Author manuscript

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

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SUMMARY

Background

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

Methods

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 We identified published and unpublished trials that completed primary data collection before July 30, 2016 (12 months before data collection began) by searching MEDLINE, Embase, CINAHL, the Maternity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.

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 16,185 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, 769 women; relative risk [RR] 0·78, 95% CI 0·68–0·90), 17-OHPC (five trials, 3,053 women; 0·83, 0·68–1·01), and oral progesterone (two trials, 183 women; 0·60, 0·41–0·90). 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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Registration: This meta-analysis is registered with PROSPERO, CRD42017068299.

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.

INTRODUCTION

Preterm birth is the most common cause of neonatal morbidity and mortality globally, with rates ranging from 5% in European to 18% in African countries.[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 experience long-term health problems such as cerebral palsy, epilepsy, cognitive disability, blindness or hearing loss. Preterm birth can have important economic consequences for families as well as for payers and purchasers of health care.[3,4] Reducing rates of preterm birth could therefore accrue significant health and fiscal benefits globally.

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 may compensate for functional decline in progesterone levels in gestational tissue or counter the inflammatory response leading to PTB.[5] Natural progesterones are similar to those produced by living organisms; semi-synthetic 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; 17-OHPC is given as a weekly intramuscular injection.

Previous reviews[7,8,9,10,11,12] (Appendix Table 1) focussed on a single form of progestogen in particular at-risk subpopulations. Uncertainty about effectiveness and the appropriateness for specific indication(s) for treatment remained. EPPPIC aimed to bring together participant-level datasets from all relevant completed RCTs to enable independent, robust and standardised evaluation of all forms of progestogen, and of potential differences in effectiveness in different types of women and pregnancies. It is the most comprehensive IPD dataset established to date. There is no existing individual participant data (IPD) meta-analysis of 17-OHPC in singleton pregnancies.

In October 2020 the FDA proposed that the synthetic drug should be removed from the market for indication to prevent recurrent spontaneous preterm birth.[13]

METHODS

This international collaborative IPD meta-analysis followed a registered (PROSPERO: CRD42017068299), published[14] protocol and a statistical analysis plan produced in advance of analysis.[15] Findings are reported in accordance with PRISMA-IPD.[16]

EPPPIC included RCTs comparing progestogen with placebo (or non-intervention), or comparing different 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. Published and unpublished trials that completed primary data collection before July 2016 (12 months before EPPPIC data collection began) were considered for inclusion. Bibliographic searches of MEDLINE, Embase, CINAHL, the Maternity and Infant Care Database and relevant trial registers were last updated 30/07/2019 (Appendix: EPPPIC study identification), trialists were invited to identify additional trials. Titles and abstracts of

identified literature were screened independently by two researchers, as were full publications of potentially relevant trials. Discrepancies were resolved by discussion. In 2020, data from a large additional trial completed outside of the EPPPIC inclusion time frame was included in a targeted update of initial analyses.

Trial investigators supplied participant-level data, which were harmonised and recoded to EPPPIC definitions by them or by the EPPPIC team. Data were requested for all women randomised, 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, the pattern of treatment allocation was examined to check whether consistent with randomisation. Risk of bias (RoB) was independently assessed by two researchers using the RoB tool[17], alongside assessment of the provided IPD. Differences were resolved by discussion; if information was insufficient, clarification was sought from trialists.

Outcomes (defined in Appendix Table 2) included preterm birth, early preterm birth and midtrimester birth (respectively: delivery before 37+0, 34+0, 28+0 weeks gestation). Adverse neonatal sequelae associated with early births were assessed using a composite of serious neonatal complications (SNC) as well as individually. The composite included severe necrotising enterocolitis (NEC) stages II/III, intraventricular haemorrhage (IVH) grades 3/4, retinopathy of prematurity (ROP) stage 3 or worse; bronchopulmonary dysplasia (BPD), confirmed sepsis, patent ductus arteriosus (PDA) and neonatal infection. Respiratory distress syndrome (RDS) was assessed individually as was neonatal respiratory support. Adverse maternal outcomes were investigated as a composite (gestational hypertension, pre-eclampsia, gestational diabetes, and maternal infection including chorioamnionitis) and individually.

All available data for each outcome of interest were analysed on an intention-to-treat basis, separately for vaginal progesterone, 17-OHPC, and oral progesterone, and also separately for singleton and multifetal pregnancies (combining twin and triplet data). Primary analyses used “one-stage” generalized linear mixed models (GLMM) which incorporated random effects to allow for heterogeneity across trials[18] fitted using R software lme4 and coxme libraries. “Two-stage” random-effects (DerSimonian-Laird)[19] meta-analyses used R meta and metafor libraries, with heterogeneity examined by visual inspection of forest plots and using I^2.[20] Potential effect modifiers (Appendix Table 2) were investigated by adding covariate parameters and interactions between covariate and progestogen to the GLMM (Appendix: Formal specification of statistical models). Network meta-analysis (NMA) included trials directly comparing different 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: Formal specification of statistical models). As only two available trials compared progestogens directly, formal tests for network inconsistency were not performed.

Aggregate data were extracted (by one researcher and checked by another) from publications for trials not supplying IPD and relative risks calculated. Sensitivity analyses combined these with the individual relative risks calculated for each trial supplying IPD in two-stage meta-analyses. Forest plots were generated using in-house R code.

Women's experience of using progestogens was gathered using focus groups and individual interviews in a linked project (Appendix: Linked Qualitative Study).

ROLE OF THE FUNDING SOURCE

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RESULTS

Searches identified 2,911 unique references (Figure 1). After screening, 49 unique completed trials were eligible for inclusion.[22-69, one unpublished] Two of these were later excluded following IPD receipt and checking[68,69]. One trial[70] (which fell outside EPPPIC inclusion dates) reported just after initial analyses were completed. Owing to its size and potential impact, IPD were obtained and included in updated meta-analyses. Overall, 31 trials (11,644 women) were included.[22-50,70, one unpublished] Trial design details including numbers of women randomised are given in Appendix Table 6 (available trials) and 7 (unavailable trials). Fourteen included trials compared VP with control[22-35] six in singleton, five in multifetal pregnancies and three with mixed populations (mainly singletons). Thirteen trials compared 17-OHPC with control,[38-48,70, one unpublished] five in singleton and eight in multifetal pregnancies. Two compared OP with placebo[36, 37], and two[49,50] compared VP and 17-OHPC directly in singleton pregnancies. Trials were generally at low risk of bias (Appendix Figure 1).

Seventeen *potentially* eligible trials were unavailable (without access to IPD we were unable to confirm eligibility or verify randomisation).[51-67] Three 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 Appendix Table 7). Together these 17 trials, which were mostly single-centre and unregistered, accounted for a relatively small proportion of data. EPPPIC included 88% of the total number of women randomised across all available eligible plus all unavailable potentially eligible VP and 17-OHPC trials. Twelve trials for which IPD were not available published sufficient aggregate data for inclusion in sensitivity meta-analyses.

Table 1 summarises the proportion of women in VP/17-OHPC versus control trials by two main risk factors. Other characteristics are shown in Appendix Table 3.

Singleton pregnancies

One-stage meta-analyses found that vaginal progesterone (RR 0·78, 95% CI 0·68-0·90) and 17-OHPC (RR 0·83, 95% CI 0·68-1.01) reduced the risk of early preterm birth before 34 weeks in singleton pregnancies (Figure 2) compared to control, although, for 17-OHPC the confidence interval just crossed the line of no effect. This is also shown in two-stage forest plots (Appendix Figure 2), where all but two trials lie to the left of equivalence. 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%, 95% CI 0-57%). For an illustrative baseline risk of 20%, the 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 PTB<28 weeks and <37 weeks were generally consistent with findings for PTB<34 weeks (Figure 2).

Analyses also suggested a possible reduced risk of perinatal death for vaginal progesterone (RR 0·74, 95% CI 0·52-1·07) and 17-OHPC (RR 0·88, 95% CI 0·59-1·31) and for composite SNC for vaginal progesterone (RR 0·82, 95% CI 0·65-1·04) and 17-OHPC (RR 0·81, 95% CI 0·60-1·09) (Figure 2).

Vaginal progesterone reduced risk of low (<2500g) and very low (<1500g) birthweight, neonatal intensive care unit (NICU) admission, RDS, and respiratory support (Figure 3). Results also suggested a possible reduction in neonatal death after live birth. No discernible impact on fetal death/stillbirth, BPD, neonatal infection, or PDA was found. Results for severe ROP, NEC, and IVH were highly uncertain. Results for 17-OHPC suggested reductions in risk of neonatal death, low birthweight, very low birthweight, RDS, BPD, sepsis and PDA (Figure 4) and no discernible effect for fetal death/stillbirth, NICU admission and respiratory support. Results for severe ROP, IVH, and NEC were highly uncertain. There was no evidence of substantial heterogeneity in any analysis.

A possible increase in composite maternal complications was suggested for vaginal progesterone (RR 1·14, 95% CI 0·93-1·40) and 17-OHPC (RR 1·18, 95% CI 0·97-1·43) (Figure 2), mostly a result of increased gestational hypertension and maternal infection events. However, each individual outcome was very uncertain (Appendix Figures 3&4). There were no maternal deaths in any trials.

Singleton pregnancies: maternal risk factors as potential effect modifiers

Analyses including cervical length were based on around 65-70% of women as not all trials recorded it (Table 1). There was no indication that the relative treatment effect for either vaginal progesterone or 17-OHPC varied between categories of women with a shorter cervix (≤25mm) and with a longer cervix (>25mm). Nor was there evidence of effect modification when cervical length was analysed as a continuous variable; all p-values for interaction were > 0·1 (Appendix Table 4). However, the distribution of cervical length within the dataset limited the potential to examine treatment effect over the full spectrum of cervical.

Prior preterm birth was analysed because data were insufficient to distinguish reliably between preterm birth and *spontaneous* preterm birth for all women in all trials. There was no consistent evidence that relative effectiveness varied between women with a previous preterm birth and those without; most p-values for interaction were >0·1. The exceptions were for vaginal progesterone for

the outcome of preterm birth before 28 weeks (p=0·012) and SNC (p=0·079), where vaginal progesterone may be less effective in women with a previous preterm birth.

Given trial eligibility criteria, women without a previous preterm birth mostly had a short cervix, whilst 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 Table 4) 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 (PTB<34 weeks p=0·06; PTB <37 weeks p=0·095).

There was evidence of treatment interaction and greater risk of composite maternal complications (defined in Appendix Table 2) with increasing BMI for vaginal progesterone (p<0·001) and 17-OHPC (p=0·052). Numbers of events were insufficient to explore this observation within individual maternal complications. 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 Table 5).

Oral progesterone

Available data (2 trials, 183 women) accounted for 46% of women recruited in all potentially eligible trials. Analyses showed that oral progesterone reduced risk of preterm birth before weeks (RR 0·60, 95% CI 0·41-0·90) compared to control (Appendix Figures 5&6); results for preterm birth before weeks, maternal complications and perinatal death were broadly consistent with those for vaginal progesterone, but CIs were wide (Appendix Figure 5).

Trials comparing vaginal progesterone *and 17-OHPC*

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 (preterm birth before 28 weeks: RR 1·06 95% CI 0·41-2·78; preterm birth before weeks: RR 1·18, 95% CI 0·69-2·03; preterm birth before weeks: RR 1·15 95%CI 0·82-1·61) (Appendix Figure 7).

Network meta-analyses

Results of NMA comparing vaginal progesterone and 17-OHPC were based mostly on indirect evidence, favoured vaginal progesterone for most main outcomes but were not conclusive (Appendix Figure 8).

Singleton pregnancy subpopulations by indication for treatment

We performed supplementary two-stage analyses of subpopulations categorised by prior preterm birth status and cervical length, using the most commonly accepted 25mm cut-off and a 30mm cut-off as a sensitivity analysis (two trials used 30mm to define short cervix as an eligibility criterion). These categorised meta-analyses required both variables to be recorded, and consequently were based on considerably fewer data than the main analysis (59% for 17-OHPC, 43% for VP). Six trials did not provide cervical length and could not be included [22, 23, 26, 34, 44, one unpublished]. Results for short

cervix groups demonstrated benefit and were generally consistent with overall effects (Appendix Figures 9&10). Results for >25mm without prior preterm birth categories were much more uncertain (Appendix Figure 9). Treatment benefit was not apparent for women with cervical length >30mm for both vaginal progesterone and 17-OHPC (Appendix Figure 10). Different trials contributed to different categories and there may 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 evidence of difference between vaginal progesterone and 17-OHPC (Appendix Figure 11). Nor did NMA restricted to women with a prior preterm birth (Appendix Figure 12).

Multifetal pregnancies

All vaginal progesterone trials in multifetal pregnancies were of twins, two 17-OHPC trials were of triplet pregnancies. Most women had no recorded risk factors other than multifetal gestation (Table 1).

For vaginal progesterone compared with control the RR of preterm birth before 34 weeks in twin pregnancies was 1·01 (95% CI 0·84-1·20). For 17-OHPC the RR for twin and triplet pregnancies was 1·04 (95% CI 0·92-1·18) (Figure 5). Two-stage forest plots (Appendix Figure 13) show that most individual trial results were highly uncertain. For other outcomes most meta-analysis effect estimates were close to one and/or had very wide confidence intervals (Appendix Figures 14-17). The main exceptions were preterm PROM, where 17-OHPC increased risk (e.g. rupture <34 weeks: RR 1·59, 95% CI 1·15-2·22) (Appendix Figure 17). Vaginal progesterone did not increase this risk (RR 0·92, 95%CI 0·62-1·35) (Appendix Figure 16).

Multifetal pregnancies: maternal risk factors as potential effect modifiers

There was no evidence of any consistent variation in the relative treatment effect with cervical length or previous preterm birth status. However, as trials did not focus on selected multifetal gestation subpopulations by indication, data were extremely limited. NMA found no evidence of any difference in effect between vaginal progesterone and 17-OHPC.

Further and sensitivity analyses

Analysis in *singleton* trials found no evidence of any trend linked to planned vaginal progesterone dose or preparation (Appendix Figure 18). As there was little variation in planned 17-OHPC dose, no such analysis was done. Sensitivity analyses for *singleton* neonatal outcomes irrespective of severity (e.g. including all IVH not just grades III-IV), or adding RDS to composite SNC (Appendix Figure 19), did not lead to different conclusions from the main analyses.

Sensitivity meta-analyses incorporating aggregate data (AD) from unavailable trials mostly gave slightly more favourable results but did not lead to different conclusions than the main IPD meta-analyses (Appendix Figures 20-24). For vaginal progesterone in multifetal pregnancies, the addition of AD from one trial gave meta-analysis results that were suggestive of possible benefit (preterm birth before 34 weeks RR 0·91, 95% CI 0·73-1·12) (Appendix Figure 20), whereas analyses of just IPD were not. Sensitivity analysis incorporating AD for unavailable trials comparing vaginal progesterone

and 17-OHPC are not given owing to a published note of concern[71] about a contemporaneous trial by the same authors as the largest.

DISCUSSION

EPPPIC addresses 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 in order that decisions made by clinicians and childbearing women can be informed by the totality of available evidence, rather than focussing on the published results of individual trials.

High-risk singleton pregnancies

Most women with singleton pregnancies enrolled in the trials included in EPPPIC were high-risk because of prior SPTB, a short cervix, or both. Results showed a consistently favourable direction of effect for birth and neonatal outcomes with clear reductions in the relative risk of early preterm birth before 34 weeks for vaginal progesterone and for 17-OHPC (although the confidence interval just crossed equivalence for 17-OHPC). Relative risks for preterm birth before 38 weeks and midtrimester birth before 28 weeks were also reduced for both agents.

Results also suggested possible reductions in composite serious neonatal complications and incidence of low birthweight infants. A possible increase in the relative risk of maternal complications was noted for both 17-OHPC and vaginal progesterone 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 (*as represented and distributed within the meta-analysis population*), or by history of a prior 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 analysis of this dataset Appendix Figures 25&26), absolute risk reductions are greater for women with a shorter cervix, hence treatment 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 irrespective of obstetric history.[8] We also found benefit for women with cervical length ≤ 30mm, for both progestogens. There was no apparent benefit in subpopulations of women with prior preterm birth and cervical length >30mm, though confidence intervals were wide and consistent with both benefit and harm. Further investigation of women with a prior preterm birth and longer cervical length (>30 mm) may be required to confirm that risk-benefit ratio in this high risk 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 the direction of favouring vaginal progesterone. NMA also found no definitive evidence of clinically important differences between vaginal progesterone and 17-OHPC when restricted to short cervix and prior 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: Linked qualitative study).

Data were too limited for oral progesterone to adequately evaluate safety and effectiveness. However, effect sizes for preterm birth outcomes were consistent with those for vaginal progesterone and 17-OHPC; data on maternal and neonatal outcomes were limited.

Multifetal pregnancies

The only risk factor for most women included in trials of multifetal gestations was their twin or triplet pregnancy. There was no evidence that either vaginal progesterone or 17-OHPC reduced the risk of preterm birth. Across outcomes most estimates were close to no effect and/or were highly uncertain, and we did not identify any consistent benefit or harm for either agent in these unselected multifetal pregnancies, although preterm PROM was increased with 17-OHPC.

EPPPIC 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 of 250 women with a short cervix and twin gestation declined to participate in EPPPIC[54] and further evaluation of IPD from this trial could be informative. A recently published trial of vaginal progesterone in twins[74] was consistent with EPPPIC in finding no overall reduction in the incidence of PTB, but a data driven *post hoc* analysis suggested that vaginal progesterone might delay birth for women with cervical length <30mm.

Comparison between EPPPIC and other recent IPD meta-analyses

EPPPIC results are generally consistent with previous IPD meta-analyses (Appendix Table 1). However, although we found no benefit of progestogen in multifetal gestations, a previous IPD meta-analysis of vaginal progesterone in women with a twin pregnancy and cervical length ≤25mm did identify benefit. In addition to the differing inclusion criteria for cervical length, two additional trials,[54,69] which accounted for 75% of the data in that IPD meta-analysis but are not included in EPPPIC. 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/exclusion of this trial had little impact. The other trial[54] declined to participate.

Strengths and limitations

Strengths include evaluation of different progestogens in 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, conducted 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. Only limited data were available for oral progesterone and for head to head trials, 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 may 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 collected data on longer-term infant outcomes, and data were too few for analyses. This is an important gap in knowledge. Data on patient-centred outcomes were also lacking in most trials.

Implications for practice

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 preterm birth before 34 weeks and for most neonatal outcomes was more certain (narrower confidence intervals) than the evidence for 17-OHPC, EPPPIC findings support both vaginal progesterone and 17-OHPC being considered as treatment options in high-risk singleton pregnancies. Owing to higher underlying risk and hence greater absolute risk reduction, treatment may 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: Linked qualitative study). Availability and costs of different forms of progestogen in different jurisdictions may also be an important component of decision-making.

EPPPIC found no evidence to support use of progestogen in *unselected multifetal pregnancies*. Effectiveness for women with multifetal gestation and short cervix or prior PRETERM BIRTH remains uncertain. Given an identified risk in multifetal pregnancies, intervention may be appropriate only in the context of research for this subpopulation.

Implications for research

Current and recently completed trials in women with multifetal gestation and short cervix (NCT03058536, NCT02518594, NCT02697331, NCT03863613, NCT03781674) have a combined target of >1600. Further trials without cervical length restriction (NCT02350231, ISRCTN69810120, and the EVENTS[74] trial mentioned above) have a combined target of almost 1500. 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 in the index pregnancy is required to further evaluate the risk-benefit ratio of intervention in this group.

Whether vaginal progesterone and 17-OHPC have equivalent effectiveness in singleton pregnancies (overall or given different indications/risk factors) would be best addressed by trials that compare them directly. Four such current or recently completed trials (NCT02304237 CTRI/2015/01/005467, NCT02913495, NCT03537287) have a combined target of >800 women. Further evaluation of oral progesterone may be warranted, in which case assessing potential harms of systemic treatment would be important. Two ongoing trials compare oral progesterone with vaginal progesterone or 17-OHPC (NCT03343795, NCT03537287).

New adequately powered trials should follow 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.

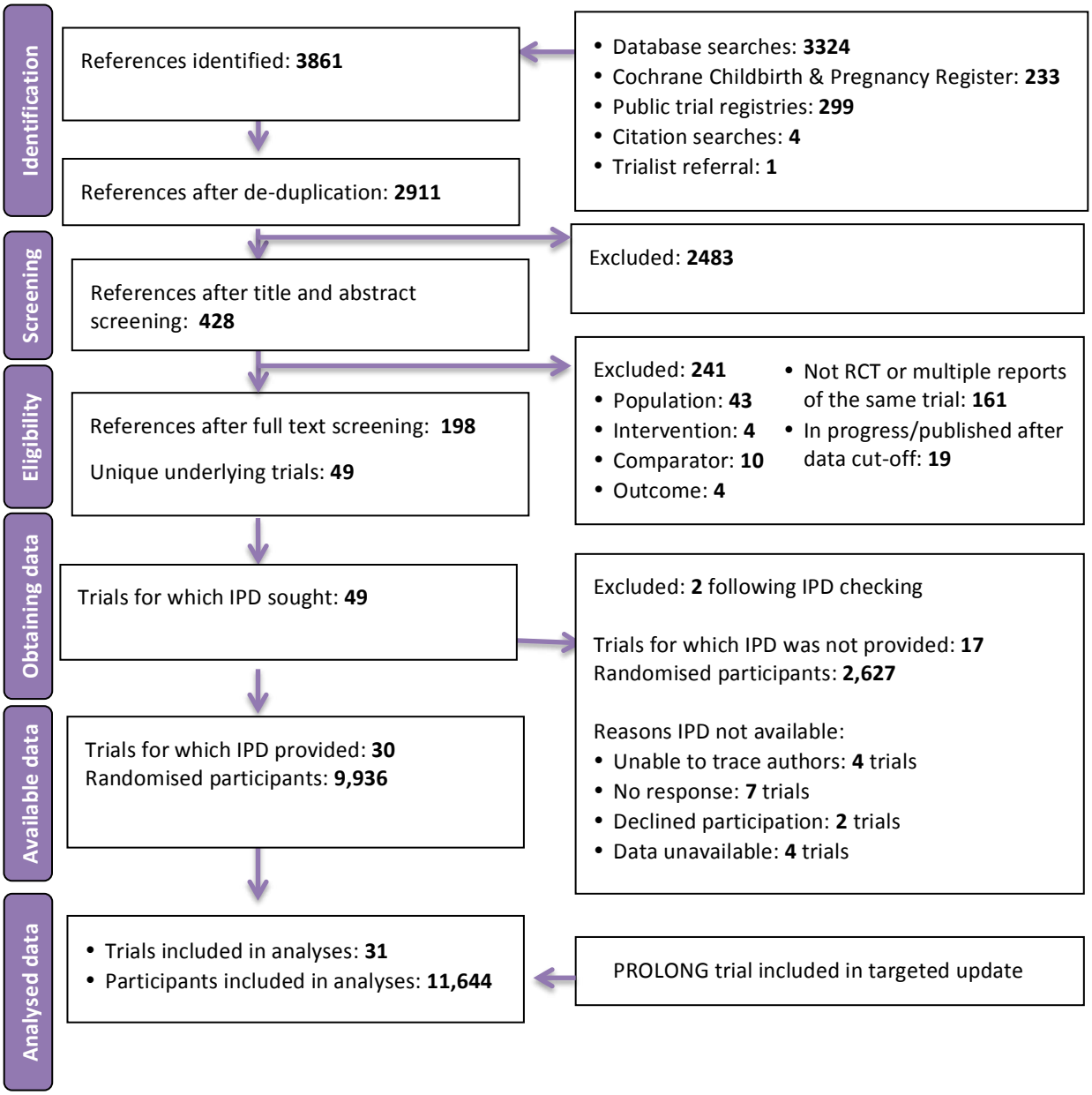

Figure 1: Trial identification (PRISMA-IPD flow diagram)
PROLONG was added in a targeted update although completed outside of EPPPIC inclusion dates, owing to its size and clinical interest.

	Cervix length ≤ 25mm n (%)	Cervix length >25mm n (%)	Cervix length unknown n (%)	Total
Single gestation VP				
Parous, with prior PTB	359 (9·4)	1218 (**31·9**)	1042 (**27·3**)	2619 (68·6)
Parous, no prior PTB	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 prior PTB	82 (2·7)	1223 (39·7)	1070 (34·7)	2375 (77·1)
Parous, no prior PTB	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 VP				
Parous, with prior PTB	1 (0)	28 (1·4)	32 (1·5)	61 (2.9)
Parous, no prior PTB	22 (1·1)	465 (**22·5**)	124 (6)	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 Prior PTB	22 (1.0)	102 (4.5)	78 (3·4)	202 (8·9)
Parous, No prior PTB	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

Table 1 : Proportion of women included in trials comparing VP or 17-OHPC with control by prior PTB status and cervix length (at randomisation) for singleton and multifetal pregnancies.
PTB: preterm birth. Categories with ≥20% of meta-analysis population are shown in bold and shaded. [$] These women are mainly from the trial in women who underwent IVF, [@] these women are from SCAN and have cervical length ≤ 30mm.

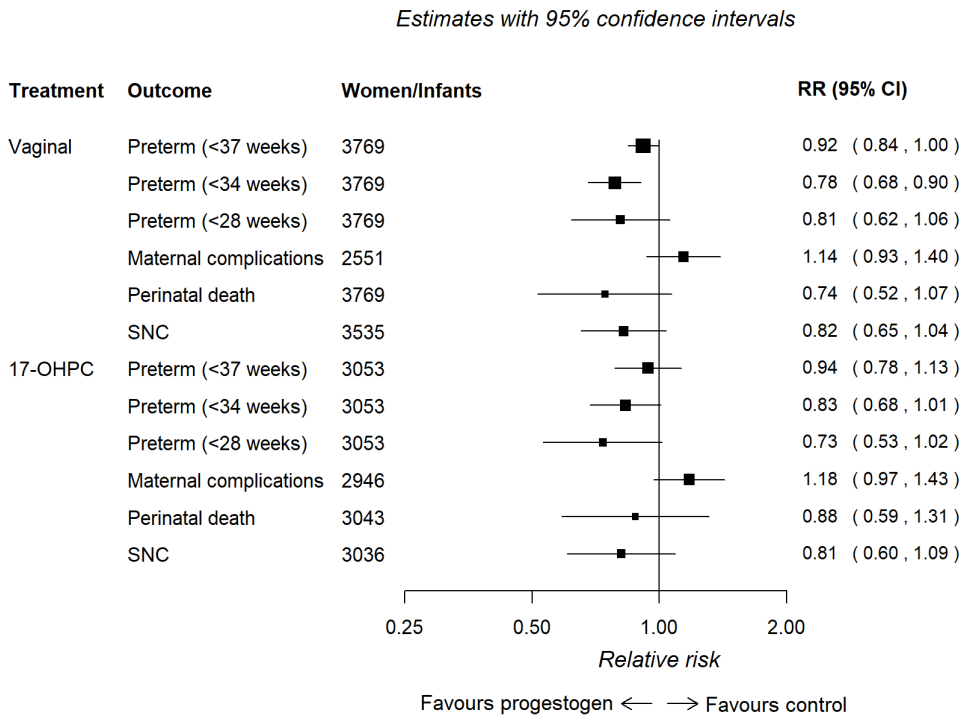

Figure 2**: Singleton pregnancies: main outcomes (one-stage meta-analysis)**

SNC: serious neonatal complications. 3 trials of VP including 230 women were unavailable, 7 trials of 17-OHPC including 776 women were unavailable. For PTB < 37 weeks VP= 661, control (C)=705; PTB<34 weeks VP= 276, C= 343; PTB 28 weeks VP= 92 C= 111; maternal complications VP=186, C=171; perinatal death VP=49, C=64 events; SNC VP= 119, C=140 events. For 17-OHPC PTB<37 weeks 17-OHPC=510, C=330 events; PTB<34 weeks 17-OHPC= 206, C= 158; PTB 28 weeks 17-OHPC= 77, C= 66; maternal complications 17-OHPC=285, C=178; perinatal death 17-OHPC=57, C=40 events; SNC 17-OHPC=95, C=75 events.

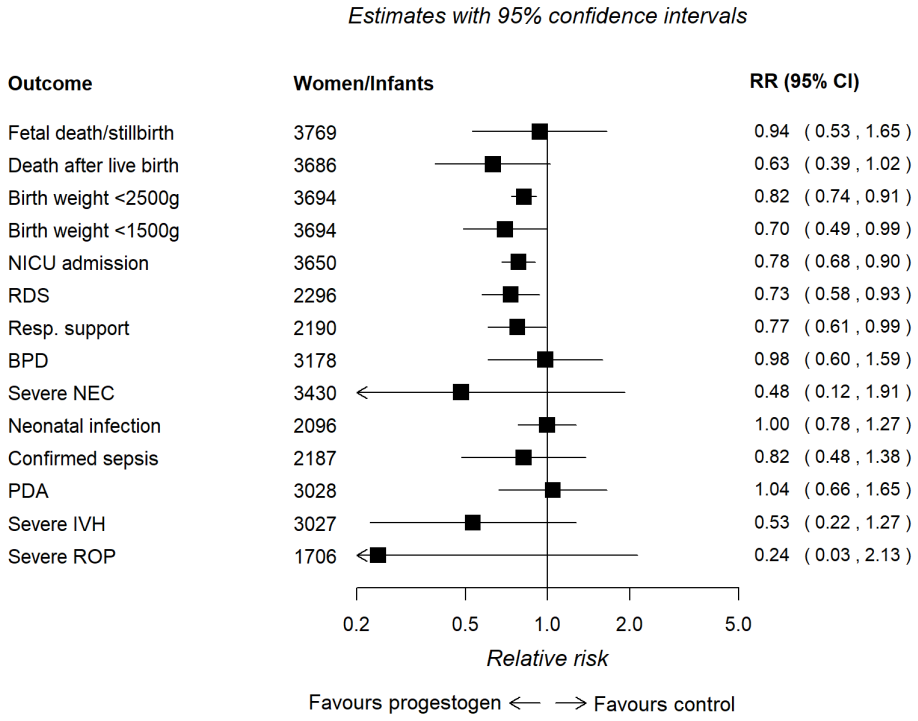

Figure 3: Singleton pregnancies: additional neonatal outcomes, VP (one-stage meta-analysis)

NICU (admission to neonatal Intensive or special care unit), RDS (respiratory distress syndrome), BDP (bronchopulmonary dysplasia), PDA (patent ductus arteriosis) Severe IVH (intraventricular haemorrhage) (grade III or IV), Severe ROP (retinopathy of prematurity) (stage 3 or worse). Severe NEC (Necrotising enterocolitis) (grade II or III). Fetal death/Stillbirth: VP= 23, C= 24 events; Death after live birth: VP= 26, C= 40; Birth weight < 2500g: VP=442, C= 524; Birth weight < 1500g: VP=131, C=168; NICU: VP= 286, C=353; RDS: VP= 99, C=132; Resp. support: VP=100, C=128; BDP: VP= 32, C=32; NEC: VP=3, C=6; Neonatal infection: VP=113, C=111; Sepsis: VP= 25, C=30; PDA: VP= 37, C=35; IVH: VP= 7, C=13; ROP: VP= 1, C=4

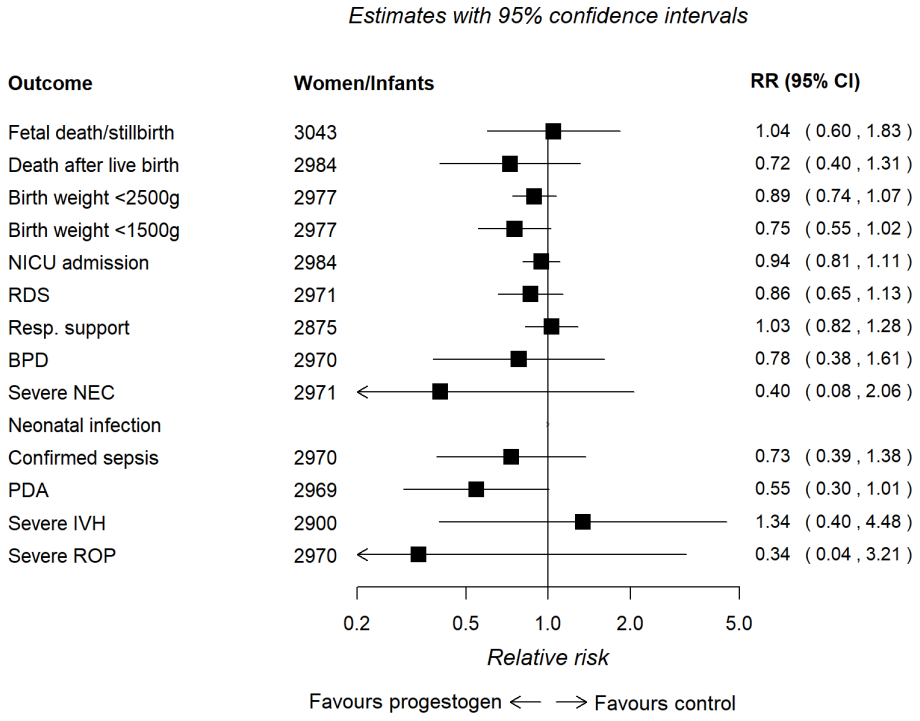

Figure 4: Singleton pregnancies: additional neonatal outcomes, 17-OHPC (one stage meta-analysis)

Note that x for relative risk denotes that the outcome is not estimable in a one-stage model (data are not sufficient for the model to converge). Fetal death/Stillbirth: 17-OHPC=34, C=19; Death after live birth: 17-OHPC=23, C=21; Birth weight < 2500g: 17-OHPC=342, C=239; Birth weight < 1500g: 17-OHPC=82, C=74; NICU: 17-OHPC= 312, C=209 events; RDS:17-OHPC = 113, C=81; Resp support: 17-OHPC=192, C=112; BDP: 17-OHPC = 16, C=14; NEC: 17-OHPC=2, C=5; Neonatal infection: 17-OHPC=0, C=0; Sepsis: 17-OHPC=20, C=19; PDA:17-OHPC = 19, C=22; IVH: 17-OHPC = 8, C=4; ROP: 17-OHPC = 1, C=3

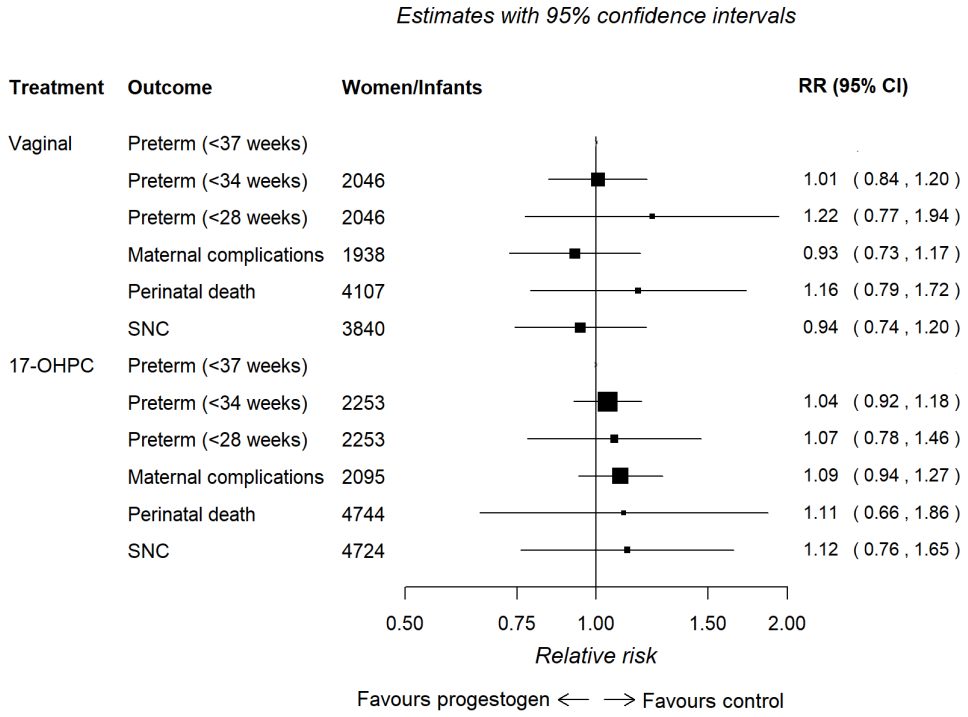

Figure 5 Multifetal pregnancies: main outcomes (one-stage meta-analyses)

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. Note that x for relative risk denotes that the outcome is not estimable in a one-stage model (data are not sufficient for the model to converge). 2 trials of VP including 350 women were unavailable, 1 trial of of 17-OHPC including 77 women were unavailable. For PTB < 37 weeks VP= 599, C=554 events; PTB<34 weeks VP= 202, C= 187; PTB 28 weeks VP= 41 C= 31; maternal complications VP=125, C=134; perinatal death VP=56, C=44 events; SNC: VP=127, C=125. For 17-OHPC PTB<37 weeks 17-OHPC=854, C=663 events; PTB<34 weeks 17-OHPC= 368, C= 285; PTB < 28 weeks 17-OHPC= 83, C= 65; maternal complications 17-OHPC=358, C=284; perinatal death 17-OHPC=112, C=85 events; SNC: 17-OHPC=287, C=229.

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Author contributions

LAS, LD and MS designed the meta-analysis and were responsible for overseeing all aspects of conduct. LB, KCD, AH, AL, SS and RAEW contributed various stages of the project including aspects of design, eligibility screening, data extraction, risk of bias assessment, IPD checking and trial analysis. LAS managed the project and collaborative process, MS carried out data synthesis, LD provided clinical oversight and KW designed and conducted the literature searches. LAS, MS and LD wrote the manuscript with input from 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 PCORI as the project progressed. Trial investigators prepared and supplied data and answered questions about their trials. All members of the EPPPIC group had the opportunity to review and provide comment on analyses and the content of the manuscript. The independent research team considered and took account of feedback from group members and were responsible for decisions about methods, analyses and content of the manuscript.

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Statement of interests

LAS and members of the project team are/were employees of the University of York which received funding from PCORI to carry out the EPPPIC project. **LD** reported grants from NIHR Programme for applied research, outside the submitted work. **KD** reported that her employer John 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** reported grants from the NIHR outside of the submitted work. No member of the project team had involvement with any of the included trials or had any conflict of interest. **SCB** presented to the FDA Advisory Board on behalf of the Sponsor (AMAG, Inc) regarding FDA approval of 17-OHPC. He did not receive any financial payments or financial support for this role. **SNC** reported grant support from Amag to perform a pharmacokinetic study on intramuscular vs subcutaneous 17-hydroxyprogesterone caproate. Amag Pharmaceuticals also supplied 17-hydroxyprogesterone caproate for a study he directs for the

NICHD- sponsored Obstetric-Fetal Pharmacology Research Centers. **CACr** reports she was lead investigator for the PROGRESS Trial one of the studies included in the IPD-MA. **AD** reported personal fees from AMAG during the conduct of the study and personal fees from Hologic outside the submitted work. **BM** declared grants from NHMRC, personal fees from ObsEva, personal fees from Merck, personal fees from Guerbet, grants from Guerbet, 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 last 3 years she has acted on a Data Safety and Monitoring Board for a study involving a preterm birth therapeutic agent for Glaxo Smith Kline, and has provided consultancy for Dilafor on drugs to alter labour progress. **JN** reported 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 (HTA) General Funding Committee 2016-2019; and is currently Chair of the UK Medical Research Council (MRC) / NIHR Efficacy and Mechanisms Evaluation (EME) 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 Pharmaceuticals, 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 obstetrical 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** reported 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, A.P. Moeller Foundation, during the conduct of the study. **EPW** and **JMC** worked for the Patient-Centered Outcomes Research Institute (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 scientific conduct of the study and there was no undue influence by PCORI through EPW or JC. Other than the fact that trial investigators contributed data from their trials and had previously reported these, no other member of the EPPPIC group declared any potential conflict of interest.

Data Sharing Statement

The EPPPIC protocol is published[13], the statistical analysis plan and data dictionary are available on request. The trial investigators who shared IPD for the purposes of the EPPPIC IPD meta-analysis retain ownership of their trial data and any requests for access to IPD should be made directly to them.

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