Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials

*The EPPPIC Group**

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Summary

Background Preterm birth is a global health priority. Using a progestogen during high-risk pregnancy could reduce preterm birth and adverse neonatal outcomes.

Methods We did a systematic review of randomised trials comparing vaginal progesterone, intramuscular 17-hydroxyprogesterone caproate (17-OHPC), or oral progesterone with control, or with each other, in asymptomatic women at risk of preterm birth. We identified published and unpublished trials that completed primary data collection before July 30, 2016, (12 months before data collection began), by searching MEDLINE, Embase, CINAHL, the Maternity and Infant Care Database, and relevant trial registers between inception and July 30, 2019. Trials of progestogen to prevent early miscarriage or immediately-threatened preterm birth were excluded. Individual participant data were requested from investigators of eligible trials. Outcomes included preterm birth, early preterm birth, and mid-trimester birth. Adverse neonatal sequelae associated with early births were assessed using a composite of serious neonatal complications, and individually. Adverse maternal outcomes were investigated as a composite and individually. Individual participant data were checked and risk of bias assessed independently by two researchers. Primary meta-analyses used one-stage generalised linear mixed models that incorporated random effects to allow for heterogeneity across trials. This meta-analysis is registered with PROSPERO, CRD42017068299.

Findings Initial searches identified 47 eligible trials. Individual participant data were available for 30 of these trials. An additional trial was later included in a targeted update. Data were therefore available from a total of 31 trials (11 644 women and 16185 offspring). Trials in singleton pregnancies included mostly women with previous spontaneous preterm birth or short cervix. Preterm birth before 34 weeks was reduced in such women who received vaginal progesterone (nine trials, 3769 women; relative risk [RR] 0·78, 95% CI 0·68–0·90), 17-OHPC (five trials, 3053 women; 0·83, 0·68–1·01), and oral progesterone (two trials, 181 women; 0·60, 0·40–0·90). Results for other birth and neonatal outcomes were consistently favourable, but less certain. A possible increase in maternal complications was suggested, but this was uncertain. We identified no consistent evidence of treatment interaction with any participant characteristics examined, although analyses within subpopulations questioned efficacy in women who did not have a short cervix. Trials in multifetal pregnancies mostly included women without additional risk factors. For twins, vaginal progesterone did not reduce preterm birth before 34 weeks (eight trials, 2046 women: RR 1·01, 95% CI 0·84–1·20) nor did 17-OHPC for twins or triplets (eight trials, 2253 women: 1·04, 0·92–1·18). Preterm premature rupture of membranes was increased with 17-OHPC exposure in multifetal gestations (rupture <34 weeks RR 1·59, 95% CI 1·15–2·22), but we found no consistent evidence of benefit or harm for other outcomes with either vaginal progesterone or 17-OHPC.

Interpretation Vaginal progesterone and 17-OHPC both reduced birth before 34 weeks' gestation in high-risk singleton pregnancies. Given increased underlying risk, absolute risk reduction is greater for women with a short cervix, hence treatment might be most useful for these women. Evidence for oral progesterone is insufficient to support its use. Shared decision making with woman with high-risk singleton pregnancies should discuss an individual's risk, potential benefits, harms and practicalities of intervention. Treatment of unselected multifetal pregnancies with a progestogen is not supported by the evidence.

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Introduction

Preterm birth is the most common cause of neonatal morbidity and mortality globally, with rates ranging from 5% in Europe to 18% in Africa.[1] Infants born prematurely are at greater risk of difficulties at birth, health problems during infancy, and death during their first year.[2] They are more likely to have long-term health problems such as cerebral palsy, epilepsy, cognitive disability, blindness, or hearing loss. Preterm birth can have economic consequences for families, and for payers and purchasers

Research in context

Evidence before this study

Preterm birth is the most common cause of neonatal morbidity and mortality globally, and it is unclear if giving a progestogen during pregnancy to asymptomatic women at high risk of preterm birth reduces the risk of preterm birth. Previous reviews focused on a single form of progestogen in at-risk subpopulations, and no individual participant data (IPD) meta-analysis of 17-hydroxyprogesterone caproate (17-OHPC) in single gestation pregnancies had been done. We considered published and unpublished trials that completed primary data collection before July 31, 2016, (12 months before data collection began). We searched MEDLINE, Embase, CINAHL, the Maternity and Infant Care Database, and relevant trial registers, with a final search date of July 30, 2019. Trialists were invited to identify additional trials. Received IPD were checked thoroughly and risk of bias was assessed.

Added value of this study

We included participant-level data from 31 trials, including more than 11 000 women and 16 000 offspring, in the largest IPD meta-analysis of progestogens used to prevent preterm birth to date. Included trials were generally at low risk of bias. For the high-risk population included in trials of singleton pregnancies (predominantly participants with a previous spontaneous preterm birth or sonographic short cervix), analyses showed that both vaginal progesterone and 17-OHPC reduced the risk of preterm birth before 34 weeks compared with control. Evidence of benefit in reducing preterm birth before 34 weeks was more certain for vaginal progesterone, but there was no clear evidence that either vaginal progesterone or 17-OHPC was superior. A consistent direction of benefit was noted for other birth and neonatal outcomes, including preterm birth before 28 weeks, preterm birth before 37 weeks, perinatal mortality, and composite serious neonatal complications. We noted possible variations in the size of treatment effect by risk factor, but there was no conclusive evidence that the relative effect of treatment varied according to participant characteristics within our high-risk dataset. There was no evidence of benefit in unselected multifetal pregnancies, although our dataset included few women with both multifetal gestation and other risk factors, such as short cervix.

Implications of all the available evidence

Vaginal progesterone and 17-OHPC both reduced birth before 34 weeks in high-risk singleton pregnancies. Given increased underlying risk, absolute risk reduction is greater for women with a short cervix, hence treatment might be most useful for these women. Maternal complications were possibly increased with exposure, indicating a need for further study of safety. Additional evaluation of long-term infant outcomes is also required. Further investigation of women with a previous preterm birth and longer cervical length (>30 mm) might be required to substantiate that the risk–benefit ratio in this group is clinically favourable. Evidence for oral progesterone was insufficient to support clinical decision making. Shared decision making with women with a high-risk singleton pregnancy should discuss individual risk, potential benefits, harms, and practicalities of intervention. Treatment of unselected multifetal pregnancies with a progestogen is not supported by the evidence.

of health care.[3,4] Reducing rates of preterm birth could therefore have significant health and fiscal benefits.

Endogenous progesterone is important in maintaining pregnancy, and decline of progesterone activity is believed to play a role in the onset of labour. Progestogens (compounds with progesterone-like action) have been regarded as promising therapeutic agents since the 1960s and could compensate for functional decline in progesterone concentrations in gestational tissue, or counter an inflammatory response leading to preterm birth.[5] Natural progesterones are similar to those produced by the body; whereas semisynthetic progestogens, including 17-hydroxyprogesterone caproate (17-OHPC), have a different chemical structure.[6] Natural progesterone is most commonly administered as a vaginal gel or suppository and 17-OHPC is given as a weekly intramuscular injection.

See Online for appendix

Most previous reviews[7–12] (appendix p 26) focused on single forms of progestogen in specific at-risk subpopulations. We aimed to bring together participant-level datasets from all relevant completed randomised controlled trials (RCTs) to enable independent, robust, and standardised evaluation of all forms of progestogen, and of potential differences in efficacy between women with different risk factors. Our analysis is the most comprehensive individual participant data (IPD) dataset on this topic established to date, and the first IPD meta-analysis of 17-OHPC in singleton pregnancies.

In October, 2020, the US Food and Drug Administration proposed that the synthetic drug should be removed from the market for the indication to prevent recurrent spontaneous preterm birth.[13]

Methods

Search strategy and selection criteria

In this international, collaborative, IPD meta-analysis, we followed a registered, published[14] protocol and a statistical analysis plan produced in advance of analysis.[15] Findings are in accordance with PRISMA-IPD.[16] We included RCTs that compared progestogen with placebo or standard care, or with other forms of progestogen, in asymptomatic women at increased risk of preterm birth. Trials where progestogens were given to prevent early miscarriage or to treat symptomatic women with signs of

threatened preterm labour were excluded. We considered published and unpublished trials that completed primary data collection before July 31, 2016, (12 months before EPPPIC data collection began). We searched MEDLINE, Embase, CINAHL, the Maternity and Infant Care Database and relevant trial registers, with a final search date of July 30, 2019, and trialists were invited to identify additional trials. For details of the search strategy, see appendix (pp 47–48). Titles and abstracts of identified literature were screened independently by two researchers, as were full publications of trials identified as potentially relevant. Discrepancies were resolved by discussion. In 2020, a large additional trial completed outside of the meta-analysis inclusion timeframe and was included in a targeted update of initial analyses.

We requested participant-level data from trial investigators for all eligible trials. The data were harmonised and recoded to our meta-analysis standardised definitions by the investigators or by the meta-analysis research team. We requested data for all women included, even if excluded from original trial analyses. Two researchers independently examined received data for missing, duplicated, or possibly erroneous values, and for internal consistency. Where data allowed, we examined the pattern of treatment allocation to check whether consistent with randomisation. Risk of bias was assessed by two researchers using the risk of bias tool[17] in tandem with IPD checking. Differences were resolved by discussion, and if information was insufficient, clarification was sought from trialists.

Outcomes included preterm birth (delivery before 37 weeks' gestation), early preterm birth (delivery before 34 weeks' gestation), and mid-trimester birth (delivery before 28 weeks' gestation). For more details on the definition of outcomes, see appendix (p 27). We assessed adverse neonatal sequelae associated with early births using a composite of serious neonatal complications (severe necrotising enterocolitis stages 2–3, intraventricular haemorrhage grades 3–4, retinopathy of prematurity stage 3 or worse, bronchopulmonary dysplasia, confirmed sepsis, patent ductus arteriosus, and neonatal infection) and individually. We also assessed respiratory distress syndrome, neonatal respiratory support, birthweight, and admission to neonatal intensive care individually. We investigated adverse maternal outcomes as a composite (gestational hypertension, pre-eclampsia, gestational diabetes, and maternal infection including chorioamnionitis) and individually.

Data analysis

We analysed all available data for each outcome of interest on an intention-to-treat basis. Separate analyses were done for vaginal progesterone, 17-OHPC, and oral progesterone, and separately for singleton and multifetal pregnancies (combining twin and triplet data). For primary IPD analyses, we used one-stage generalised linear mixed models that incorporated random effects to allow for heterogeneity across trials[18] fitted using R software lme4 and coxme libraries. For two-stage random effects (DerSimonian-Laird)[19] meta-analyses, we used R meta and metafor libraries. Heterogeneity was examined by visual inspection of forest plots and using I^2.[20] We investigated potential effect modifiers by

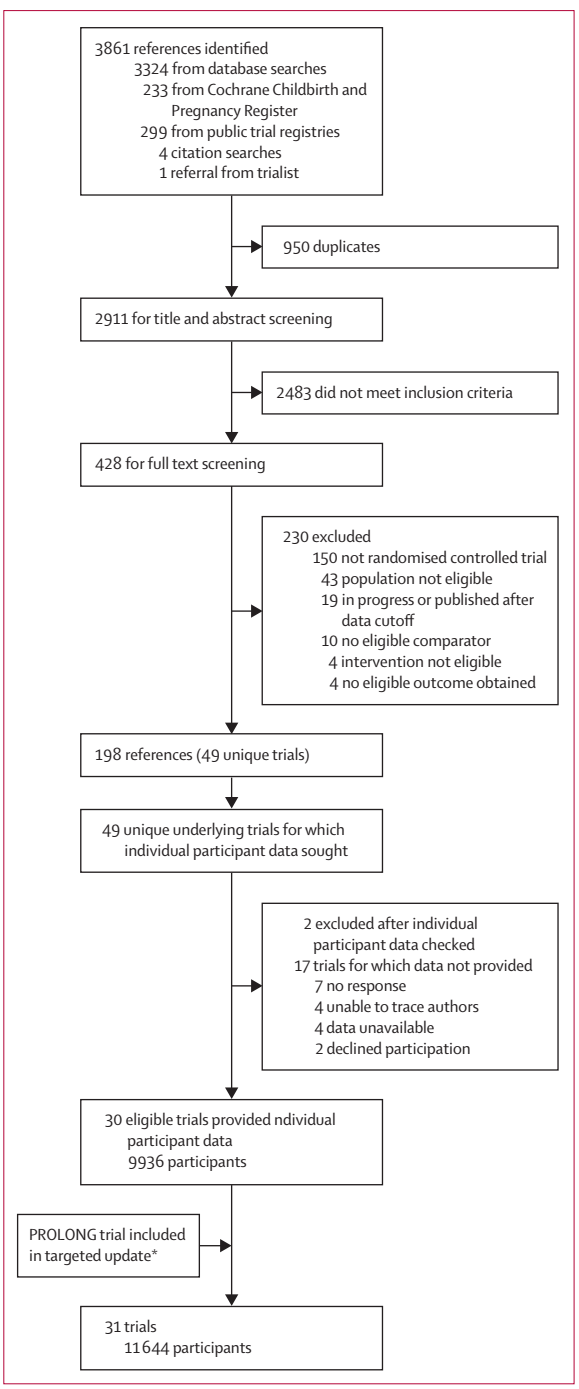

Figure 1: **Study selection**
*PROLONG was added in a targeted update although completed outside of inclusion dates, owing to its size and clinical interest.

adding covariate parameters and interactions between covariate and progestogen to the generalised linear mixed models (appendix pp 49–50). Network meta-analysis (NMA) included trials directly comparing progestogens (without a control arm) and indirect evidence from trials comparing each form with control, using a Bayesian network model analysed in OpenBugs[21] (appendix pp 50–51). As only two available trials compared progestogens directly, we did not do formal tests for network inconsistency.

We extracted aggregate data (extracted by one researcher and checked by another) from publications for trials that did not supply IPD, and calculated relative risks. Sensitivity analyses combined these with the individual relative risks calculated for each trial supplying IPD in two-stage meta-analyses. We generated forest plots by use of in-house R code.

We gathered women's experience of using progestogens using focus groups and individual interviews in a linked project (appendix pp 52–62).

This IPD meta-analysis is registered with PROSPERO, CRD42017068299.

Role of the funding source

Research reported in this article was funded through a Patient-Centered Outcomes Research Institute (PCORI) award, PPA-1608-35707. The views presented are solely the responsibility of the authors and do not necessarily represent the views of PCORI, its Board of Governors or Methodology Committee. Through two of its employees, PCORI had the opportunity to comment on the draft protocol and project outputs and was responsible for establishing the Advisory Group and for convening teleconferences and meetings. PCORI had no role in data collection or data analysis. March of Dimes funded meetings of the Secretariat and Advisory Group. One member of its staff was involved in establishing the Secretariat and had an opportunity to comment on the draft protocol, two members had opportunity to comment on project outputs.

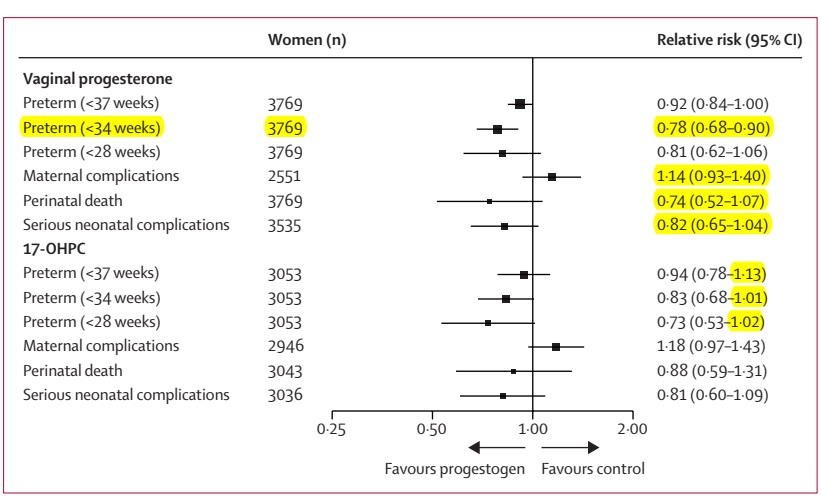

Figure 2: **Main outcomes in singleton pregnancies for vaginal progesterone and 17-OHPC trials**
17-OHPC=17-hydroxyprogesterone caproate. For vaginal progesterone: preterm birth <37 weeks number of events (n)=661, control n=705; preterm birth <34 weeks n=276, control n=343; preterm birth <28 weeks n=92, control n=111; maternal complications n=186, control n=171; perinatal death n=49, control n=64; serious neonatal complications n=119, control n=140. For 17-OHPC: preterm birth <37 weeks n=510, control n=330; preterm birth <34 weeks n=206, control n=158; preterm birth <28 weeks n=77, control n= 66; maternal complications n=285, control n=178; perinatal death n=57, control n=40; serious neonatal complications n=95, control n=75.

Results

We identified 2911 unique references (figure 1). 2483 were excluded after title and abstract screening, and 230 were excluded after full text screening. 49 unique completed trials were considered eligible for inclusion.[22–69] Two were later excluded after IPD receipt and checking.[68,69] PROLONG[70] was reported just after initial analyses were completed. Although completed outside inclusion dates, because of its size and potential impact, IPD were obtained and included in updated meta-analyses. 17 potentially eligible trials were unavailable (without access to IPD we were unable to confirm eligibility or verify randomisation).[51–67] Three of these trials could not be traced, no response was obtained from eight, and two declined to participate. Data were no longer stored for four trials, including three completed before 1985. Together these 17 trials, which were mostly single-centre and unregistered, accounted for a small proportion of data. IPD were obtained for 31 trials (11 644 women, 16185 offspring).[22–50,70] This accounts for 88% of women entered across all potentially eligible trials of vaginal progesterone or 17-OHPC compared with control (11 237/12 237). Trial design details, including number of women included, are given in the appendix (pp 32–46).

14 included trials compared vaginal progesterone with control (13 placebo, two standard care; six in singleton pregnancies, five in multifetal pregnancies, three with mixed populations [mainly singletons]).[22–35] 13 trials compared 17-OHPC with control (11 placebo, two standard care; five in singleton pregnancies, eight in multifetal pregnancies).[38–48,70] Two trials compared oral progesterone with placebo,[36,37] and two trials compared vaginal progesterone and 17-OHPC directly in singleton pregnancies.[49,50] Trials were generally at low risk of bias (appendix p 2). 12 trials for which IPD were not available published enough aggregate data for inclusion in sensitivity meta-analyses. The proportion of women enrolled in trials of vaginal progesterone or 17-OHPC by two main risk factors is shown in the table, and proportions by other characteristics are shown in the appendix (pp 28–29).

One-stage meta-analyses found that vaginal progesterone reduced the risk of early preterm birth (<34 weeks' gestation) in singleton pregnancies (relative risk [RR] 0·78, 95% CI 0·68–0·90) compared with control (figure 2), as did 17-OHPC (0·83, 0·68–1·01) although the CI for 17-OHPC just crossed the line of no effect. Two-stage forest plots for preterm birth earlier than 34 weeks show that all but two trials (one vaginal

progesterone, one 17-OHPC) lie to the left of equivalence (appendix p 3). Some heterogeneity between vaginal progesterone trials was evident (I^2=23%, 95% CI 0–59%) but there was less variation for 17-OHPC (I^2=0%, 0–57%). For an illustrative baseline risk of 20%, RR of 0·78 equates to an absolute risk reduction of 4·4%, whereas for a baseline of 60%, the same RR gives an absolute risk reduction of 13·2%. Results for mid-trimester preterm birth (<28 weeks) and preterm birth (<37 weeks) were generally consistent with findings for early preterm birth (<34 weeks; figure 2).

Analyses also suggest a possible reduced risk of perinatal death in participants who received vaginal progesterone (RR 0·74, 95% CI 0·52–1·07) and 17-OHPC (0·88, 0·59–1·31), and possible reduced risk of composite serious neonatal complications for vaginal progesterone (0·82, 0·65–1·04) and 17-OHPC (0·81, 0·60–1·09; figure 2).

Vaginal progesterone reduced risk of low birthweight (<2500 g, 0·82; 0·74–0·91), very low birthweight (<1500 g, 0·70; 0·49–0·99), neonatal intensive care unit admission (0·78, 0·68–0·90), respiratory distress syndrome (0·73, 0·58–0·93), and respiratory support (0·77, 0·61–0·99; figure 3). Vaginal progesterone also reduced risk of neonatal death after livebirth, although the upper CI just crossed the line of no effect (RR 0·63, 0·39–1·02). We found no discernible effect on fetal death or stillbirth, bronchopulmonary dysplasia, neonatal infection, or patent ductus arteriosis. Results for severe retinopathy of prematurity, necrotising enterocolitis, and intraventricular haemorrhage were highly uncertain. Results for 17-OHPC suggested reductions in risk of neonatal death (RR 0·72, 0·40–1·31), low birthweight (0·89, 0·74–1·07), very low birthweight (0·75, 0·55–1·02), respiratory distress syndrome (0·86, 0·65–1·13), bronchopulmonary dysplasia (0·78, 0·38–1·61), sepsis (0·73, 0·39–1·38), and patent ductus arteriosis (0·55, 0·30–1·01), compared with control (figure 4), and no discernible effect for fetal death or stillbirth, neonatal intensive care unit admission, or respiratory support, compared with control. Results for severe retinopathy of prematurity, intraventricular haemorrhage, and necrotising enterocolitis were highly uncertain. There was no evidence of substantial heterogeneity in any analysis.

A possible increase in composite maternal complications was seen for vaginal progesterone (RR 1·14, 95% CI 0·93–1·40) and 17-OHPC (1·17, 0·97–1·42; figure 2) compared with control, mostly a result of increased gestational hypertension and maternal infection events. However, individual outcomes were uncertain (appendix pp 4–5). There were no maternal deaths in any trials.

Cervical length was not recorded in all studies, so analyses were based on around 65–70% of women (table). There was no indication that the relative treatment effect for either vaginal progesterone or 17-OHPC varied between women with a shorter cervix (≤25 mm) and with a longer cervix (>25 mm). There was no evidence of effect modification when cervical length was analysed as a continuous variable, all p values for interaction were >0·1 (appendix p 30). However, the distribution of cervical length within the dataset limited the potential to examine treatment effect over the full spectrum of cervical lengths

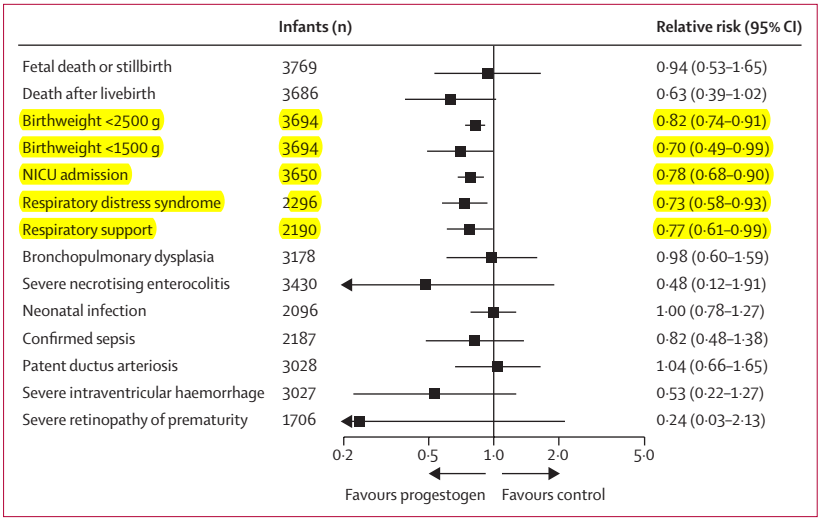

Figure 3: **Vaginal progesterone: additional neonatal outcomes in singleton pregnancies**
NICU=neonatal intensive care unit. Severe intraventricular haemorrhage was grade III or IV. Severe retinopathy of prematurity was stage 3 or worse. Severe necrotising enterocolitis was grade II or III. Fetal death or stillbirth number of events (n)=23, control n=24; death after livebirth n=26, control n=40; birthweight <2500 g n=442, control n=524; birthweight <1500 g n=131, control n=168; NICU admission n=286, control n=353; respiratory distress syndrome n=99, control n=132; respiratory support n=100, control n=128; bronchopulmonary dysplasia n=32, control n=32; severe necrotising enterocolitis n=3, control n=6; neonatal infection n=113, control n=111; sepsis n=25, control n=30; patent ductus arteriosis n=37, control n=35; severe intraventricular haemorrhage n=7, control n=13; retinopathy of prematurity n=1, control n=4.

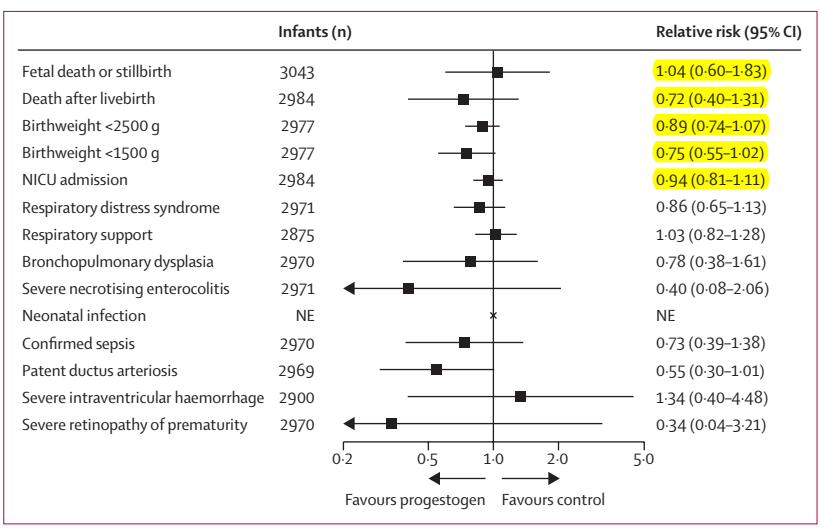

Figure 4: **17-OHPC: additional neonatal outcomes in singleton pregnancies**
NE=not estimable. 17-OHPC=17-hydroxyprogesterone caproate. Severe intraventricular haemorrhage was grade III or IV. Severe retinopathy of prematurity was stage 3 or worse. Severe necrotising enterocolitis was grade II or III. Fetal death or stillbirth number of events (n)=34, control n=19; death after livebirth n=23, control n=21; birthweight <2500 g n=342, control n=239; birthweight <1500 g n=82, control n=74; NICU admission n=312, control n=209; respiratory distress syndrome n=113, control n=81; respiratory support n=192, control n=112; bronchopulmonary dysplasia n=16, control n=14; severe necrotising enterocolitis n=2, control n=5; neonatal infection n=0, control n=0; sepsis n=20, control n=19; patent ductus arteriosis n=19, control n=22; severe intraventricular haemorrhage n=8, control n=4; retinopathy of prematurity n=1, control n=3.

	Cervix length ≤25 mm	Cervix length >25 mm	Cervix length unknown	Total
Single gestation vaginal progesterone				
Parous, with previous preterm birth	359 (9·4%)	1218 (31·9%*)	1042 (27·3%*)	2619 (68·6%)
Parous, no previous preterm birth	277 (7·3%)	213 (5·5%)	73 (1·9%)	563 (13.7%)
Nulliparous	365 (9·6%)	32 (0·8%)	0 (0)	397 (10·4%)
Parity unknown	13 (0·3%)	222 (5·8%)†	2 (0·1%)	237 (6·2%)
Total	1014 (26·6%)	1685 (44·0%)	1117 (29·3%)	3816
Single gestation 17-OHPC				
Parous, with previous preterm birth	82 (2·7%)	1223 (39·7%)	1070 (34·7%)	2375 (77·1%)
Parous, no previous preterm birth	14 (0·5%)	0 (0)	1 (0)	15 (0·5%)
Nulliparous	340 (11%)	348 (11·3%)‡	0 (0)	688 (22·3%)
Parity unknown	4 (0·1%)	1 (0)	0 (0)	5 (0·1%)
Total	440 (14·3%)	1572 (51·0%)	1071 (34·7%)	3083
Twin gestation vaginal progesterone				
Parous, with previous preterm birth	1 (0)	28 (1·4%)	32 (1·5%)	61 (2·9%)
Parous, no previous preterm birth	22 (1·1%)	465 (22·5%*)	124 (6·0%)	611 (29·6%)
Nulliparous	49 (2·4%)	576 (27·7%*)	433 (20·9%*)	1058 (51·0%)
Parity unknown	0 (0)	86 (4·2%)	252 (12·2%)	338 (16·4%)
Total	72 (3·5%)	1155 (55·8%)	841 (40·6%)	2068
Multifetal gestation 17-OHPC (twins and triplets)				
Parous, with previous preterm birth	22 (1·0%)	102 (4.5%)	78 (3·4%)	202 (8·9%)
Parous, no previous preterm birth	61 (2·7)	453 (20%*)	358* (15·8%*)	872 (38·5%)
Nulliparous	141 (6·2%)	566 (24·9%*)	484 (21·3%*)	1191 (52·4%)
Parity unknown	3 (0·1%)	0 (0)	2 (0·1%)	5 (0·2%)
Total	227 (10·0%)	1121 (49·4%)	922 (40·6%)	2270

Data are n (%) or n. 17-OHPC=17-hydroxyprogesterone caproate. *At least 20% of meta-analysis population. †Mainly from the trial in women who underwent IVF.[22] ‡patients from SCAN,[42] with cervical length 30mm or less.

Table: **Women included in trials comparing vaginal progesterone or 17-OHPC with control by previous preterm birth status and cervix length (at randomisation) for singleton and multifetal pregnancies**

(38% women in vaginal progesterone trials with measured cervical length were ≤25 mm; table).

Previous preterm birth was analysed as a potential effect modifier rather than previous spontaneous preterm birth as planned. This was because data were insufficient to determine reliably whether births were spontaneous for all women in all trials. There was no consistent evidence that relative efficacy varied between women with a previous preterm birth and those without (most p values for interaction were >0·1 [appendix, p 30]). Exceptions were for participants who received vaginal progesterone for the outcomes of mid-trimester preterm birth (p=0·012) and serious neonatal complications (p=0·079), where vaginal progesterone might be less efficacious in women with a previous preterm birth.

Given trial eligibility criteria, women without a previous preterm birth mostly had a short cervix, and those with a previous preterm birth mostly did not have a short cervix at trial entry. To reduce this confounding, we analysed cervical length and preterm birth covariates jointly (appendix p 30) and consider this to be the most robust analysis of effect modification. We found some evidence suggesting a possible reduction in benefit of 17-OHPC with increasing cervix length (early preterm birth p=0·06; preterm birth p=0·095).

We found evidence of treatment interaction and greater risk of composite maternal complications (appendix p 31) with increasing body-mass index (BMI) for vaginal progesterone (p<0·001) and 17-OHPC (p=0·052). Numbers of events were insufficient to explore potential interaction between BMI and individual maternal complications, and this observation is best interpreted as hypothesis generating, particularly as some composite elements are known to be more frequent in women with high BMI as pregnancy advances. There was no clear or consistent indication that the effects of intervention differed by any other risk factor examined (appendix p 31).

Available data on participants receiving oral progesterone (two trials, 183 women) accounted for 46% of women recruited in all potentially eligible trials. Oral progesterone reduced risk of early preterm birth (RR 0·60, 95% CI 0·40–0·90) compared with control (appendix p 6). Results for preterm birth, maternal complications, and perinatal death in participants who received oral progesterone were broadly consistent with those for vaginal progesterone, but CIs were wide (appendix p 6).

Only two of five potentially eligible trials (224 women) comparing vaginal progesterone and 17-OHPC directly provided data (18% of women entered in all potentially eligible trials), and only gestational age at birth was available for both. Results showed no clear difference between agents (early preterm birth <34 weeks RR 1·18, 95% CI 0·69–2·03 [appendix p 7]; mid-trimester preterm birth <28 weeks 1·06, 0·41–2·78; preterm birth <37 weeks 1·15, 0·82–1·61; data not shown).

Results of NMA comparing vaginal progesterone and 17-OHPC, based mostly on indirect evidence, favoured vaginal progesterone for most main outcomes, but were not conclusive (appendix p 7).

We did supplementary two-stage analyses of subpopulations categorised by previous preterm birth status and cervical length, using the most commonly accepted 25 mm cutoff, and a 30 mm cutoff as a sensitivity analysis (two trials used 30 mm to define short cervix as an eligibility criterion). These categorised meta-analyses required both variables to be recorded, and consequently were based on considerably less data than the main analysis (59% for 17-OHPC, 43% for vaginal progesterone). Six trials did not provide cervical length and could not be included.[22,23,26,34,44] Results for short cervix groups showed benefit and were broadly consistent with overall effects. Results for groups with cervical length greater than 25 mm without previous preterm birth categories were much less certain (appendix p 8). Treatment benefit was not apparent for women with cervical length greater than 30 mm for either vaginal progesterone or 17-OHPC (appendix p 9). In these analyses, some trials contributed to some categories but not others, such that there might be differences between

categories other than the main factors by which they are grouped, which confounds interpretation.

NMA restricted to women with a short cervix found no clear evidence of difference between vaginal progesterone and 17-OHPC (appendix p 10). Nor did NMA restricted to women with a previous preterm birth (appendix p 11).

Analyses of multifetal pregnancies included eight trials of vaginal progesterone (all twins) and eight trials of 17-OHPC (two of which were of triplets). Most women had no recorded risk factors other than multifetal gestation (table). There was no evidence that early preterm birth was reduced for participants with multifetal pregnancies who received vaginal progesterone (RR 1·01, 95% CI 0·84–1·20), or 17-OHPC (1·04, 0·92–1·18; figure 5). Two-stage forest plots show that most individual trial results were inconclusive (appendix p 12). For other outcomes most meta-analysis effect estimates were close to 1, or had wide CIs (appendix pp 13–16). Exceptions were preterm premature rupture of membranes, where 17-OHPC increased risk compared to control (eg, rupture <34 weeks RR 1·59, 95% CI 1·15–2·22; appendix p 16). Vaginal progesterone did not increase this risk compared to control (0·92, 0·62–1·35; appendix p 15). There was no evidence of any consistent variation in the relative treatment effect with cervical length or previous preterm birth status. However, these analyses were limited because trials did not focus on selected multifetal gestation subpopulations by indication and consequently included few women with a multifetal pregnancy and a short cervix or previous preterm birth (table). NMA found no evidence of any difference in effect between vaginal progesterone and 17-OHPC.

Analysis in singleton trials found no evidence of any trend linked to planned vaginal progesterone dose or preparation (appendix p 17). As there was little variation in planned 17-OHPC dose, no such analysis was done. Sensitivity analyses for singleton neonatal complications of all severities (eg, including all grades of intraventricular haemorrhage), or adding respiratory distress syndrome to composite serious neonatal complications (appendix p 18), did not lead to different conclusions from the main analyses.

Sensitivity meta-analyses incorporating aggregate data from unavailable trials generally gave slightly more favourable results, but did not lead to conclusions different from the main IPD meta-analyses (appendix pp 19–22). For vaginal progesterone in multifetal pregnancies, the addition of aggregate data from one trial gave meta-analysis results that were suggestive of possible benefit (early preterm birth RR 0·91, 95% CI 0·73–1·12; appendix p 23), whereas analyses of just IPD did not. Sensitivity analyses incorporating aggregate data for unavailable trials comparing vaginal progesterone and 17-OHPC are not shown, due to a published note of concern[71] about a contemporaneous trial by the same authors as the largest unavailable trial.

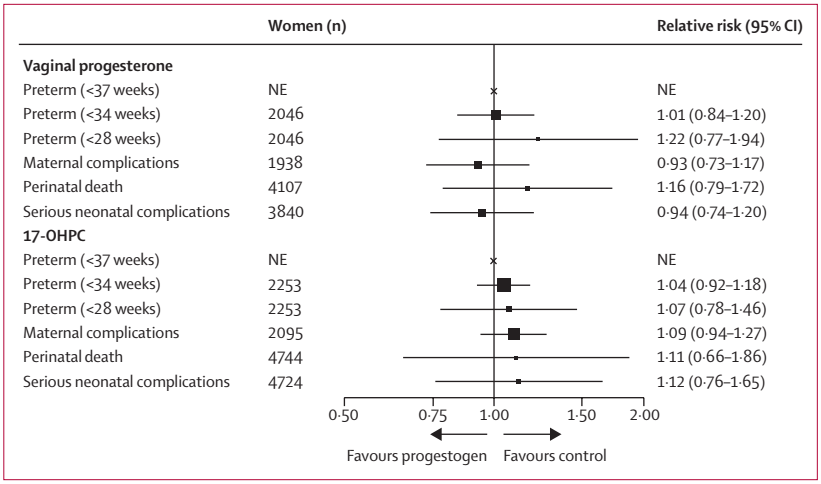

Figure 5: **Main outcomes in multifetal pregnancies for vaginal progesterone and 17-OHPC trials**
NE=not estimable. 17-OHPC=17-hydroxyprogesterone caproate. Models for birth <37 weeks did not converge for either agent, but there was no evidence of effect in the equivalent two-stage meta-analyses. For vaginal progesterone: preterm birth <37 weeks number of events (n)=599, control n=554; preterm birth <34 weeks n=202, control n=187; preterm birth <28 weeks n=41, control n=31; maternal complications n=125, control n=134; perinatal death n=56, control n=44; serious neonatal complications n=127, control n=125. For 17-OHPC: preterm birth <37 weeks n=854, control n=663; preterm birth <34 weeks n=368, control n=285; preterm birth <28 weeks n=83, control n=65; maternal complications n=358, control n=284; perinatal death n=112, control n=85; serious neonatal complications n=287, control n=229.

Discussion

In this IPD meta-analysis, we address an important global health issue, about which there continues to be much debate. Our aim was to provide an independent, comprehensive, and robust evaluation of IPD from all relevant RCTs so that decisions made by clinicians and childbearing women can be informed by the totality of available evidence, rather than focusing on the published results of individual trials.

Most women with singleton pregnancies enrolled in the analysed trials were at high risk because of previous spontaneous preterm birth, a short cervix, or both. Results showed a consistently favourable direction of effect for birth and neonatal outcomes, with a clear reduction in the RR of early preterm birth before 34 weeks for both vaginal progesterone and 17-OHPC, although CIs just crossed equivalence for 17-OHPC. RR of preterm birth (<37 weeks) and mid-trimester birth (<28 weeks) were also reduced for both agents. Our results also suggest possible reductions in serious neonatal complications and incidence of low birthweight infants. A possible increase in the RR of maternal complications was noted for both 17-OHPC and vaginal progesterone. However, caution should be exercised when interpreting these findings, as only four of nine vaginal progesterone trials and four of five 17-OHPC trials contributed maternal complication data, and some had data for some components only.

Analyses of treatment covariate interactions found no clear evidence that the relative effects of vaginal progesterone or 17-OHPC differed by cervix length, or by history of a previous preterm birth. Therefore, the overall pooled risk reduction is the most robust estimate of

treatment effect for each type of progestogen. However, because underlying risk of preterm birth is greater at shorter cervical lengths[72,73] (supported by exploratory analyses of this dataset, appendix pp 24–25), absolute risk reductions are greater for women with a shorter cervix, hence threatment might be most useful for these women.

Supplementary analyses of subpopulations with a short cervix were in line with the main results, and support previous observations of treatment benefit for women with cervical length of 25 mm or less, irrespective of obstetric history.[8] We also found benefit for women with cervical length 30 mm or less with either progestogen. There was no apparent benefit in subpopulations of women with previous preterm birth and cervical length greater than 30 mm, although CIs were wide and consistent with both benefit and harm. Further investigation in women with a previous preterm birth and longer cervical length (>30 mm) might be required to establish whether the risk–benefit ratio in this group is clinically favourable.

We obtained little evidence comparing vaginal progesterone and 17-OHPC directly. No clear difference in effect between the two agents was identified. Similarly, the NMA, which was based mostly on indirect evidence, provided no definitive evidence of difference between vaginal progesterone and 17-OHPC in preventing preterm birth, although findings for most main outcomes tended in to favour vaginal progesterone. NMA also found no definitive evidence of clinically important differences between vaginal progesterone and 17-OHPC when restricted to short cervix and previous preterm birth subpopulations. Our linked study exploring the experience of 11 women who had used progestogen during pregnancy found that some women experienced long-lasting pain from 17-OHPC injection and some women found using vaginal progesterone unpleasant and inconvenient. They were, however, prepared to accept personal risk to prevent preterm birth (appendix pp 52–65).

Insufficient data were available for oral progesterone to evaluate safety and efficacy adequately. However, effect sizes for preterm birth outcomes were consistent with those for vaginal progesterone and 17-OHPC.

The only risk factor for most women included in trials of multifetal gestations was twin or triplet pregnancy. There was no evidence that either vaginal progesterone or 17-OHPC reduced the risk of preterm birth in these unselected multifetal pregnancies. Across outcomes, most estimates were close to no effect or were very uncertain, and we did not identify any consistent benefit or harm for either agent, although preterm premature rupture of membranes increased with 17-OHPC. Our study population included few women with multifetal gestations and additional risk factors, such as short cervix or previous preterm birth, and for such women a benefit of progestogen cannot be excluded. The authors of a vaginal progesterone trial[54] of 250 women with a short cervix and twin gestation declined to participate, and further examination of IPD from this trial could be important. Results of a trial[74] (completed outside of our inclusion timeframe) of vaginal progesterone in twins were consistent with our results in finding no overall reduction in the incidence of preterm birth, but a data-driven post-hoc analysis suggested that vaginal progesterone might delay birth for women with cervical length less than 30 mm.

Our results are generally consistent with previous IPD meta-analyses (appendix p 26). However, although we found no benefit in multifetal pregnancies, a previous IPD meta-analysis[9] of vaginal progesterone in women with a twin pregnancy and cervical length 25 mm or less did identify benefit. In addition to the differing inclusion criteria on cervical length, two trials[54,69] accounted for 75% of the data in that IPD meta-analysis, but are not included in our meta-analysis. We obtained partial data (twins but not singletons) for the smaller of these trials,[69] but excluded it because we were unable to confirm adequate randomisation. Sensitivity analyses showed that inclusion or exclusion of this trial had little effect.

Strengths of our study include evaluation of different types of progestogen and of singleton and multifetal pregnancies using the same protocol. We provide the first IPD NMA on this topic, and the first IPD meta-analysis of 17-OHPC in singleton pregnancies. Included trials were generally at low risk of bias. Other strengths include standardisation of definitions and outcomes, detailed analysis including exploration of potential effect modifiers, and extensive data checking with trial investigators to ensure the quality of the dataset. IPD were unavailable for 17 potentially eligible trials, but these were mostly small, unregistered, done at a single centre, and accounted for a small proportion of all possible data from vaginal progesterone and 17-OHPC trials. With one exception (vaginal progesterone in multifetal pregnancies), sensitivity analyses incorporating published aggregate data from unavailable trials did not alter conclusions. Our IPD meta-analysis had some limitations. Available data for oral progesterone and for head to head trials were scarce, and these findings should be interpreted accordingly. We were unable to determine whether preterm birth was spontaneous for all women in all trials, and so analyses of effect modification and categorised analyses of subpopulations assessed women with any previous preterm birth. However, as previous spontaneous preterm birth was an inclusion criterion for many trials, and because available data showed that most previous preterm births were spontaneous, most of the data included in these analyses were from previous spontaneous preterm birth. Supplementary analyses of subpopulations were also based on fewer data and at risk of confounding. NMA was based mostly on indirect comparison, and results could be at risk of bias and confounding. Because many analyses were done, chance

alone might be responsible for some statistically significant findings, although consistency across our main and additional outcomes and between progestogens provides reassurance.

Some trials collected only immediate birth outcomes, and data on maternal complications were available for just over half of singleton trials. Few trials collected data on longer-term infant outcomes, and data were inadequate for analyses. This is an important gap in knowledge. Data on patient-centred outcomes were also seldom collected.

Both vaginal progesterone (suppositories or gels) and intramuscular 17-OHPC injections reduced the relative risk of early preterm birth in high-risk singleton pregnancies. Progestogen administration had a consistent pattern of benefit for other birth and neonatal outcomes. Although based on limited data and inconclusive, a potential increase in maternal complications should provide caution against overprescribing. Although the evidence for vaginal progesterone in reducing early preterm birth and for most neonatal outcomes was more certain (narrower CIs) than the evidence for 17-OHPC, our findings support both vaginal progesterone and 17-OHPC to be considered as treatment options in high-risk singleton pregnancies. Owing to higher underlying risk and hence greater absolute risk reduction, treatment might be most useful in women with a short cervix.

Shared decision making[75] with women with a high-risk singleton pregnancy, for whom a progestogen is being considered, should include discussion of their own risk profile and how this might be altered by intervention in terms of both absolute and relative risk reductions and lived experience. In our small linked qualitative study, women reported that they believed that women should be given the opportunity to make an informed decision about progestogen and suggested that more information about possible benefits, harms and mechanisms of action was needed (appendix pp 52–65). Availability and costs of various forms of progestogen between jurisdictions might also be an important component of decision making.

We found no evidence to support use of progestogen in unselected multifetal pregnancies. Efficacy for women with multifetal gestation and short cervix or previous preterm birth remains uncertain. Given an identified risk in multifetal pregnancies, intervention might be appropriate only in the context of research for this subpopulation. Current and recently completed trials in women with multifetal gestation and short cervix (NCT03058536, NCT02518594, NCT02697331, NCT03863613, NCT03781674) have a combined target of more than 1600 women. Further trials without cervical length restriction (NCT02350231, ISRCTN69810120, and the EVENTS[74] trial) have a combined target of almost 1500 women. It might be prudent to wait for the results of these trials before designing new ones.

For singleton pregnancies, further study of women considered at high risk of preterm birth but who do not have a short cervix is required to evaluate the risk–benefit ratio of intervention in this group. Whether vaginal progesterone and 17-OHPC have equivalent efficacy in singleton pregnancies (overall, or given different indications or risk factors) would be best addressed by trials that compare them directly. Four such ongoing or recently completed trials (NCT02304237 CTRI/2015/01/005467, NCT02913495, NCT03537287) have a combined target of more than 800 women. Further evaluation of oral progesterone might be warranted, in which case assessing potential harms of systemic treatment would be important. Two ongoing trials are comparing oral progesterone with vaginal progesterone or 17-OHPC (NCT03343795, NCT03537287).

New adequately powered trials should follow up offspring into childhood and study long-term outcomes. Data on maternal outcomes should also be collected and potential interaction with maternal BMI investigated. Collecting data on maternal behavioural outcomes including breastfeeding, mother–baby attachment, and maternal mood would also be valuable, as would further qualitative research exploring women's experience of using progestogen during pregnancy, and their decision making needs.

Finally, our need to update initial analyses to include PROLONG and subsequent and forthcoming completion of further trials highlights the value of a living review[76] approach to IPD meta-analyses, whereby new trial data are obtained and incorporated as they emerge.

Contributors

LAS, LD, and MS designed and were responsible for overseeing all aspects of the study. LB, KCD, AH, AL, SS, and RAEW contributed to various stages of the project including aspects of design, eligibility screening, data extraction, risk of bias assessment, individual participant data checking, and trial analysis. LAS managed the project and collaborative process, MS did data synthesis, LD provided clinical oversight and KW designed and did the literature searches. LAS, MS, and LD wrote the manuscript with input from ZA, LB, AL, SS, and RAEW. KS designed, conducted, analysed, and wrote the report for the qualitative study with input from KD and LAS. Secretariat members had opportunity to comment on the initial scope, draft protocol, and draft statistical analysis plan, and participated in telephone meetings convened by Patient-Centered Outcomes Research Institute as the project progressed. Trial investigators prepared and supplied data and answered questions about their trials. All members of the collaborative group had the opportunity to review and provide comment on analyses and the content of the manuscript. The independent research team (LAS, MS, LD, AH, AL, KCD, SS, RAEW) considered and took account of feedback from group members and were responsible for decisions about methods, analyses, and content of the manuscript. The corresponding author and members of the research team had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Declaration of interests

LAS and members of the research team are or were employees of the University of York, which received funding from the PCORI for the EPPPIC project. LD reports grants from the National Institute for Health Research (NIHR) programme for applied research, outside the submitted work. KD reports that her employer, Johns Hopkins Bloomberg School of Public Health, received funding through a sub-contract from York for patient engagement and conduct of the study of patient experience. MS and LAS report grants from the NIHR outside of the submitted work. No member of the project team was involved with any of the included trials or had any conflict of interest. SCB presented to the US Food and Drug Administration (FDA) Advisory Board on behalf of the sponsor (AMAG) regarding FDA approval of 17-OHPC. He did not receive any financial payments or financial support for this role. SNC reports grant support from AMAG to do a pharmacokinetic study on intramuscular versus subcutaneous 17-OHPC. AMAG also supplied 17-OHPC for a study he directs for the National Institute of Child Health and Human Development-sponsored Obstetric-Fetal Pharmacology Research Centers. CACr was lead investigator for the PROGRESS Trial, one of the studies included in the analysis. AFD reports personal fees from AMAG during the study and personal fees from Hologic outside the submitted work. BWM declared grants from the National Health and Medical Research Council, personal fees from ObsEva, personal fees from Merck, personal fees from Guerbet, grants from Guerbet, and grants from Merck, outside the submitted work. JEN chaired the 2015 UK NICE Guideline on preterm labour and birth and received fees for this activity. She has received grants from government and charitable bodies for research into understanding the mechanism of term and preterm labour and understanding treatments. Within the past 3 years she has acted on a Data Safety and Monitoring Board for a study involving a preterm birth therapeutic agent for GlaxoSmithKline and has provided consultancy for Dilafor on drugs to alter labour progress. JNo reports grants from University of Edinburgh and grants from University of Aberdeen, outside the submitted work. He was Deputy Chair of the UK NIHR Health Technology Assessment General Funding Committee 2016–19; and is Chair of the UK Medical Research Council/NIHR Efficacy and Mechanisms Evaluation Funding Committee (2019–present). JMO was involved in studies of progesterone gel treatment for preterm birth prevention sponsored by a maker of progesterone gel. He was a principal investigator for studies published in 2011 and 2007. He once served on Advisory Boards and as a consultant for Watson, a company with a financial interest in marketing vaginal progesterone gel for preterm birth prevention. He is a cofounder of a company interested in developing and marketing interventions to prevent preterm birth, but that entity does not have an approved or commercially available intervention to date. He and others are listed in a patent on the use of progesterone compounds to prevent preterm birth (USA Patent Number 7884093: Progesterone for the Treatment and Prevention of Spontaneous Preterm Birth). He has received other patents for devices to treat obstetric patients, including subpopulations at increased risk for preterm birth. He has not received any funds from a royalty agreement or licensing of any patent to date, nor has his university. AT and LR report grants from the Danish Medical Research Council, Fetal Medicine Foundation, Copenhagen University Hospital's Research Fund, Aase and Ejnar Danielsens Fund, Augustinus Fund, Ivan Nielsen Fund, Doctor Sofus Carl Emil Friis and wife Olga Doris Friis' Fund, The Simon Fougner Hartmanns Family Fund, Danish Medical Society in Copenhagen, AP Moeller Foundation, during the study. EPW and JMC worked for the PCORI at the time the work was competitively awarded and funded by PCORI. The disclosure provided by the corresponding author, is intended to transparently reassure readers that the investigator team had complete authority and independence over the study and there was no undue influence by PCORI through EPW or JMC. Other than the fact that trial investigators contributed data from their trials, no other member of the EPPPIC group declared any potential competing interests.

Data sharing

The EPPPIC protocol is published, the statistical analysis plan and data dictionary are available on request. The trial investigators who shared individual participant data for the purposes of the meta-analysis retain ownership of their trial data and any requests for access to individual participant data should be made directly to them.

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