oral progesterone with control, or with each other. Primary among the many reported outcomes were spontaneous preterm birth before 34 weeks, perinatal death, a composite of serious neonatal complications, and adverse maternal outcomes.

Compared with controls, both vaginal progesterone and 17-OHPC reduced the risk of spontaneous preterm birth before 34 weeks for singleton pregnancies in women at high risk, with a 22% reduction in the relative risk (RR) for participants who received vaginal progesterone (nine trials, 3769 women: RR 0·78, 95% CI 0·68–0·90), and 17% reduction for participants who received 17-OHPC (five trials, 3053 women: 0·83, 0·68–1·01). Data were too scarce to evaluate safety and efficacy of oral progesterone (two trials, 181 women: 0·60, 0·40–0·90). The authors obtained little evidence comparing vaginal progesterone with 17-OHPC directly, and while the network meta-analysis slightly favoured vaginal progesterone, there was no clear difference in effect between vaginal progesterone and 17-OHPC, even within the short cervical length or previous spontaneous preterm birth subgroups. Analyses within

subpopulations indicated poor efficacy in women who did not have a short cervix (>30 mm), but the authors stressed that the pooled analysis retained the greatest strength. The individual participant data substantiated previous data that progestogens do not reduce spontaneous preterm birth in unselected multifetal pregnancies. A possible increase in the RR of maternal complications (driven mostly by gestational hypertension and infections) was reported, but not all trials contributed the same or any maternal complication data, and interpretation of these data requires further study.

EPPPIC[10] is, to our knowledge, the largest individual participant data meta-analysis of progestogens used to prevent spontaneous preterm birth to date, and contributes to the large breadth of data examining the efficacy of progestogens in preventing spontaneous preterm birth. These data are more consistent in supporting the use of either 17-OHPC or vaginal progesterone to prolonged pregnancy, even with the inclusion of the negative findings from PROLONG.[9]

Counselling at-risk women on patient-centred, shared decision-making strategies to improve outcomes has become more complicated because of the results of OPPTIMUM[8] and PROLONG.[9] However, the results of EPPPIC[10] give clear evidence of progestogens improving several maternal and infant outcomes, with some potential safety concerns. The authors also note that patient-centred outcomes and experiences should be incorporated into future trials. Both the Society for Maternal-Fetal Medicine[11] and the National Institute for Health and Care Excellence (NICE) guidelines on preterm labour and birth[12] recommend a full discussion of the risks and benefits of options for women at risk to make a shared decision that takes into account the uncertainty that may also be involved. The conclusions of EPPPIC[10] should be incorporated into counselling women when determining if they wish to use progestogens based on their personal risk–benefit analysis.

The authors detail four currently ongoing trials directly comparing vaginal progesterone and 17-OHPC, highlighting the need for this to become a so-called living review and individual participant data meta-

analysis. This model of data synthesis on the individual participant level, along with addition and reanalysis when significant new data arrive, should become a standard throughout medicine. There are several areas of obstetric and gynaecological therapy where this model could be immediately relevant. Diligently compiling studies, harmonising outcomes through core outcome sets, and requiring registration and commitment to share data will greatly help author groups to provide the most robust recommendations for clinicians and guideline developers.

We declare no competing interests.

References

1. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths, modifications recommended by FIGO as amended October 14, 1976. *Acta Obstet Gynecol Scand* 1977; **56:** 247–53.
2. Chawanpaiboon S, Vogel JP, Moller AB, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019; **7:** 37–46.
3. Goldenberg RL, Culhane JF, Iams J, Romero R. The epidemiology and etiology of preterm birth. *Lancet* 2008; **371:** 75–84.
4. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003; **348:** 2379–85.
5. Da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2003; **188:** 419–24.
6. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2011; **38:** 18–31.
7. Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev* 2013; **7:** CD004947.

8. Norman JE, Marlow N, Messow CM, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. *Lancet* 2016; **387:** 2106–16.
9. Blackwell SC, Gyamfi-Bannerman C, Biggio JR, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): a multicenter, international, randomized double-blind trial. *Am J Perinatol* 2020; **37:** 127–36.
10. The EPPPIC study group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. *Lancet* 2021; **397:** 1183–94.
11. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. SMFM statement: use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. *Am J Obstet Gynecol* 2020; **223:** 16–18.
12. Sarri G, Davies M, Gholitabar M, Norman JE. Preterm labour: summary of NICE guidance. *BMJ* 2015; **351:** h6283.