Re: Effect of progestogen for women with threatened miscarriage: a systematic review and meta-analysis. (First comment on BJOG-19-1550.R1)

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Dear Editor,

We would like to comment on the systematic review by Li et al.(1)

The use of steroid hormones in the first trimester is a serious issue as organogenesis takes place at this time and therefore there is the possibility of harm from not only congenital anomalies, but also long-term, and even inter-generational effects. Anyone investigating the use of steroid hormones in the first trimester should remember the diethylstilbestrol legacy of devastating harm. Oestrogen ($C_{18}H_{24}O_2$) and diethylstilbestrol ($C_{18}H_{20}O_2$) have similar molecular composition, but their effects are poles apart. In this review, the authors have combined progesterone with progestogens; however they are not the same, in the same way that oestrogen and diethylstilbestrol are not the same. Vaginal micronized progesterone, which we used in our large and high-quality trials (the PROMISE (2) and PRISM (3) trials), has identical molecular structure to natural progesterone, but the other drugs included in this review do not (Table 1). We chose to study vaginal micronized progesterone, as it is identical in structure to natural progesterone, and the available evidence and expert opinion suggested that this is least likely to cause harm. It is important to note that there is evidence of potential harm from dydrogesterone, particularly congenital heart disease.(4)

The authors make a bold statement in the abstract about the effects of dydrogesterone on live birth rate. However, they don't fully address the weaknesses in the evidence. Therefore, we wish to highlight the

significant deficiencies in the two trials that contributed live birth data that led to the assertion of beneficial effects from dydrogesterone. Both studies were single centre, open-label studies without placebo control. El-Zibdeh et al did not randomise participants, but instead allocated patients to dydrogesterone on Saturdays, Mondays and Wednesdays, and to no treatment on Sundays, Tuesdays and Thursdays. The trial by Pandian RU was not just a single-centre, but also a single-author study, with insufficient details of the methods to assess its quality. Thus, the effectiveness evidence from these trials cannot be considered reliable.

Approximately 80% (4038 of 5056) of the data used in this systematic review come from our PRISM trial.(3) The PRISM trial is a prospectively-registered, randomised, placebo-controlled, multi-centre trial conducted to the highest standards in the UK. The trial found a 3% increase in live birth rate, but with borderline statistical significance (RR, 1.03; 95% CI, 1.00 to 1.07; P=0.08). A pre-specified subgroup analysis in women with the dual risk factors of current pregnancy bleeding and one or more previous miscarriages found a 5% increase in live birth rate (RR, 1.09; 95% CI, 1.03-1.15; P=0.003). In those with three or more previous miscarriages, a 15% increase in live birth rate was observed (RR, 1.28; 95% CI, 1.08 to 1.51; P=0.004).(3, 5) No short-term safety concerns were identified. Based on these data, our recommendation is to consider vaginal micronized progesterone for women with early pregnancy bleeding and one or more previous miscarriages. As for the role of dydrogesterone, we need not only high-quality, randomised trial evidence of its effects but also credible evidence of its safety. As dydrogesterone is a synthetic progesterone-like drug, i.e. a progestogen but not progesterone, the burden of proof to demonstrate short- and long-term safety rests on those promoting this drug.

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Table 1. Molecular structure of natural progesterone and progestogens used for the prevention of miscarriage

Drug	**Chemical structure**
Natural progesterone	$C_{21}H_{30}O_2$
Micronized progesterone	$C_{21}H_{30}O_2$
Dydrogesterone	$C_{21}H_{28}O_2$
17-hydroxyprogesterone	$C_{21}H_{30}O_3$