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Effectiveness of Oral and Vaginal Progesterone for The Prevention of Preterm Birth: A Systematic Review and Meta-Analysis

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ABSTRACT

This systematic review and meta-analysis aimed to compare the effectiveness of oral and vaginal progesterone in preventing spontaneous preterm birth (sPTB). Relevant electronic databases were searched for studies published between January 2000 and May 2025, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Randomized controlled trials (RCTs) and observational studies evaluating oral micronized progesterone, vaginal progesterone, or intramuscular 17α-hydroxyprogesterone caproate (17-OHPC) for preterm birth prevention in high-risk pregnancies were considered for inclusion. The risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials and the Newcastle–Ottawa Scale (NOS) for eligible observational studies. Pooled risk ratios (RRs) were calculated using the Mantel–Haenszel fixed-effect model in Review Manager (RevMan) version 5.4.1. Funnel plots were used to explore potential publication bias. Twenty-five studies, comprising 21 double-blind RCTs, three comparative cohort studies, and one cross-sectional study, included 7,045 pregnant women at increased risk of preterm birth due to a history of preterm birth, a short cervix, or twin gestation. Progesterone treatment was initiated between 14 and 24 weeks of gestation. The pooled findings did not demonstrate a statistically significant reduction in preterm birth with oral or vaginal progesterone across the included populations. Differences in baseline risk, pregnancy characteristics, progesterone formulations, and study methodologies may have contributed to the observed findings. Although progesterone plays a physiological role in maintaining uterine quiescence and cervical function, the clinical effectiveness of progesterone supplementation may vary according to patient characteristics, particularly cervical length. Vaginal progesterone may offer benefits for selected patients with a short cervix; however, the available findings do not support a generalized conclusion that all progesterone formulations or routes of administration significantly reduce spontaneous preterm birth.

INTRODUCTION

Preterm birth (PTB), defined as delivery before 37 completed weeks of gestation, affects approximately 15 million infants annually worldwide and remains a major cause of neonatal mortality, long-term neurodevelopmental disabilities, and substantial healthcare expenditures (Choi, 2017; Sykes & Bennett, 2018). The burden is particularly high in low- and middle-income countries, where PTB rates may reach 18%, highlighting the need for effective, accessible, and evidence-based preventive strategies (Choi, 2017; Dodd & Crowther, 2009).

Progesterone plays an essential physiological role in maintaining uterine quiescence, modulating inflammatory pathways, and supporting cervical integrity throughout pregnancy (Dodd & Crowther, 2009; Khashukoyeva et al., 2024). Progesterone-based interventions have therefore been investigated for preventing spontaneous preterm birth (sPTB) in women with specific risk factors. Available formulations include oral micronized progesterone, vaginal progesterone, and intramuscular 17α-hydroxyprogesterone caproate (17-OHPC), a synthetic progestogen distinct from natural progesterone (Crowther, Ashwood, McPhee, Flenady, Tran, Dodd, et al., 2017; Cuijpers, Van't Hooft, Schneeberger, Van Der Lee, Simons, Van Os, et al., 2021; Mclindon et al., 2023; van Dijk, van Gils, van Zijl, Koullali, van der Weide, van den Akker, et al., 2024). Vaginal administration avoids gastrointestinal and hepatic first-pass metabolism and may provide favorable local uterine exposure. Evidence suggests that vaginal progesterone can reduce the risk of PTB in selected women with singleton pregnancies and a sonographically identified short cervix (Romero et al., 2024). Oral progesterone offers a convenient, noninvasive route of administration; however, its clinical effectiveness for PTB prevention remains uncertain because of limited and inconsistent evidence across studies (Boelig et al., 2022; Iqbal et al., 2023a).

Although evidence supports the use of vaginal progesterone in selected high-risk pregnancies, uncertainties remain regarding optimal treatment regimens, long-term neonatal outcomes, and appropriate patient selection. The role of oral progesterone also remains insufficiently established, particularly in resource-limited settings where ease of administration may influence treatment accessibility and adherence. Consequently, a systematic synthesis of the available evidence is needed to clarify the effectiveness of oral and vaginal progesterone for preventing PTB, taking into account differences in patient characteristics, clinical indications, and treatment regimens.

Accordingly, this systematic review and meta-analysis aimed to evaluate the effectiveness of oral and vaginal progesterone in preventing PTB among women at increased risk. Specifically, the review sought to estimate the pooled effects of vaginal progesterone on PTB before 37 and 34 weeks of gestation and the pooled effect of oral progesterone on PTB before 37 weeks of gestation. The findings were interpreted in the context of the multifactorial etiology of PTB and differences in maternal risk profiles, particularly cervical length and previous obstetric history. This review was intended to provide an evidence-based synthesis to inform clinical decision-making regarding progesterone administration in appropriately selected pregnant patients.

METHOD

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) reporting guidelines to evaluate the effectiveness of oral and vaginal progesterone in preventing preterm birth. A comprehensive literature search was conducted across PubMed/MEDLINE, ScienceDirect, the Cochrane Library, and Google Scholar using combinations of the following search terms: "oral progesterone," "vaginal progesterone," "preterm birth," "randomized controlled trial," "cohort," "case-control," and "cross-sectional." Additional studies were identified through manual screening of reference lists. Pooled effect estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs) using Mantel–Haenszel fixed-effect or random-effects models, depending on the degree of heterogeneity, which was assessed using the Higgins I^2 statistic. Potential publication bias was explored using funnel plots. All statistical analyses were performed using Review Manager (RevMan), version 5.4.1, with a two-sided p value < 0.05 considered statistically significant.

RESULTS AND DISCUSSION

Literature Search

The literature search yielded 471 records were identified through database and citation searching. After duplicate removal and screening, 25 studies met the eligibility criteria and were included in the systematic review and meta-analysis (Figure 1).

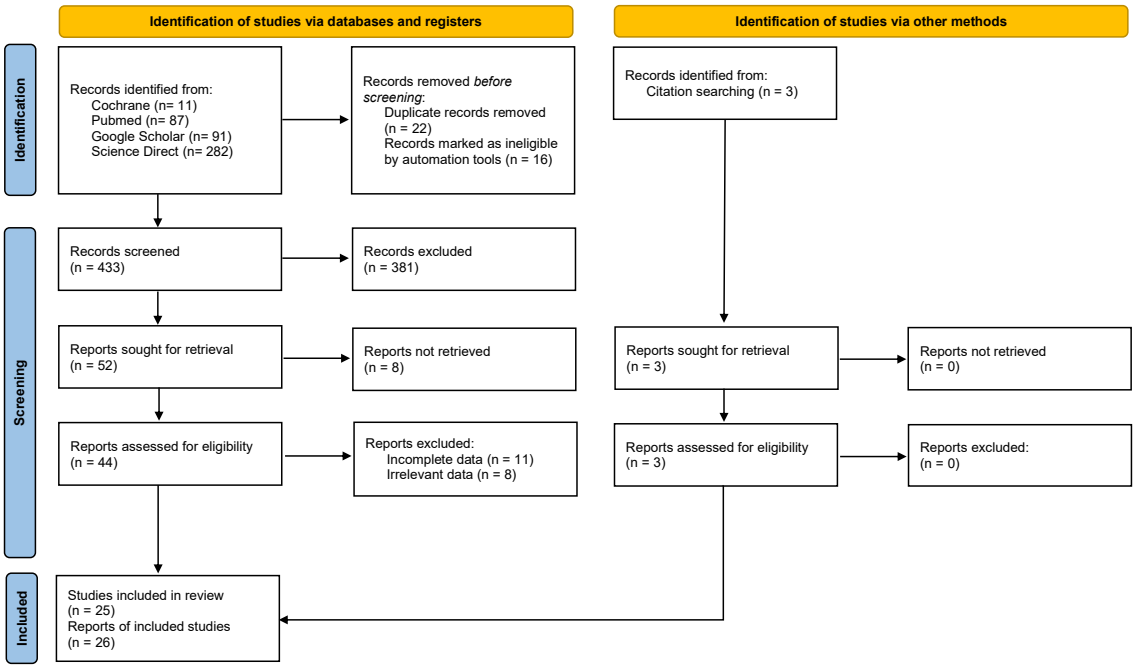


Figure 1. PRISMA Flowchart

Study Characteristics

Twenty-five clinical studies involving more than 7,000 women were included, of which 21 were randomized, double-blind, placebo-controlled trials. Studies were conducted across 12 countries and enrolled women at high risk of preterm birth, including those with singleton or twin pregnancies, previous spontaneous preterm birth, short cervical length, and

second-trimester bleeding. Progesterone therapy was initiated between 14 and 24 weeks of gestation in all studies.

Interventions included oral micronized progesterone, vaginal progesterone (200–600 mg/day), and intramuscular 17α-hydroxyprogesterone caproate (250 mg/week), compared with placebo, vaginal progesterone, mechanical interventions, or historical controls. Follow-up continued until delivery, with four studies extending neonatal follow-up to two years of corrected age. Detailed study characteristics are presented in Table 1.

Table 1. Study characteristics

Authors, Year	Location	Study Design	Population	Intervention	Comparator
Ashoush et al., 2017(Palareti et al., 2016)	Cairo, Egypt	Randomized controlled trial, double-blind, placebo-controlled	Singleton pregnancies with prior spontaneous preterm delivery before thirty-seven weeks	Oral micronized progesterone	Identical placebo
Azargoon et al., 2016(Azargoon et al., 2016a)	Iran	Randomized controlled trial	High-risk singleton pregnancies with a previous history of preterm birth and cervical length ≤28 mm	Vaginal progesterone	Placebo
Brizot et al., 2015(Brizot, Hernandez, Liao, Bittar, Francisco, Krebs, et al., 2015)	São Paulo, Brazil	Randomized controlled trial, double-blind, placebo-controlled	Naturally conceived twin pregnancies without a history of preterm delivery	Vaginal natural progesterone ovules	Placebo vaginal ovules
Care et al., 2019(Care et al., 2019)	United Kingdom	Retrospective cohort	High-risk, asymptomatic singleton pregnancies with a history of sPTB and a short cervix	Vaginal progesterone	Cervical Arabin pessary
Crowther et al., 2017 (PROGRESS)(Crowther, Ashwood, McPhee, Flenady, Tran, Dodd, et al., 2017)	Australia, New Zealand, Canada	Multicenter randomized controlled trial, double-blind, placebo-controlled	Singleton or twin pregnancies with prior spontaneous preterm birth before thirty-seven weeks, between eighteen and fewer than twenty-four weeks of gestation	Vaginal progesterone pessaries	Placebo pessaries
Cuijpers et al., 2021 (Triple P follow-up)(Cuijpers, Van't Hooft, Schneeberger, Van Der Lee, Simons, Van Os, et	Amsterdam, Netherlands and Clayton, Australia	Randomized controlled trial	Low-risk women with singleton pregnancy and cervical length thirty millimeters or less at eighteen to twenty-two weeks of gestation	Vaginal progesterone	Placebo

al., 2021)					
Dang et al., 2019(Dang, Dang, et al., 2020)	Ho Chi Minh City, Vietnam	Randomized controlled trial	Women with twin pregnancies and cervical length less than thirty-eight millimeters	Vaginal progesterone	Arabin cervical pessary
Dijk et al., 2024(van Dijk, van Gils, van Zijl, Koullali, van der Weide, van den Akker, et al., 2024)	Netherlands	Multicenter randomized controlled trial	Singleton pregnancies with no prior spontaneous preterm birth before thirty-four weeks and cervical length of thirty-five millimeters or less at eighteen to twenty-two weeks	Vaginal progesterone	Arabin cervical pessary
Elimian et al., 2016(Elimian et al., 2016a)	United States	Randomized controlled trial	Singleton pregnancies with prior spontaneous preterm birth before twenty weeks of gestation	Intramuscular hydroxyprogesterone caproate	Vaginal progesterone suppository
Frey et al., 2019(Frey, Finneran, Hade, Waickman, Lynch, Iams, et al., 2019)	United States	Retrospective cohort		Vaginal progesterone	Intramuscular 17a-hydroxyprogesterone caproate
He et al., 2025	Vietnam	multicenter, two-by-two factorial randomized controlled trial	Asymptomatic women with twin pregnancies and a cervical length of 28 mm	Cerclage or Arabin pessary plus progesterone	Cerclage or Arabin pessary alone
Hezelgrave et al., 2024 (SuPPoRT) (Hezelgrave, Suff, Seed, Robinson, Carter, Watson, et al., 2024)	United Kingdom (19 NHS obstetric units)	Multicenter randomized controlled trial	Asymptomatic singleton pregnancies with cervical length < 25 mm at 14+0 to 23+6 wk	Cervical cerclage; cervical pessary; vaginal progesterone	Two of the three active arms
Hina et al., 2024(Hina, Nisa, Nisa, Nisa, et al., 2024)	Pakistan	Cross-sectional	Women who have a viable fetus, a singleton pregnancy, a gestational age under 37 weeks, and at least one risk factor for premature delivery	Vaginal progesterone	Intramuscular 17a-hydroxyprogesterone caproate
Iqbal et al., 2023(Iqbal et al., 2023b)	Pakistan	Randomized controlled trial	Individuals over the age of eighteen who have had at least two previous cesarean sections due to preterm births, a lengthy stay in the hospital, and a small cervical length (between 2.5 and 3 cm) on an abnormality scan	Oral progesterone	Progesterone pessary
Kabiri et al., 2022(Kabiri, Raif	Israel	Retrospective cohort	Women with a short cervix assessed between 24+0 and 33+6 weeks, a singleton pregnancy, and a risk of	Vaginal progesterone	Non-treatment

Nesher, Luxenbourg, Rottenstreich, Rosenbloom, Ezra, et al., 2023)			premature labor		
Le et al., 2020(Le et al., 2020)	Vietnam	Randomized controlled trial	Between weeks 16 and 22, women with twin pregnancies and CL < 38 mm	Vaginal progesterone	Cervical pessary
McLindon et al., 2023 (STOP trial)(Mclindon et al., 2023)	Brisbane, Australia (Mater Mothers' Hospital etc.)	Randomized controlled trial, double-blind, placebo-controlled	Women < 10 wk gestation with threatened miscarriage (vaginal bleeding, viable intrauterine pregnancy)	Vaginal progesterone pessary	Identical placebo pessary
Nelson et al., 2022(Nelson, Lafferty, Venkatraman, McDonald, Eckert, McIntire, et al., 2022)	United States (single academic center database, 1998–2011)	Retrospective cohort study	Women with prior spontaneous preterm birth receiving prophylaxis	Vaginal progesterone	Historical cohort on 17-OHPC
Norman et al., 2016(Norman, Marlow, Messow, Shennan, Bennett, Thornton, et al., 2016)	UK	Multicenter randomized controlled trial	Women who had a singleton pregnancy, with clinical risk factors for preterm birth (previous spontaneous birth at ≤34 weeks and 0 days of gestation, or a cervical length ≤25 mm, or positive fetal fibronectin test combined with other clinical risk factors for preterm birth [previous pregnancy of preterm birth, second-trimester loss, preterm premature fetal membrane rupture, or a history of a cervical procedure to treat abnormal smears])	Vaginal progesterone	Placebo
Norman et al., 2018	UK	Randomized controlled trial	Women at risk of preterm birth, specifically those with a cervical length of 25 mm or less	Vaginal progesterone	Placebo
Rehal et al., 2020(Rehal, Benkő, De Paco Matallana, Syngelaki, Janga, Cicero, et al., 2021)	UK	Randomized, placebo-controlled, double-blinded trial	Women with twin pregnancies	Vaginal progesterone	Placebo

Vaginal progesterone effect on preterm birth

A total of ten studies were included, encompassing 1,654 participants in the vaginal progesterone group and 1,769 participants in the comparator group. The pooled odds ratio (OR) was 0.80 (95% CI: 0.65–0.99; p = 0.04), indicating a statistically significant 20% reduction in the odds of preterm birth before 37 weeks with vaginal progesterone. Moderate heterogeneity was observed among studies (I^2 = 42%; p = 0.08), suggesting some variability in patient populations, timing of intervention, or comparator protocols. Ten studies including 3,423 women showed that vaginal progesterone significantly reduced PTB before 37 weeks (OR 0.80, 95% CI 0.65–0.99; p=0.04) with moderate heterogeneity (I^2=42%) (Figure 2).

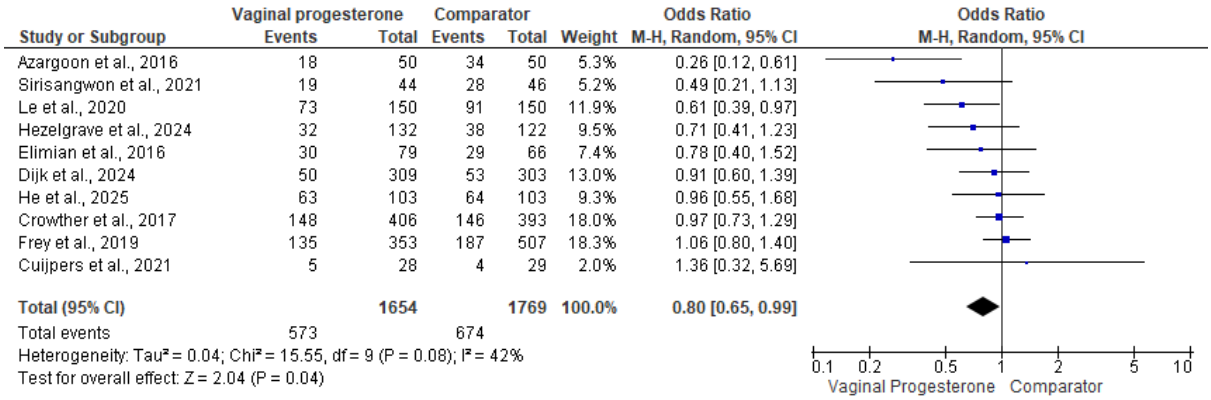


Figure 2. Vaginal progesterone effect on preterm birth <37 weeks

A total of 19 studies were analyzed, comprising 3,766 participants receiving vaginal progesterone and 3,941 in the comparator group. The pooled odds ratio was 1.03 (95% CI: 0.85–1.24) with a p-value of 0.75, indicating no statistically significant effect of vaginal progesterone in preventing birth prior to 34 weeks. Heterogeneity was moderate (I^2 = 40%, p = 0.04), suggesting some variability among the included studies, possibly arising from differences in baseline risk factors, progesterone dosing regimens, or cervical length at initiation of treatment. Nineteen studies (n=7,707) demonstrated no significant reduction in PTB before 34 weeks (OR 1.03, 95% CI 0.85–1.24; p=0.75; I^2=40%) (Figure 3).

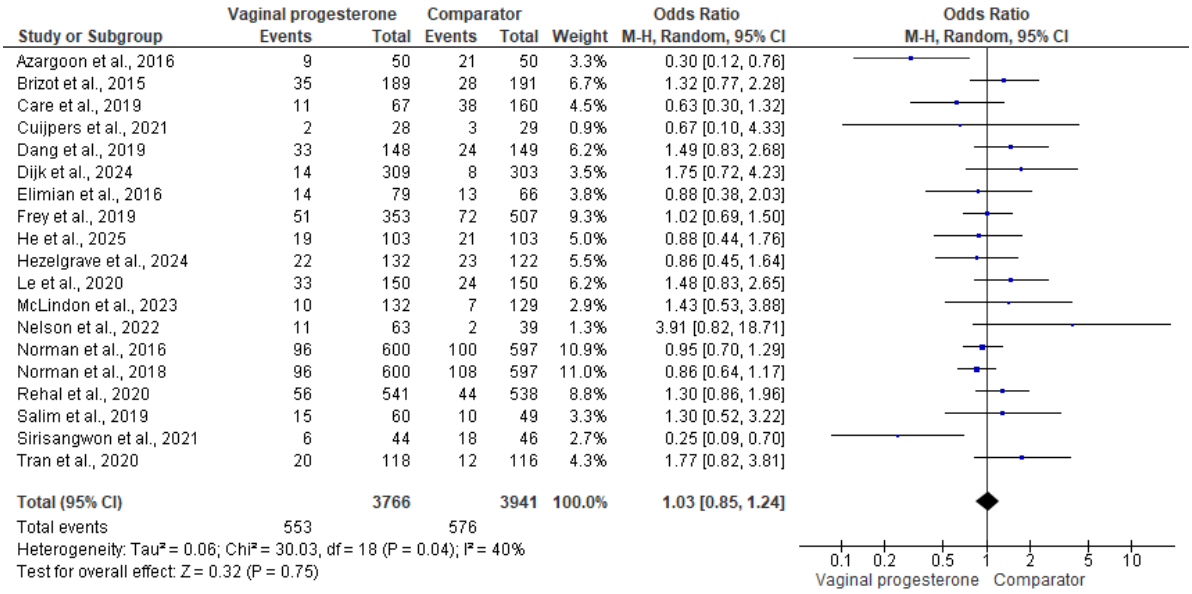


Figure 3. Vaginal progesterone effect on preterm birth <34 weeks

Oral progesterone effect on preterm birth

Three studies involving 347 women showed no significant benefit of oral progesterone in preventing PTB before 37 weeks (OR 1.87, 95% CI 0.59–5.89; p=0.29), although heterogeneity was substantial (I^2=81%) (Figure 4).

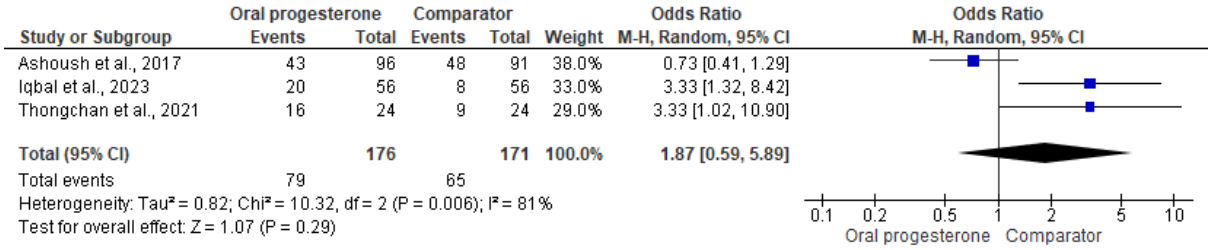


Figure 4. Oral progesterone effect on preterm birth <37 weeks

This systematic review and meta-analysis found that neither oral nor vaginal progesterone significantly reduced the overall incidence of preterm birth. These findings differ from previous meta-analyses that consistently reported benefits of vaginal progesterone, particularly among women with a short cervix. The discrepancy may reflect the multifactorial etiology of spontaneous preterm birth, involving infection, inflammation, cervical insufficiency, placental dysfunction, and genetic factors, which cannot be fully addressed by progesterone alone. In addition, heterogeneity in study populations, treatment initiation, dosage, progesterone formulation, and outcome definitions may have reduced the ability to detect consistent treatment effects. Consistent with previous evidence, oral progesterone appears to be more effective in women with a short cervix, whereas its benefit is less evident in unselected high-risk populations. Similarly, vaginal progesterone may provide greater efficacy than oral formulations in women with cervical shortening because of its higher local bioavailability (Azargoon et al., 2016b; Brizot, Hernandez, Liao, Bittar,

Francisco, & Krebs, 2015; Care et al., 2019; Hina, Nisa, Nisa, & Khan, 2024; Palareti et al., 2016).

Progesterone prevents preterm birth by maintaining myometrial quiescence, preserving cervical integrity, and suppressing inflammatory pathways associated with the initiation of labor. Current guidelines recommend initiating progesterone therapy between 16 and 24 weeks of gestation in women at increased risk of preterm birth, such as those with a previous spontaneous preterm birth or a short cervix. Treatment is generally continued until 36 weeks of gestation. Oral micronized progesterone is commonly administered at 200 mg daily, while vaginal progesterone is typically given at 200 mg/day, with higher doses reserved for selected high-risk patients (Crowther, Ashwood, McPhee, Flenady, Tran, & Dodd, 2017; Cuijpers, Van't Hooft, Schneeberger, Van Der Lee, Simons, & Van Os, 2021; Dang, He, et al., 2020; Elimian et al., 2016b; Frey, Finneran, Hade, Waickman, Lynch, & Iams, 2019; van Dijk, van Gils, van Zijl, Koullali, van der Weide, & van den Akker, 2024).

Both formulations demonstrated favorable safety profiles. Oral progesterone is generally associated with mild systemic adverse effects, including dizziness and drowsiness, whereas vaginal progesterone commonly causes local irritation or vaginal discharge. Importantly, neither formulation has been associated with increased congenital anomalies or adverse neurodevelopmental outcomes, supporting their overall safety during pregnancy (Hezelgrave, Suff, Seed, Robinson, Carter, & Watson, 2024; Kabiri, Raif Nesher, Luxenbourg, Rottenstreich, Rosenbloom, & Ezra, 2023; Le et al., 2020; McLindon et al., 2023).

Beyond delaying preterm birth, progesterone may improve neonatal outcomes by prolonging gestation, thereby allowing greater fetal maturation. Even modest prolongation of pregnancy contributes to increased birth weight, improved lung maturation, and reduced risks of respiratory distress syndrome, sepsis, necrotizing enterocolitis, and intraventricular hemorrhage. Consequently, progesterone therapy may also reduce neonatal intensive care unit (NICU) admission and neonatal mortality, particularly among high-risk pregnancies (Elimian et al., 2016a; Hezelgrave, Suff, Seed, Robinson, Carter, Watson, et al., 2024; Nelson, Lafferty, Venkatraman, McDonald, Eckert, & McIntire, 2022; Norman, Marlow, Messow, Shennan, Bennett, & Thornton, 2016; Rehal, Benkő, De Paco Matallana, Syngelaki, Janga, & Cicero, 2021).

The route of administration may influence clinical effectiveness. Oral progesterone provides greater convenience and patient acceptability but undergoes first-pass hepatic metabolism, resulting in greater systemic exposure. In contrast, vaginal progesterone achieves higher local uterine concentrations through the first uterine pass effect while minimizing systemic adverse effects. These pharmacokinetic advantages may explain why vaginal progesterone appears more effective in women with a short cervix, although both formulations share the common therapeutic goal of prolonging gestation and improving neonatal outcomes (Azargoon et al., 2016a; Hina, Nisa, Nisa, Nisa, et al., 2024; Iqbal et al., 2023b; Nelson, Lafferty, Venkatraman, McDonald, Eckert, McIntire, et al., 2022; Rehal, Benkő, De Paco Matallana, Syngelaki, Janga, Cicero, et al., 2021).

CONCLUSION

This systematic review and meta-analysis demonstrated that vaginal progesterone was associated with a statistically significant reduction in the risk of preterm birth before 37 weeks of gestation (odds ratio [OR] = 0.80; 95% confidence interval [CI]: 0.65–0.99; p = 0.04). However, no statistically significant reduction was observed for preterm birth before 34 weeks of gestation (OR = 1.03; 95% CI: 0.85–1.24; p = 0.75). Similarly, oral progesterone was not associated with a statistically significant reduction in preterm birth before 37 weeks of gestation (OR = 1.87; 95% CI: 0.59–5.89; p = 0.29). The effectiveness of progesterone supplementation may vary according to cervical length, gestational age at treatment initiation, dosage, formulation, and baseline risk of preterm birth. Vaginal progesterone may offer greater clinical benefits in selected women with a short cervix, although this interpretation requires confirmation through appropriate subgroup analyses. Further high-quality randomized controlled trials with standardized treatment protocols and comprehensive assessments of long-term maternal and neonatal outcomes are needed to clarify the optimal indications, formulations, and administration routes for progesterone in preventing preterm birth.

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CONFLICT OF INTEREST

The author states that there is no conflict of interest in the preparation of this article.

AUTHOR CONTRIBUTIONS

All authors contributed to conceptualization, search and synthesis of literature, interpretation of results, manuscript preparation, and critical review of manuscripts. All authors have read and approved the final version of the manuscript.

GENERATIVE AI STATEMENT

The authors declare that Generative Artificial Intelligence (Generative AI) was used solely to assist with language refinement, grammatical correction, and improvement of manuscript readability. All scientific concepts, interpretations, literature synthesis, analyses, and conclusions were developed by the authors. All AI-assisted content was carefully reviewed, verified, and revised by the authors, who take full responsibility for the accuracy, integrity, and final content of the manuscript.

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