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*DOI:*
10.1111/1471-0528.17705



*Document Version*
Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*
Melo, P, Devall, A, Shennan, AH, Vatish, M, Becker, CM, Granne, I, Papageorghiou, AT, Mol, BW & Coomarasamy, A 2023, 'Vaginal micronised progesterone for the prevention of hypertensive disorders of pregnancy: A systematic review and meta-analysis', *BJOG: An International Journal of Obstetrics & Gynaecology*. https://doi.org/10.1111/1471-0528.17705

Accepted: 20 October 2023

DOI: 10.1111/1471-0528.17705

BJOG An International Journal of Obstetrics and Gynaecology

SYSTEMATIC REVIEW

# Vaginal micronised progesterone for the prevention of hypertensive disorders of pregnancy: A systematic review and meta-analysis

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**Abstract**

**Background:** Treatment with vaginal progesterone reduces the risk of miscarriage and preterm birth in selected high-risk women. The hypothesis that vaginal progesterone can reduce the risk of hypertensive disorders of pregnancy (HDP) is unexplored.

**Objectives:** To summarise the evidence on the effectiveness of vaginal progesterone to reduce the risk of HDP.

**Search strategy:** We searched Embase (OVID), MEDLINE (OVID), PubMed, CENTRAL and clinicaltrials.gov from inception until 20 June 2023.

**Selection criteria:** We included placebo-controlled randomised trials (RCTs) of vaginal progesterone for the prevention or treatment of any pregnancy complications.

**Data collection and analysis:** We extracted absolute event numbers for HDP and pre-eclampsia in women receiving vaginal progesterone or placebo, and meta-analysed the data with a random effects model. We appraised the certainty of the evidence using GRADE methodology.

**Main results:** The quantitative synthesis included 11 RCTs, of which three initiated vaginal progesterone in the first trimester, and eight in the second or third trimesters. Vaginal progesterone started in the first trimester of pregnancy lowered the risk of any HDP (risk ratio [RR] 0.71, 95% confidence interval [CI] 0.53–0.93, 2 RCTs, $n = 4431$ women, $I^2 = 0\%$; moderate-certainty evidence) and pre-eclampsia (RR 0.61, 95% CI 0.41–0.92, 3 RCTs, $n = 5267$ women, $I^2 = 0\%$; moderate-certainty evidence) when compared with placebo. Vaginal progesterone started in the second or third trimesters was not associated with a reduction in HDP (RR 1.19, 95% CI 0.67–2.12, 3 RCTs, $n = 1602$ women, $I^2 = 9\%$; low-certainty evidence) or pre-eclampsia (RR 0.97, 95% CI 0.71–1.31, 5 RCTs, $n = 4274$ women, $I^2 = 0\%$; low-certainty evidence).

**Conclusions:** Our systematic review found first-trimester initiated vaginal micronised progesterone may reduce the risk of HDP and pre-eclampsia.

KEYWORDS
hypertensive disorders of pregnancy, pre-eclampsia, progesterone

## 1 | INTRODUCTION

Hypertensive disorders of pregnancy (HDP), including gestational hypertension and pre-eclampsia, affect an estimated 18 million pregnant women worldwide every year.[1] Women with HDP in previous pregnancies have an increased risk of spontaneous preterm birth[2] and, conversely, women with spontaneous preterm births in previous pregnancies have an increased risk of HDP.[3] The overlap in the groups of women who have these outcomes suggests common aetiological pathways, which could include: altered remodelling of uterine spiral arteries in

early pregnancy, resulting in impaired placental perfusion and maternal endothelial dysfunction; the existence of systemic inflammation in preterm birth concurrently with endothelial changes; and a possible effect of abnormal vaginal and decidual microbiota, resulting in local infection or dysbiosis.[2,3] The common aetiology hypothesis is strengthened by the meta-analyses findings which suggest that aspirin, used to prevent pre-eclampsia,[4] may exert a protective effect against preterm birth.[5]

Is it therefore possible that progesterone, when administered for the prevention of pregnancy loss or preterm birth, could protect against pre-eclampsia? In the PROMISE trial, we investigated first-trimester initiation of vaginal progesterone versus placebo for the prevention of miscarriage in 836 women with unexplained recurrent pregnancy losses. We identified a 25% reduction in the risk of pre-eclampsia in the progesterone group (relative risk [RR] 0.75, 95% confidence interval [CI] 0.29–1.96); however, this was a secondary outcome and had substantial statistical uncertainty, as can be seen from the confidence interval.[6] Our subsequent PRISM trial, comparing vaginal progesterone with placebo for the prevention of pregnancy loss in a much larger sample of 4153 women with threatened first-trimester miscarriage, added support to the above finding by identifying a 37% lower risk of pre-eclampsia among participants receiving progesterone (RR 0.63, 95% CI 0.39–1.01).[7]

The most recent Cochrane review on the effects of progesterone for pre-eclampsia prevention dates to 2006,[8] preceding these large trials. We therefore undertook a systematic review and meta-analysis to synthesise and appraise the existing evidence on the effectiveness of vaginal micronised progesterone to reduce the risk of HDP.

## 2 | METHODS

### 2.1 | Registration

We registered this systematic review with PROSPERO before commencement (CRD42022371676).

### 2.2 | Search strategy

We conducted systematic searches of the following electronic platforms, from database inception until 20 June 2023: MEDLINE (OVID platform), Embase (OVID platform), PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and clinicaltrials.gov. Using the terms progest* AND pregnan*, we searched for randomised controlled trials (RCTs) in which pregnant women received vaginal progesterone in any available formulation and dose compared with a placebo. Details of the search strategy are shown in Appendix S1. We excluded studies in which participants were not pregnant, or where non-vaginal routes of progesterone were compared with one another or placebo in the absence of a trial arm receiving vaginal progesterone. We sought additional studies by reviewing the reference lists of all identified publications, including relevant systematic reviews and meta-analyses. We applied no language restrictions to our searches. Where data were missing or unclear, we contacted study authors directly for additional information.

### 2.3 | Selection criteria

Two review authors (PM and AD) independently selected the titles and abstracts of studies for full-text screening using EndNote 20.[9] We then retrieved the full texts of relevant publications, and two investigators (PM and AD) independently performed the final study selection, data extraction and quality assessment.

### 2.4 | Quality assessment

We conducted a trustworthiness check of all studies meeting our eligibility criteria, in accordance with Cochrane recommendations.[10] We assessed the quality of included RCTs with the Cochrane Risk of Bias 2 tool, which evaluates the risk of bias of RCTs according to the following domains: selection, performance, detection, attrition, reporting and other biases.[10] Based on the assessments of the studies against these domains, we judged each RCT as being at low, high or unclear risk of bias for each domain. We resolved disagreements by consensus.

### 2.5 | Study outcomes

The main outcomes were the rate of HDP per woman randomised, defined as the new onset of systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions, 4 hours apart after 20 weeks of gestation, with or without proteinuria[11]; and the rate of pre-eclampsia per woman randomised, defined as HDP with proteinuria or evidence of maternal acute kidney impairment, liver dysfunction, neurological features, haemolysis or thrombocytopaenia or fetal growth restriction.[12]

### 2.6 | Data synthesis and analysis

For each included study, we extracted the following data: authors, year of publication, country, inclusion criteria, exclusion criteria, intervention, timing of progesterone initiation, comparator and outcomes. We created forest plots on REVIEW MANAGER 5.4.1 using a random effects model.[13] The primary analysis focused on two groups which varied in the timing of progesterone commencement: first-trimester initiation (where the addition of exogenous progesterone may have affected placentation) and second- or third-trimester initiation (where exogenous progesterone initiation was unlikely

to affect placentation). For each outcome, we reported effect measures as risk ratio and 95% confidence intervals. We described statistical heterogeneity using the $I^2$ statistic and considered $I^2$ <50% to represent low heterogeneity.

The primary analysis was restricted to studies deemed to be trustworthy and at a low risk of selection bias. We conducted a subgroup analysis according to the total daily dose of progesterone administration (e.g. 400 mg daily versus 800 mg daily). We performed sensitivity analyses including all studies, irrespective of trustworthiness or the risk of selection bias and used a fixed-effect model to evaluate whether our conclusions would have differed compared with a random effects model.

We undertook a Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of the certainty of the evidence, which considers the following five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias.[10] We summarised the main results in a Summary of Findings Table.

# 3 | RESULTS

## 3.1 | Study selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram detailing the study selection process is shown in Figure S1 (Data S1). The bibliographic searches conducted on 20 June 2023 identified a total of 5134 references. Following removal of duplicates, we screened 3322 titles and abstracts, of which 3212 were excluded because they were not relevant. Among the 110 full-text manuscripts screened for eligibility, we included 11 in the quantitative synthesis, of which three were single-centre[14–16] and eight were multicentre studies.[6,7,17–22] Two studies were conducted in the UK,[7,18] one each in Australia,[14] Brazil,[15] Iran,[16] Spain[21] and the Netherlands,[22] and four studies were collaborations between two or more countries.[6,17,19,20] Details of the included studies are given in Table 1. The reasons for excluding studies are given in Table S2. We attempted to contact the authors of 41 studies for additional information or clarification of data and received answers from five investigators (Table S3).

## 3.2 | Participants

In aggregate, the included studies evaluated a total of 11 640 women. Participants' ages ranged from 16 years to no specified upper age limit. Participating women were pregnant in all studies, with gestational age at randomisation ranging between <6 weeks[6] to 36 weeks.[16] Three studies included only women carrying singleton pregnancies,[16,18,22] four included only women carrying twin pregnancies[15,19–21] and the remaining four trials included women with singleton or twin pregnancies.[6,7,14,17] None of the included studies reported on whether participants had a history of HDP in a previous pregnancy.

## 3.3 | Interventions

Among the included RCTs, three investigated progesterone commenced in the first trimester to prevent miscarriage ($n$ = 5267 women)[6,7,14] and eight investigated progesterone commenced in the second or third trimesters to prevent preterm birth ($n$ = 6373 women).[15–22] The total daily dose of vaginal micronised progesterone ranged between 100 and 800 mg, and all trials were placebo-controlled.

## 3.4 | Outcomes

A total of five trials reported on the rate of HDP[7,14,18,21,22] and 11 trials reported on the pre-eclampsia rate.[6,7,14–22]

### 3.4.1 | Hypertensive disorders of pregnancy

Vaginal progesterone commenced in the first trimester of pregnancy lowered the risk of HDP compared with placebo (RR 0.71, 95% CI 0.53–0.93, 2 RCTs,[7,14] $n$ = 4431 women, $I^2$ = 0%; moderate-certainty evidence) (Figure 1A). The subgroup analysis according to progesterone dose showed a benefit in using the 400-mg twice daily regimen (RR 0.74, 95% CI 0.55–0.99, 1 RCT,[7] $n$ = 4153 women), whereas the 400-mg once daily regimen was not confidently associated with a reduction in HDP (RR 0.53, 95% CI 0.24–1.15, 1 RCT,[14] $n$ = 278 women) (Figure S2A). There were no additional studies for sensitivity analysis.

Vaginal progesterone commenced in the second or third trimesters of pregnancy resulted in no difference in HDP rates compared with placebo (RR 1.19, 95% CI 0.67–2.12, 3 RCTs,[18,21,22] $n$ = 1602 women, $I^2$ = 9%; low-certainty evidence) (Figure 2B). The subgroup analysis did not change the results (Figure S2). There were no additional studies for sensitivity analysis.

### 3.4.2 | Pre-eclampsia

Vaginal progesterone commenced in the first trimester of pregnancy reduced the risk of pre-eclampsia compared with placebo (RR 0.61, 95% CI 0.41–0.92, 3 //RCTs,[6,7,14] $n$ = 5267 women, $I^2$ = 0%; moderate-certainty evidence) (Figure 2A). The subgroup analysis according to progesterone dose showed a benefit in using the 400 mg twice daily regimen (RR 0.65, 95% CI 0.42–0.99, 2 RCTs,[6,7] $n$ = 4989 women), whereas the 400-mg once daily regimen was not confidently associated with a reduction in pre-eclampsia (RR 0.29, 95% CI 0.06–1.35, 1 RCT,[14] $n$ = 278 women) (Figure S3A). There were no additional studies for sensitivity analysis.

Vaginal progesterone commenced in the second or third trimesters of pregnancy resulted in no difference in pre-eclampsia rates compared with placebo (RR 0.97, 95% CI 0.71–1.31, 5 RCTs,[15,17–20] $n$ = 4274 women, $I^2$ = 0%; low-certainty evidence) (Figure 2B). The subgroup (Figure S3) and sensitivity (Figure S4) analyses did not change the results.

### 3.4.3 | Quality assessment

Table S1 shows details of the risk of bias assessment. All included studies were judged to be at low risk of performance and detection bias. One study was judged to be at unclear risk of selection bias because of a lack of detail on randomisation sequence generation and allocation concealment, resulting in its exclusion from the primary analysis.[16] We deemed two studies to be at high risk of attrition bias because >10% of participants discontinued the intervention.[18,21] Lastly, two studies exhibited high risk of other bias owing to a lack of prospective registration[15,16]

**TABLE 1** Characteristics of included studies.

| Study | Study design, duration and location | *n* | Inclusion criteria |
|---|---|---|---|
| First-trimester progesterone initiation | | | |
| Coomarasamy, 2015 | Multicentre, double-blind, placebo-controlled, randomised trial, conducted between 23 June 2010 and 23 October 2013 in hospitals in the Netherlands and the UK | 836 | Age 18–39 years; actively trying to conceive naturally after having received a diagnosis of unexplained recurrent miscarriage (defined as three or more consecutive or non-consecutive losses of pregnancy in the first trimester) |
| Coomarasamy, 2019 | Multicentre, double-blind, placebo-controlled, randomised trial, conducted between 19 May 2015 and 27 July 2017 in UK hospitals | 4153 | Age 16–39 years; <12 completed weeks of pregnancy; vaginal bleeding; and an intrauterine gestational sac that visible on ultrasonography |
| McLindon, 2023 | Double-blind, placebo controlled randomised trial conducted between February 2012 and April 2019 in a single hospital in Australia | 278 | Women with threatened miscarriage, defined as vaginal bleeding with or without pain; live intrauterine pregnancy with a fetal heart rate on ultrasound; gestational age <10 weeks |
| Second- or third-trimester progesterone initiation | | | |
| Brizot, 2015 | Double-blind, placebo-controlled randomised trial conducted in a single hospital, conducted between 1 June 2007 and 31 October 2013 in Brazil | 390 | Naturally conceived diamniotic twin pregnancies; no history of preterm delivery (<37 weeks' gestation); gestational age of 18–$21^{+6}$ weeks randomisation; absence of major fetal abnormalities (such as neural tube defects, abdominal wall defects, cardiac defects, hydrocephalus, and malformations that are associated with polyhydramnios) at the anomaly scan; no allergies to progesterone or peanuts; and the absence of hepatic dysfunction, porphyria, otosclerosis, malignant disease, severe depressive state, current or previous thromboembolic disease, uterine malformation, and prophylactic cerclage |

and in one study it was unclear whether registration had been undertaken.[22]

Table 2 summarises the findings of this review, including a GRADE assessment of the evidence. The certainty of the evidence ranged from low to moderate, owing to serious imprecision and serious indirectness.

# 4 | DISCUSSION

## 4.1 | Main findings

This systematic review and meta-analysis of RCTs investigated the effect of vaginal progesterone versus placebo

| Exclusion criteria | Vaginal progesterone dose | Timing of progesterone administration | Control | Outcomes |
|---|---|---|---|---|
| Unable to conceive naturally within 1 year after recruitment; antiphospholipid syndrome or other recognised thrombophilia; uterine cavity abnormalities (as assessed with the use of ultrasonography, hysterosonography, hysterosalpingogram, or hysteroscopy); abnormal parental karyotype or other identifiable cause of recurrent miscarriage such as diabetes, thyroid disease, or systemic lupus erythematosus (tests were initiated only if clinically indicated); currently receiving heparin therapy; or contraindications to progesterone use | 400 mg of natural micronised progesterone (Utrogestan®, Besins Healthcare) twice daily | From the time of a positive urine pregnancy test (and before 6 weeks of gestation) until 12 completed weeks of gestation | Placebo | Pre-eclampsia |
| Fetal crown–rump length ≥7 mm with no visible heartbeat; gestational sac was a mean of ≥25 mm in diameter with no visible fetal pole on ultrasonography; evidence of ectopic pregnancy; life-threatening bleeding; current or recent use of progesterone supplementation; contraindications to progesterone therapy (i.e., a history of liver tumours; current genital or breast cancer, severe arterial disease, or acute porphyria; or a history during pregnancy of idiopathic jaundice, severe pruritus, or pemphigoid gestationis); or participation in any other blinded, placebo-controlled trials of medicinal products in pregnancy | 400 mg of natural micronised progesterone (Utrogestan®, Besins Healthcare) twice daily | From the time of early pregnancy bleeding (<12 weeks of gestation) until 16 completed weeks of gestation | Placebo | Hypertensive disorders of pregnancy, pre-eclampsia |
| Assisted reproductive technologies due to luteal phase/early pregnancy hormonal support | 400 mg progesterone (Perrigo Australia) | From the time of bleeding until 12 weeks' gestation | Placebo | Hypertensive disorders of pregnancy, pre-eclampsia |
| Subsequent diagnosis of major fetal abnormalities; the presence of ovular infection; or being lost to follow up | 200 mg of natural micronised progesterone (Utrogestan®, Besins Healthcare) | From 18 and 21 weeks until 34 weeks and 6 days' gestation | Placebo | Pre-eclampsia |

(Continues)

**TABLE 1** (Continued)

| Study | Study design, duration and location | *n* | Inclusion criteria |
|---|---|---|---|
| Crowther, 2017 | Multicentre, placebo-blinded, randomised controlled trial at 39 Australian, New Zealand, and Canadian maternity hospitals, conducted between February 2006 and September 2012 | 787 | Live singleton or twin pregnancy between 18 and <24 weeks' gestation and a history of prior preterm birth (either vaginal or caesarean birth) at >20 weeks' gestation and <37 weeks' gestation in their preceding pregnancy where the onset of labour occurred spontaneously or in association with cervical incompetence or following preterm prelabour rupture of membranes. If the women had received progesterone therapy prior to 16 weeks' gestation, they remained eligible |
| Norman, 2016 | Multicentre, double-blind, placebo-controlled, randomised trial, conducted between 2 February 2009 and 12 April 2013 in UK hospitals | 1228 | Age 16 years or older; singleton pregnancy, with gestational age established by ultrasound scan before 16 weeks; clinical risk factors for preterm birth (any of a history in a previous pregnancy of preterm birth, or second trimester loss, or preterm premature fetal membrane rupture, or any history of a cervical procedure to treat abnormal smears) and either a positive or negative fetal fibronectin test at 22–24 weeks' gestation |
| Rehal, 2021 | Multicentre, double-blind, placebo-controlled, randomised trial, conducted between May 2017 and April 2019 in England, Spain, Bulgaria, Italy, Belgium and France | 1169 | Age >18 years; dichorionic or monochorionic diamniotic twin pregnancy; two live foetuses at the 11- to 13-week scan; fluent in the local language |
| Rode, 2011 | Multicentre, double-blind, placebo-controlled, randomised trial, conducted between 1 June 2006 and 31 October 2008 in Denmark and Austria | 2256 | Women with a live, diamniotic twin pregnancy and chorionicity assessed by ultrasound before 16 weeks' gestation |

| Exclusion criteria | Vaginal progesterone dose | Timing of progesterone administration | Control | Outcomes |
|---|---|---|---|---|
| Preceding preterm birth at less than 37 weeks' gestation associated with placental abruption or placenta praevia, if it was a multiple pregnancy, or if there had been an iatrogenic decision for early birth, for example, related to fetal distress or pre-eclampsia | 100 mg progesterone administered each evening | From 20 weeks' gestation, or from randomisation if this occurred after 20 weeks' gestation, until birth or 34 weeks' gestation, whichever occurred first | Placebo | Pre-eclampsia |
| Known significant congenital structural or chromosomal fetal anomaly; known sensitivity or listed contraindication to progesterone (known allergy or hypersensitivity to progesterone, severe hepatic dysfunction, undiagnosed vaginal bleeding, mammary or genital tract carcinoma, thrombophlebitis, thromboembolic disorders, cerebral haemorrhage, porphyria) or intolerance to progesterone or excipient; suspected or proven rupture of the fetal membranes at the time of recruitment; multiple pregnancy | 200 mg progesterone daily (Utrogestan®, Besins Healthcare) | From about 22–24 weeks of gestation until 34 weeks or delivery of the baby, whichever was sooner | Placebo | Hypertensive disorders of pregnancy, pre-eclampsia |
| Monoamniotic pregnancies, monochorionic diamniotic pregnancies with early signs of twin-to-twin transfusion syndrome, defined as >20% discordance in crown-rump length at the 11–13 weeks' scan; major fetal abnormality or nuchal translucency thickness >3.5 mm identified at the 11–13 weeks' scan; women who were unconscious or severely ill, those with learning difficulties or serious mental illness; hypersensitivity to progesterone; regular treatment with progesterone within the previous 7 days; severe hepatic dysfunction; mammary or genital tract carcinoma, thrombophlebitis or thromboembolic disorders; porphyria; cerebral haemorrhage; allergy to sunflower oil, soya lecithin, gelatin, glycerol (E422), titanium dioxide (E171); and participation in another drug trial within 28 days | 600 mg progesterone daily | From 11–14 until 34 weeks' gestation[a] | Placebo | Pre-eclampsia |
| Age < 18 years; known allergy to progesterone or peanuts (as the active treatment contained peanut oil); history of hormone-associated thrombophilias; rupture of membranes; treatment for or signs of twin-to-twin transfusion syndrome; intentional fetal reduction; known major structural or chromosomal fetal abnormality; known or suspected malignancy in genitals or breasts; known liver disease; women with higher-order multiple pregnancies; women who did not speak and understand Danish or German, as appropriate | 200 mg progesterone daily (Utrogestan®, Besins Healthcare) | From 20 + 0 weeks and 23 + 6 weeks' gestation until 33 + 6 weeks' gestation or until occurrence of either rupture of membranes or delivery. | Placebo | Pre-eclampsia |

(Continues)

**TABLE 1** (Continued)

| Study | Study design, duration and location | *n* | Inclusion criteria |
|---|---|---|---|
| Serra, 2013 | Multicentre, controlled, double-blind, phase-III trial, with balanced randomisation into three parallel groups (allocation ratio 1:1:1), conducted in Spain | 290 | Maternal age ≥18 years; dichorionic diamniotic twin pregnancy diagnosed by ultrasound |
| Sharami, 2010 | Double-blind, placebo controlled randomised trial conducted between June 2007 and May 2009 in a single hospital in Iran. | 173 | Singleton pregnancy with gestational ages between 28 and 36 weeks; admission for threatened preterm birth |
| van Os, 2015 | Multicentre, double-blind, placebo-controlled, randomised trial, conducted between 1 November 2009 and 1 August 2013 in The Netherlands | 80 | Low-risk singleton pregnancy and a cervical length ≤ 30 mm; low-risk pregnancy was defined as nulliparous, or multiparous women without a history of spontaneous preterm birth <34 weeks of gestation |

[a]Median age of initiation >12 weeks in both trial arms, so the decision was made to include these in the 'second-trimester initiation' group.

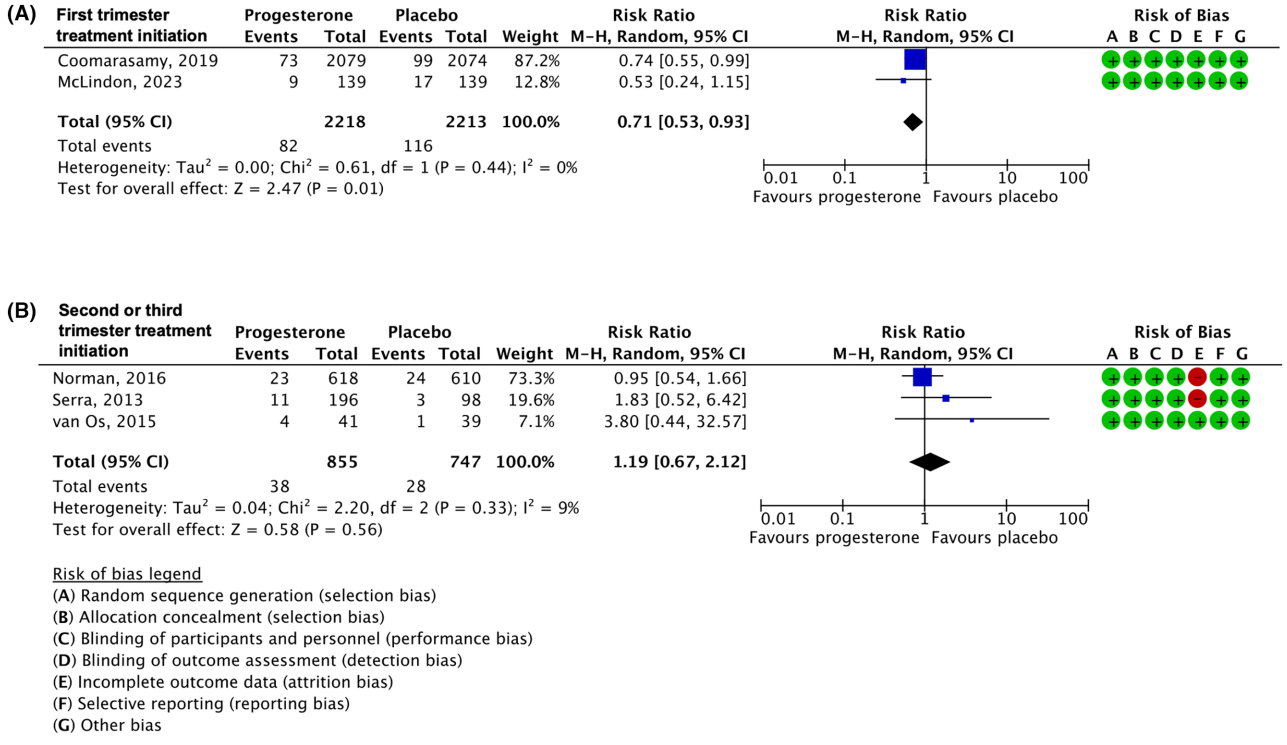


**FIGURE 1** Meta-analysis of RCTs investigating vaginal micronised progesterone in comparison with placebo on the rate of hypertensive disorders of pregnancy. (A) Treatment commenced in the first trimester of pregnancy. (B) Treatment commenced in the second or third trimesters of pregnancy. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel test; RCT, randomised controlled trial.

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| Exclusion criteria | Vaginal progesterone dose | Timing of progesterone administration | Control | Outcomes |
|---|---|---|---|---|
| Singleton pregnancies; monochorionic twin pregnancies; triplets or higher order multiple pregnancies; elective cervical cerclage prior to 14 weeks of gestation; history of hepatic problems or gestational cholestasis; abnormal liver enzymes; abnormal kidney function; local allergy to micronised natural progesterone; allergy to peanuts (because of the excipient used in the vaginal pessaries); recurrent vaginal bleeding; recurrent vaginal infections; fetal anomalies diagnosed by ultrasound; alcohol or illicit drug consumption; and smoking greater than or equal to 10 cigarettes/day | 200 or 400 mg of micronised natural progesterone taken daily | From 20 weeks of gestation to 34 weeks of gestation or delivery | Placebo | Hypertensive disorders of pregnancy |
| Intrauterine infection, vaginal bleeding, pre-eclampsia, urinary tract infection established by clinical and laboratory exam, intrauterine growth retardation as established by ultrasound, chronic diseases such as hypertension and heart disease, in addition to dilatation ≥2 cm, fetal distress and fetal abnormalities | 200 mg progesterone daily | From 28–36 weeks until delivery. | Placebo | Pre-eclampsia |
| Age less than 18 years, cervical cerclage, previous preterm birth less than 34 weeks, preterm labour, or known congenital malformations | 200 mg progesterone daily (Utrogestan®, Besins Healthcare) | From 22 to 34 weeks of gestation | Placebo | Hypertensive disorders of pregnancy |

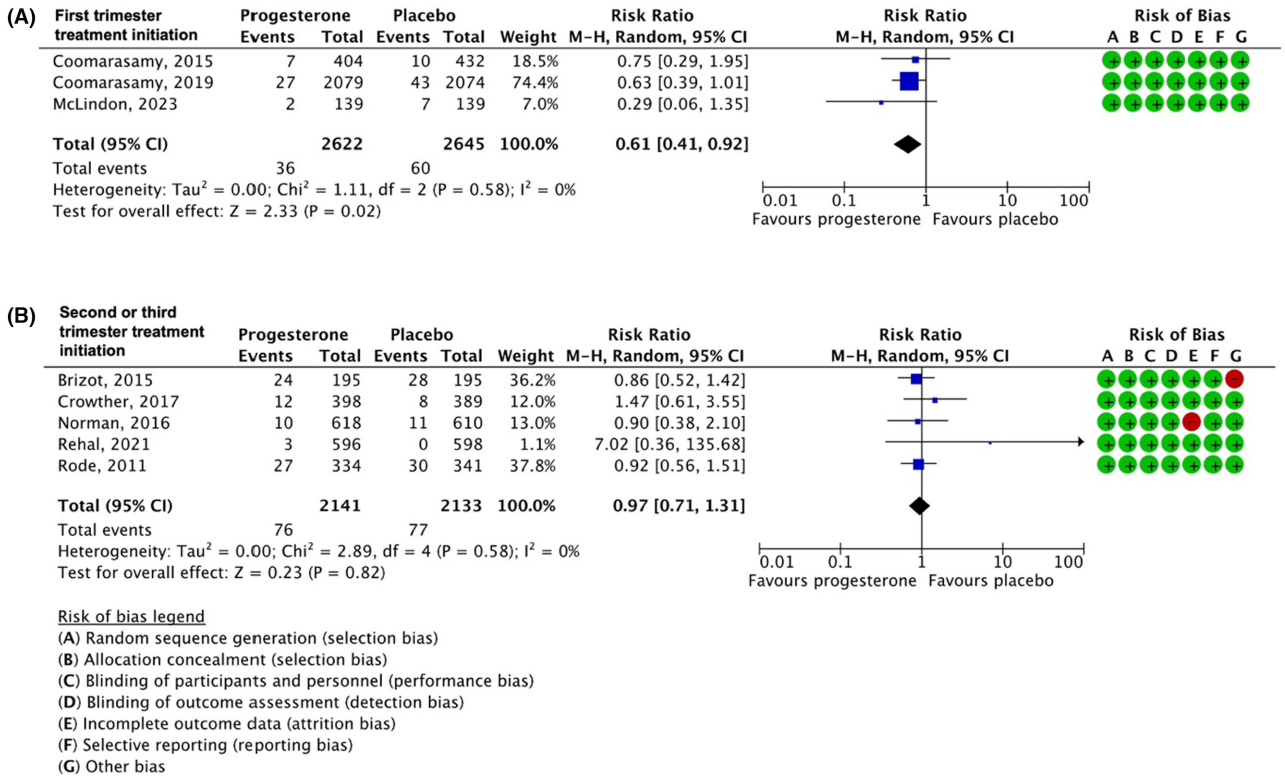


**FIGURE 2** Meta-analysis of RCTs investigating vaginal micronised progesterone in comparison with placebo on the rate of pre-eclampsia. (A) Treatment commenced in the first trimester of pregnancy. (B) Treatment commenced in the second or third trimesters of pregnancy. CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel test; RCT, randomised controlled trial.

**TABLE 2** Summary of findings of included randomised controlled trials for the outcomes of hypertensive disorders of pregnancy and pre-eclampsia.

| Outcome/timing of treatment initiation | Anticipated absolute effects (95% CI) | | Risk ratio (95% CI) | Number needed to treat | Number of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with vaginal micronised progesterone | | | | |
| Hypertensive disorders of pregnancy | | | | | | |
| First-trimester treatment initiation | 52 per 1000 | 37 per 1000 (28– 49) | 0.71 (0.53–0.93) | 67 | 4431 (2 studies) | ⨁⨁⨁◯ Moderate[a] |
| Second- or third-trimester treatment initiation | 37 per 1000 | 45 per 1000 (25– 79) | 1.19 (0.67–2.12) | 125 | 1602 (3 studies) | ⨁⨁◯◯ Low[a,b] |
| Pre-eclampsia | | | | | | |
| First-trimester treatment initiation | 23 per 1000 | 14 per 1000 (9–21) | 0.61 (0.41–0.92) | 111 | 5267 (3 studies) | ⨁⨁⨁◯ Moderate[a] |
| Second- or third-trimester treatment initiation | 36 per 1000 | 35 per 1000 (26–47) | 0.97 (0.71–1.31) | 1000 | 4274 (5 studies) | ⨁⨁◯◯ Low[a,b] |

*Note*: GRADE Working Group grades of evidence: *High certainty*: we are very confident that the true effect lies close to that of the estimate of the effect. *Moderate certainty*: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. *Low certainty*: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. *Very low certainty*: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI, confidence interval.

[a]Downgraded once for serious indirectness because the included studies evaluated only participants at risk of miscarriage or preterm birth, thus limiting the applicability of the findings to other subgroups.

[b]Downgraded once for serious imprecision due to wide confidence intervals.

on the risk of HDP and pre-eclampsia. The quantitative synthesis included 11 RCTs evaluating 11 640 women. We found moderate-certainty evidence that first-trimester initiation of vaginal progesterone treatment resulted in a 29% reduction in HDP rates and a 39% reduction in pre-eclampsia rates. The evidence did not identify a difference in HDP or pre-eclampsia rates in women who received progesterone starting in the second or third trimesters of pregnancy, suggesting that early progesterone initiation may be critical to the protective effect identified against HDP and pre-eclampsia.

## 4.2 | Strengths

We conducted extensive searches of large electronic databases to identify RCTs investigating vaginal micronised progesterone treatment versus a placebo drug in pregnancy. The primary analysis included solely studies deemed to be trustworthy, and most of the included trials were judged to be at low risk of bias. In addition, we restricted our searches to vaginal progesterone, reducing clinical heterogeneity within the meta-analyses.

## 4.3 | Limitations

The included studies focused mainly on restricted groups of pregnant women. For example, the trials investigating first-trimester initiation of progesterone included only participants presenting with a history of recurrent pregnancy loss[6] or threatened miscarriage.[7,14] The lack of studies investigating an unselected sample of pregnant women resulted in serious indirectness, which may in turn have limited the generalisability of our findings. In addition, none of the included studies evaluated HDP or pre-eclampsia as primary outcomes. Future RCTs should focus firstly on investigating whether progesterone protects against HDP in a population deemed to be at high risk of pre-eclampsia (in whom we hypothesise the effect size would be even larger), and secondly on whether its prophylactic effect may also extend to an unselected population of pregnant women.

The meta-analyses investigating progesterone initiation in the second and third trimesters suffered from a lack of precision owing to wide confidence intervals, which reduced the certainty of the evidence. Furthermore, there was substantial variation in participant characteristics, with studies including women carrying singleton pregnancies, twins or both, as well as participants with or without a previous history of preterm birth. We were unable to adjust for important confounders including age, body mass index and multiple pregnancy, all of which are known risk factors for pre-eclampsia.[23–25] In addition, it was impossible to quantify the number of women who started aspirin for pre-eclampsia prevention from the late first trimester onwards. Such an intervention may have exerted a confounding or synergistic effect to that of progesterone on the rate of HDP which our analyses have been unable to elucidate. Finally, the findings of our review are restricted to vaginal formulations of progesterone and are thus not generalisable to other progesterone preparations. Intramuscular progesterone is not currently marketed in the UK. Only vaginal, rectal and subcutaneous formulations are available, with limited effectiveness data for non-vaginal routes.

### 4.4 | Interpretation

Successful implantation depends on the adequate supply of progesterone by the corpus luteum. Various mechanistic studies have described the role of progesterone in inducing a state of receptiveness within the endometrium.[26] This includes progesterone-mediated interleukin-15 secretion by decidualised stromal cells, exerting a critical role in natural killer (NK) cell differentiation and proliferation, which in turn impacts successful spiral artery remodelling and normal placentation.[26,27] In addition, although uterine NK cells do not have classical progesterone receptors, progesterone indirectly reduces their cytotoxicity by suppressing progesterone-induced blocking factor.[28] Progesterone may also affect decidual metabolism by modulating the activity of glucose transporters within the endometrium[29] and endometrial gland synthesis of glycoproteins.[30] Systemically, progesterone has been shown to exert anti-inflammatory effects and promote a shift from T helper-1 to T helper-2 mediated responses.[26] Data also suggest a regulatory role of progesterone upon maternal cardiovascular adaptations in pregnancy.[31] Evidence of this includes an association between high serum progesterone in early pregnancy and lower blood pressure measurements in late gestation,[32] and a vasodilatory effect of progesterone through nitric oxide- and prostaglandin I2-mediated mechanisms.[33,34]

Altered endometrial function has been associated with errors in placental angiogenesis, leading to heightened local vessel resistance and the release of cardiovascular mediators that negatively affect the systemic vasculature.[35] There is a strong association between poor placentation secondary to abnormal endometrial receptivity and increased risk of HDP, pre-eclampsia and fetal growth restriction.[36,37] This has enabled the use of several placental biomarkers to confirm pre-eclampsia and fetal growth restriction, including placental growth factor (PlGF)[38] and the ratio of soluble fms-like tyrosine kinase 1 (sFlt-1) to PlGF.[39] It is plausible that by remedying a possible hypo-progestogenic state associated with altered corpus luteal function in early pregnancy, the administration of exogenous vaginal progesterone may at least partly correct abnormal implantation.

Future trials should focus on the effectiveness of initiating vaginal micronised progesterone in the first trimester of pregnancy to prevent the primary outcome of pre-eclampsia in high-risk women. This will require standardisation of the timing of progesterone commencement and discontinuation, in addition to accounting for confounders (e.g. the concomitant administration of aspirin and/or calcium). Such trials should also be designed specifically to allow for the detection of differences in the rates of early- versus late-onset pre-eclampsia.

Future meta-analyses should include individual participant data (IPD) to allow for confounder adjustment. The EPPPIC study presented an IPD meta-analysis of 30 trials investigating progestogens for the prevention of preterm birth. The minimum gestational age at which vaginal progesterone was commenced in the included studies was 15 weeks, after placental implantation would be expected to have occurred. The meta-analysis did not identify an effect of vaginal progesterone upon the outcomes of gestational hypertension (RR 1.17, 95% CI 0.74–1.86) or pre-eclampsia (RR 1.10, 95% CI 0.64–1.90), adding strength to the hypothesis that second or third trimester progesterone initiation is ineffective. Furthermore, it is possible that any protective effect against HDP from progesterone initiation to prevent preterm birth may have been offset by the increase in HDP risk associated with pregnancy prolongation. There is a need for an IPD meta-analysis focusing on studies where progesterone was initiated in the first trimester. This should account for individual-level confounders to investigate the adjusted effect of first-trimester progesterone in preventing HDP and pre-eclampsia, including the dose and frequency of progesterone administration. Lastly, an IPD meta-analysis may help elucidate whether progesterone is equally efficacious in protecting against both early- (<34 weeks) and late-onset (≥34 weeks) pre-eclampsia.

In addition to investigating further the proposed effect of vaginal progesterone in preventing HDP and pre-eclampsia, future research should also focus on long-term safety of in utero exposure to vaginal progesterone.[40] Data on long-term follow-up of children conceived following progesterone treatment are lacking, and secondary analyses of existing RCTs would help clarify the safety profile of exogenous progesterone.[41]

Finally, it should be explored how screening for pre-eclampsia and spontaneous preterm birth might be integrated. Given the mutual recurrence risk,[2,4] and the fact that both aspirin and progesterone might reduce HDP including pre-eclampsia and spontaneous preterm birth, it might be that one screening tool with multiple components identifies women at risk for pre-eclampsia or spontaneous preterm birth who might then benefit from aspirin, progesterone or a combination.

## 5 | CONCLUSION

Pregnant women commencing vaginal progesterone treatment in the first trimester were found to have a 29% reduction in HDP and a 39% reduction in pre-eclampsia compared with placebo. There is a need for additional studies investigating the mechanistic pathways through which progesterone may prevent placental maladaptation, and for randomised controlled trials evaluating first-trimester initiation of vaginal progesterone to prevent pre-eclampsia in high-risk women.

### AUTHOR CONTRIBUTIONS

PM, AD and AC conceived the study. PM registered the protocol, conducted the searches, screened and selected the studies, extracted data and wrote the draft. AD screened and selected the studies, extracted data and revised the draft. AC provided substantial input into all stages of the review process. AHS, MV, CMB, IG, ATP and

BWM provided critical input into the drafts of the paper. All authors have approved and accepted responsibility for the paper as published.

## ACKNOWLEDGEMENTS

The investigators thank all trial authors who provided information about their own studies, including Zarko Alfirevic, Ana Luisa Areia, Camil Castelo-Branco, Ozlem Erdem, Fabio Facchinetti, Luke McLindon, Ben Willem Mol, Kypros Nicolaides and Ariel Weissman.

## FUNDING INFORMATION

We did not seek funding for the completion of this work. PM is supported by an NIHR Academic Clinical Lectureship grant.

## CONFLICT OF INTEREST STATEMENT

PM, AD, AHS, MV, CMB, ATP, IG and AC have no conflicts of interest to declare in relation to this work. BWM is supported by a NHMRC Investigator grant (GNT1176437). BWM reports consultancy for Merck and research funding from Merck.

## DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

## ETHICS STATEMENT

Not applicable.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Melo P, Devall A, Shennan AH, Vatish M, Becker CM, Granne I, et al. Vaginal micronised progesterone for the prevention of hypertensive disorders of pregnancy: A systematic review and meta-analysis. BJOG. 2023;00:1–13. https://doi.org/10.1111/1471-0528.17705