

Vaginal Progesterone in Pregnancies with a Short Cervix: Reassessment of Aggregate Trial Data and Methodological Limitations

¹Rahmat Arfandi*, ²Rizky Arifin, ³Izfathania

¹ Department of Obstetrics and Gynecology, Arifin Achmad Hospital, Riau, Indonesia*;

email: rahmatarfandi152@gmail.com

² Department of Obstetrics and Gynecology, Arifin Achmad Hospital, Riau, Indonesia;

email: arifinrizky1304@gmail.com

³ Department of Obstetrics and Gynecology, Arifin Achmad Hospital, Riau, Indonesia;

email: izfhaniah@gmail.com

*Corresponding

Article Information

Submitted: 07 October 2026

Accepted: 18 October 2026

Publish: 20 October 2026

Keyword: Vaginal Progesterone; Short Cervix; Preterm Birth; Singleton Pregnancy; Meta-Analysis;

Copyright holder: Rahmat Arfandi, Rizky Arifin, Izfathania

Year: 2026

This is an open access article under the [CC BY-SA](https://creativecommons.org/licenses/by-sa/4.0/) license.



Abstract

Introduction: Cervical shortening increases spontaneous preterm birth risk, while vaginal progesterone may provide preventive benefits. **Objective:** To assess whether aggregate evidence supports singleton-specific estimates of vaginal progesterone effectiveness. **Method:** This critical reassessment examined searches of PubMed and Google Scholar, identifying 49 records, three quantitatively synthesized reports, and OPPTIMUM for qualitative assessment. The retracted Cetingoz trial was excluded. **Results and Discussion:** Random-effects analyses reported reduced risks of preterm birth at approximately ≤ 35 weeks (RR 0.65; 95% CI 0.46–0.92), spontaneous birth before 34 weeks (RR 0.56; 0.36–0.86), respiratory distress syndrome (RR 0.50; 0.29–0.86), and birth weight below 1,500 g (RR 0.57; 0.38–0.85). Neonatal intensive care admission was not significantly reduced (RR 0.80; 0.54–1.18). However, mixed-plurality populations, inconsistent outcomes, uncertain denominators, and nonreproducible extraction limited validity. **Conclusion:** Favorable estimates cannot establish singleton-specific effectiveness without dataset reconciliation. Clinical interpretation should prioritize broader participant-level evidence

Introduction

Preterm birth continues to impose a substantial burden on families and health systems. A global analysis estimated 13.4 million preterm live births in 2020, corresponding to approximately 9.9% of live births. Prevention is therefore relevant not only to gestational age at delivery but also to neonatal care requirements and the long-term consequences of early birth. Effective preventive strategies depend on identifying a population in whom an intervention can modify risk. (Ohuma et al., 2023). Transvaginal cervical length provides an objective marker of spontaneous preterm birth risk. The association is graded: a shorter cervix is associated with a greater probability of early delivery. Cervical shortening nevertheless occurs within a heterogeneous clinical syndrome, rather than representing a single disease mechanism. Obstetric history, plurality, gestational age at assessment, and the degree of shortening must therefore remain part of the interpretation of treatment evidence. (Iams et al., 1996; Romero et al., 2014)

Vaginal progesterone has been evaluated in trials recruiting women on the basis of a short cervix and in subgroups drawn from broader high-risk populations. The principal reports relevant to the supplied review are those by Fonseca, Hassan, DeFranco, and the OPPTIMUM investigators. Their different eligibility criteria and reporting practices make careful extraction essential: a trial-level result is not necessarily equivalent to a result restricted to singleton pregnancies with a specific cervical-length threshold. (Fonseca et al., 2007; Hassan et al., 2011; DeFranco et al., 2007; Norman et al., 2016)

Individual participant data meta-analyses published in 2012 and 2018 assessed this clinical question using participant-level eligibility criteria, and an updated singleton-specific analysis was published in 2025. These reports form the context against which any aggregate-data synthesis must be evaluated. A smaller review should not imply that it supersedes a more comprehensive analysis solely because its manuscript was prepared later. (Romero et al., 2012; Romero et al., 2018; Romero et al., 2025)

Evidence integrity is an additional consideration. The 2011 Cetingoz trial was retracted in 2024, and a subsequent corrigendum to another evidence synthesis documented changes after its exclusion. Retraction status should therefore be checked explicitly, while the effect of removing a study must be distinguished from changes caused by eligibility criteria, omitted trials, or different outcome definitions. (Cetingoz et al., 2011; Cetingoz et al., 2024; Wennerholm et al., 2025). The objective was to reassess the supplied aggregate trial data on vaginal progesterone for pregnancies with a sonographically short cervix and to determine whether the reported estimates validly represent the intended singleton population. Rather than claiming an additional efficacy estimate beyond existing participant-level meta-analyses, this review identifies the eligibility, outcome-definition, denominator, and reporting conditions required for a reproducible singleton-specific synthesis.

Methods

This study critically reassessed a supplied aggregate-data systematic review and meta-analysis comparing vaginal progesterone with placebo, following PRISMA 2020 and PRISMA-S reporting standards. Original search logs, extraction sheets, and detailed risk-of-bias assessments were unavailable; therefore, documented procedures were distinguished from reassessment findings (Page et al., 2021); (Rethlefsen et al., 2021).

Eligible studies were randomized controlled trials involving asymptomatic women with singleton pregnancies and sonographically detected short cervixes. The retracted

Cetingoz trial was excluded, while OPPTIMUM was retained for qualitative assessment. Cervical-length thresholds varied (≤ 15 mm, 10–20 mm, and < 28 mm), requiring clarification before pooling. Mixed-plurality studies required extractable singleton data, and related publications were considered a single trial to prevent duplication (O'Brien et al., 2007).

PubMed and Google Scholar were the reported information sources, identifying 49 records, four reports for qualitative synthesis, and three for quantitative synthesis. However, search dates, complete strategies, screening procedures, and exclusion reasons were unavailable. Extracted outcomes included preterm birth before 35 and 34 weeks, respiratory distress syndrome, birth weight below 1,500 g, and NICU admission. Outcome definitions, event counts, and treatment-specific denominators required verification. The supplied risk-of-bias judgments were considered preliminary because supporting assessments were unavailable. These judgments followed terminology consistent with the original Cochrane framework rather than a verified RoB 2 assessment (Higgins et al., 2011); (Sterne et al., 2019). Evidence certainty could not be formally established and requires assessment of bias, inconsistency, indirectness, imprecision, and publication bias (Guyatt et al., 2011)

Result and Discussion

1. Result

Statistical analysis

The source reports Mantel–Haenszel random-effects meta-analysis using RevMan, with RRs and 95% CIs. The supplied plots identify DerSimonian–Laird estimation of between-study variance and Wald-type confidence intervals. An RR below 1 favors progesterone for all listed adverse outcomes. Where only one trial contributes, its estimate is reported as a single-study result and between-study heterogeneity is not applicable. (DerSimonian & Laird, 1986). Heterogeneity was described using I^2 where supplied. A value of zero indicates no observed inconsistency under the available data; it does not prove that treatment effects are identical. With one or two contributing studies, heterogeneity estimation is especially uncertain. The displayed source P values are transcribed rather than represented as independently reproduced analyses. (Higgins et al., 2003)

No completed sensitivity analyses, meta-regressions, or publication-bias tests were supplied. Funnel-plot asymmetry tests would not be informative with so few studies. Essential sensitivity analyses for a revised dataset include excluding the < 28 -mm subgroup, restricting all outcomes to singleton pregnancies, and testing the effect of including recoverable OPPTIMUM subgroup data. These are proposed analyses, not completed results. (Sterne et al., 2011). The quantitative values below are transcribed from the supplied figures and abstract to evaluate their eligibility and interpretation. They are not presented as a newly completed meta-analysis. Recalculation, sensitivity analysis, and outcome-level certainty grading were not possible without a verified extraction dataset. Each estimate is therefore labeled by the number and type of contributing reports, with explicit attention to mixed plurality, outcome boundaries, and neonatal denominators.

Vaginal Progesterone in Pregnancies with a Short Cervix: Reassessment of Aggregate Trial Data and Methodological Limitations

Study selection and characteristics

The source review identified Fonseca 2007, Hassan 2011, and DeFranco 2007 for quantitative analysis and OPPTIMUM 2016 for qualitative review. The original total of 754 is the sum of 250, 458, and 46 as reported in the source; it is not a verified total of eligible singleton participants. Table 1 distinguishes these source counts from their population qualifications. The Cetingoz trial was excluded because of its documented retraction.

Table 1
Characteristics of the study reports in the supplied review

Study	Population and reported size	Regimen and comparator	Use and qualification
Fonseca 2007 (Fonseca et al., 2007)	Cervical length ≤ 15 mm; 250 randomized pregnancies, including singletons and twins	Vaginal progesterone 200 mg nightly versus placebo; 24–34 weeks	Source quantitative analysis used the full trial. Singleton subgroup comprised 226 women; re-extract eligible outcomes.
Hassan 2011 (Hassan et al., 2011)	Singleton pregnancy; cervical length 10–20 mm at 19+0–23+6 weeks; 465 randomized, 458 analyzed	Vaginal progesterone gel 90 mg daily versus placebo	Quantitative source report; distinguish randomized and outcome-specific analyzed denominators.
DeFranco 2007 (DeFranco et al., 2007)	Multinational trial subgroup with previous spontaneous preterm birth and cervical length < 28 mm; 46 women	Vaginal progesterone gel 90 mg daily versus placebo	Secondary analysis; threshold differs from ≤ 25 mm; not an independent trial from O'Brien 2007.
OPPTIMUM 2016 (Norman et al., 2016)	Broader high-risk singleton population; 1,228 randomized in the full trial	Vaginal progesterone 200 mg daily versus placebo; 22–24 to 34 weeks	Qualitative in source; full-trial size is not the eligible short-cervix subgroup size.

**Counts describe different populations and analysis sets and must not be added indiscriminately. The table is an evidence inventory, not a finalized singleton-only analytical dataset.*

Reported effects on preterm birth

The supplied two-study analysis labeled < 35 weeks reported RR 0.65 (95% CI 0.46–0.92; $P=0.01$; $I^2=0\%$). It contained 41/254 events with progesterone and 65/250 with placebo. The DeFranco component, however, corresponds to a ≤ 35 -week endpoint. This result is therefore described as birth at approximately 35 weeks or earlier until the outcome boundary is harmonized. The original plot and its interpretation are presented in Figure 1.

Vaginal Progesterone in Pregnancies with a Short Cervix: Reassessment of Aggregate Trial Data and Methodological Limitations

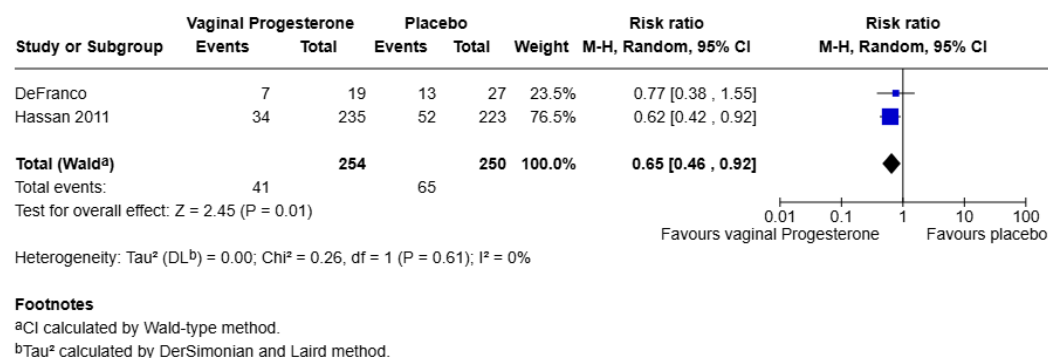


Figure 1. Original forest plot of preterm birth around 35 weeks or earlier

The displayed pooled estimate favors vaginal progesterone (RR 0.65, 95% CI 0.46–0.92; P=0.01), corresponding to a 35% relative risk reduction in the analyzed populations. Hassan contributes 76.5% of the weight and shows a statistically significant effect (RR 0.62, 95% CI 0.42–0.92), whereas the smaller DeFranco subgroup contributes 23.5% and its interval crosses 1 (RR 0.77, 95% CI 0.38–1.55). Both point estimates favor treatment. No statistical heterogeneity was detected (I²=0%; heterogeneity P=0.61), although only two reports contribute.

The <34-week plot contained only Fonseca, with 24/125 versus 43/125 events and RR 0.56 (95% CI 0.36–0.86; P=0.008). It represents the original mixed-plurality trial population, rather than a pooled singleton-specific result. Heterogeneity is not applicable. Replacing this population requires corresponding singleton-specific event counts; changing only its denominator would be invalid. Figure 2 reproduces this single-study analysis.

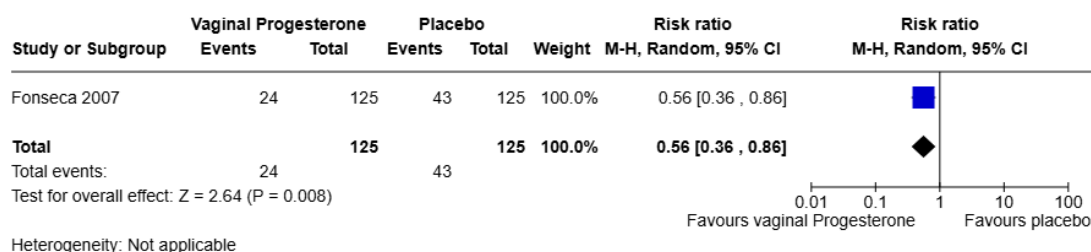


Figure 2. Original single-study forest plot of spontaneous preterm birth before 34 weeks

Fonseca reports 24/125 events (19.2%) with progesterone and 43/125 (34.4%) with placebo. The displayed RR of 0.56 (95% CI 0.36–0.86; P=0.008) corresponds to a 44% relative reduction, with the confidence interval excluding no effect. The diamond represents the same single-study estimate; it does not provide additional evidence from other trials. Between-study heterogeneity cannot be assessed.

Reported neonatal outcomes

The source reported lower risks of respiratory distress syndrome and birth weight below 1,500 g, whereas the NICU estimate was imprecise and its confidence interval crossed 1 (Table 2). These are provisional source estimates. The Fonseca neonatal denominator exceeds the number of randomized women because infants from twin pregnancies were included, and both neonatal analyses require verification of singleton-

Vaginal Progesterone in Pregnancies with a Short Cervix: Reassessment of Aggregate Trial Data and Methodological Limitations

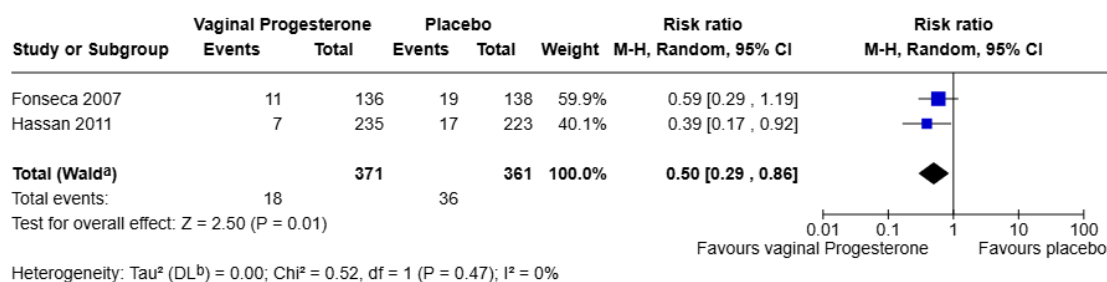
only eligibility. A distinct NICU plot supporting the stated estimate was not available in the embedded image set. Figures 3–5 reproduce the source images with outcome-specific interpretations and explicit notes on the unresolved discrepancies.

Table 2

Outcome estimates transcribed from the supplied analysis

Outcome	RR and 95% CI	P value	Interpretive status
Birth around 35 weeks or earlier	0.65 (0.46–0.92)	0.01	Two reports; $I^2=0\%$. Resolve <35 versus ≤ 35 boundary.
Spontaneous birth <34 weeks	0.56 (0.36–0.86)	0.008	Single mixed-plurality trial; not a pooled singleton estimate.
Respiratory distress syndrome	0.50 (0.29–0.86)	0.01	Two reports; $I^2=0\%$. Singleton-only neonatal data required.
Birth weight $<1,500$ g	0.57 (0.38–0.85)	0.006	Two reports; $I^2=0\%$. Plot agrees with the textual estimate; singleton-only neonatal data required.
NICU admission	0.80 (0.54–1.18)	0.25	Trial-level contributions and corresponding plot unavailable.

*RR, risk ratio; CI, confidence interval; NICU, neonatal intensive care unit. Values are preserved for traceability to the source abstract and are not certified as final results. This table is not a GRADE Summary of Findings table. No overall analysis was rerun for this draft.



Footnotes

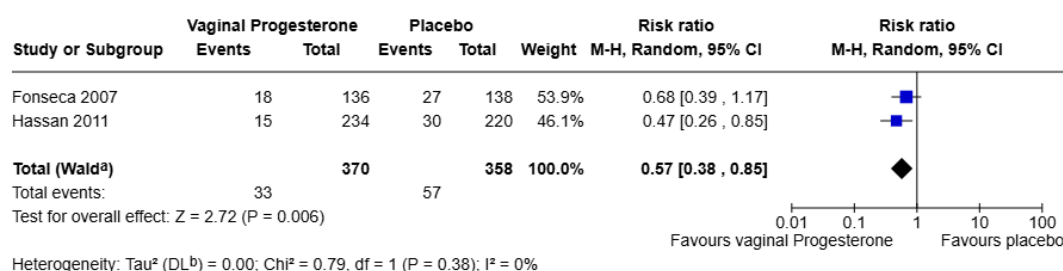
^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

Figure 3. Original forest plot of neonatal respiratory distress syndrome

The displayed pooled RR is 0.50 (95% CI 0.29–0.86; $P=0.01$), corresponding to a 50% relative reduction in respiratory distress syndrome in the included analysis. Both study point estimates favor progesterone, but the Fonseca interval crosses 1 (RR 0.59, 95% CI 0.29–1.19), whereas the Hassan interval does not (RR 0.39, 95% CI 0.17–0.92). Their weights are 59.9% and 40.1%, respectively. No heterogeneity was detected ($I^2=0\%$; heterogeneity $P=0.47$).

Vaginal Progesterone in Pregnancies with a Short Cervix: Reassessment of Aggregate Trial Data and Methodological Limitations



Footnotes

^aCI calculated by Wald-type method.

^bTau² calculated by DerSimonian and Laird method.

Figure 4. Original forest plot supplied for birth weight below 1,500 g

The image displays a pooled RR of 0.57 (95% CI 0.38–0.85; P=0.006), corresponding to a 43% relative reduction in the analyzed population. The displayed study estimates are 0.68 (0.39–1.17) for Fonseca and 0.47 (0.26–0.85) for Hassan, with weights of 53.9% and 46.1%. Thus, the plotted overall interval excludes 1, while the Fonseca interval does not. The image reports I²=0% and a heterogeneity P value of 0.38. NICU admission was reported in the supplied abstract as RR 0.80 (95% CI 0.54–1.18; P=0.25), but no distinct supporting forest plot or trial-level contributions were available. The duplicated birth-weight image has therefore been removed. The confidence interval is compatible with both benefit and some increase in risk, so the estimate does not establish a reduction or equivalence between groups.

Qualitative evidence and study quality

OPPTIMUM evaluated a broader high-risk population and did not establish a statistically significant benefit for its primary outcomes in the overall trial. That result cannot be substituted for the effect in the short-cervix subgroup. Conversely, retaining OPPTIMUM only narratively can reduce the completeness of a targeted quantitative review. Its full report and relevant subgroup evidence should be examined before concluding that usable data are unavailable. (Norman et al., 2018). The supplied risk-of-bias statements cannot support a finalized domain-level table without their evidence. No numerical certainty ratings, sensitivity results, or publication-bias conclusions are presented. The current result set therefore remains subject to data verification and outcome-level reassessment.

2. Discussion

Principal findings

The supplied estimates consistently favor vaginal progesterone for early birth and selected neonatal outcomes, but the dataset does not support their interpretation as a validated singleton-specific synthesis. This reassessment adds a structured audit of the analytical population: it links subgroup reports to parent trials, identifies mixed-plurality contamination, separates incompatible gestational-age boundaries, flags uncertain neonatal denominators, and removes a duplicated outcome figure. These issues alter the estimand itself, not merely the presentation of results.

The central finding is therefore not a new treatment-effect estimate. It is that an apparently favorable aggregate result can remain analytically non-reproducible even when its direction agrees with stronger evidence. Participant-level meta-analyses, including the 2025 update, remain the appropriate basis for singleton-specific efficacy

estimates because they can apply cervical-length and plurality criteria to individual participants (Romero et al., 2012, 2018, 2025).

Relationship to the wider evidence

Agreement with wider evidence should be interpreted cautiously because reviews may contain overlapping trials and answer different questions. EPPPIC evaluated progestogens in broader high-risk singleton populations, while the network meta-analysis by Care and colleagues compared several preventive interventions (EPPPIC Group, 2021; Care et al., 2022). Neither estimate can validate an aggregate dataset whose eligible population and denominators remain unresolved. The defensible incremental contribution here is the transparent identification of those discrepancies and the specification of corrections needed before reanalysis.

Clinical interpretation and applicability

Current SMFM guidance for individuals without previous spontaneous preterm birth defines a short cervix as ≤ 25 mm. It recommends vaginal progesterone for an asymptomatic singleton pregnancy with a transvaginal cervical length ≤ 20 mm diagnosed before 24 weeks, and consideration at 21–25 mm through shared decision-making. These thresholds illustrate why a < 28 -mm subgroup cannot automatically represent the same target population. (Society for Maternal-Fetal Medicine, 2024). ACOG's updated practice advisory also distinguishes recurrent preterm birth with a shortened cervix from prior preterm birth without cervical shortening. Evidence in one risk group should not be generalized to the other. This manuscript likewise does not establish efficacy for multiple pregnancies, symptomatic preterm labor, ruptured membranes, or cervical shortening first detected outside the studied gestational windows. (American College of Obstetricians and Gynecologists, 2025)

The review cannot determine whether one vaginal preparation or dose is superior. Nor does a placebo-controlled comparison establish comparative superiority over cerclage or pessary. Direct comparative studies such as SuPPoRT address a different question and should be interpreted with their own eligibility criteria, design, and published correction. Their existence reinforces the need to distinguish whether the clinical decision concerns treatment versus no active treatment or selection among preventive options. (Hezelgrave et al., 2024; Hezelgrave et al., 2025). For Indonesian clinical practice, translating trial efficacy into benefit requires reliable transvaginal cervical-length assessment, timely identification of eligible women, access to the relevant formulation, and continuity of antenatal follow-up. This is an implementation inference, not a result measured by the present review. Local absolute benefit, adherence, costs, and service feasibility cannot be estimated from the supplied data.

Neonatal outcomes and uncertainty

Gestational age and neonatal morbidity are related outcomes, but improvement in one does not establish improvement in every other endpoint. The NICU confidence interval in the source is compatible with both benefit and some increase in risk; a nonsignificant P value does not establish equivalence. Admission also reflects local clinical thresholds and available services, so its interpretation should remain separate from a specific neonatal diagnosis. Absolute risk reduction and the number needed to treat would be useful for clinical counseling, but require a valid baseline risk in the eligible population. Pooling crude totals across studies with different eligibility criteria is

not an adequate substitute. These measures have therefore not been calculated from the current unverified dataset. Maternal adverse effects and longer-term child outcomes also require explicit extraction before any broad safety conclusion can be made.

Limitations and implications for further analysis

The first limitation is incomplete reproducibility. The source gives aggregate screening counts but does not document when or how the searches were performed, how records were deduplicated, or why full texts were excluded. A review based only on PubMed and an undocumented Google Scholar search may miss eligible studies. Additional searches should be documented and the screening flow regenerated from the resulting log, rather than reconstructed by subtraction from incomplete totals. The second limitation concerns the analytical population. The listed sample sizes mix full trials and secondary subgroups, and neonatal denominators can refer to infants rather than pregnancies. Population restrictions must be applied to both the numerator and denominator for every outcome. A study may be eligible for narrative discussion while its published overall results remain ineligible for a specific pooled estimate. The third limitation is the small number of contributing studies. The supplied <34-week result is a single-study estimate; several other outcomes rely on only two reports. $I^2=0\%$ in this setting should not be used to claim strong consistency or high certainty. The data also do not support reliable exploration of treatment interactions by dose, previous preterm birth, or degree of cervical shortening. (Higgins et al., 2003; Sterne et al., 2011). Finally, excluding retracted evidence is necessary but does not alone establish novelty or eliminate bias. The historical IPD reports and later updates must be distinguished, the current evidence search must be completed, and the role of omitted eligible subgroup data must be resolved. A revised analysis should first prioritize accurate eligibility and extraction, then consider sensitivity to outcome boundaries and statistical assumptions. Only after those steps should the abstract and clinical conclusion be finalized. (Cetingoz et al., 2024; Wennerholm et al., 2025; Romero et al., 2025)

Conclusion

The broader evidence base supports vaginal progesterone for appropriately selected singleton pregnancies with a short cervix. This reassessment does not provide a new efficacy estimate; it establishes that the supplied aggregate analysis cannot yet answer that population-specific question because mixed-plurality data, inconsistent gestational-age thresholds, uncertain neonatal denominators, incomplete search documentation, and a duplicated outcome figure compromise reproducibility. Its validated contribution is a traceable methodological audit and a defined correction pathway: reconstruct the search record, restrict every numerator and denominator to eligible singleton pregnancies, harmonize outcome boundaries, link subgroup reports to parent trials, reassess OPPTIMUM subgroup data, and then repeat risk-of-bias, certainty, and sensitivity analyses. Until those steps are completed, clinical conclusions should rely on the current participant-level evidence rather than the unverified aggregate estimates.

Declaration of AI Assistance

AI tools, including ChatGPT, Gemini, or Claude AI, were used during the preparation of this manuscript for grammar checking, paraphrasing, and translation. The authors reviewed and verified the final content and take full responsibility for its accuracy and scientific integrity

References

- American College of Obstetricians and Gynecologists. (2025, April 11). Updated clinical guidance for the use of progestogen supplementation for the prevention of recurrent preterm birth. <https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2023/04/updated-guidance-use-of-progestogen-supplementation-for-prevention-of-recurrent-preterm-birth>
- Care, A., Nevitt, S. J., Medley, N., Donegan, S., Goodfellow, L., Hampson, L., et al. (2022). Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: Systematic review and network meta-analysis. *BMJ*, 376, e064547. <https://doi.org/10.1136/bmj-2021-064547>
- Cetingoz, E., Cam, C., Sakalli, M., Karateke, A., Celik, C., & Sancak, A. (2011). Progesterone effects on preterm birth in high-risk pregnancies: A randomized placebo-controlled trial [Retracted article]. *Archives of Gynecology and Obstetrics*, 283(3), 423-429. <https://doi.org/10.1007/s00404-009-1351-2>
- Cetingoz, E., Cam, C., Sakalli, M., Karateke, A., Celik, C., & Sancak, A. (2024). Retraction note: Progesterone effects on preterm birth in high-risk pregnancies: A randomized placebo-controlled trial. *Archives of Gynecology and Obstetrics*, 310(3), 1777. <https://doi.org/10.1007/s00404-024-07658-0>
- DeFranco, E. A., O'Brien, J. M., Adair, C. D., Lewis, D. F., Hall, D. R., Fusey, S., et al. (2007). Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: A secondary analysis from a randomized, double-blind, placebo-controlled trial. *Ultrasound in Obstetrics & Gynecology*, 30(5), 697-705. <https://doi.org/10.1002/uog.5159>
- DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials*, 7(3), 177-188. [https://doi.org/10.1016/0197-2456\(86\)90046-2](https://doi.org/10.1016/0197-2456(86)90046-2)
- EPPPIC Group. (2021). Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): Meta-analysis of individual participant data from randomised controlled trials. *The Lancet*, 397(10280), 1183-1194. [https://doi.org/10.1016/S0140-6736\(21\)00217-8](https://doi.org/10.1016/S0140-6736(21)00217-8)
- Fonseca, E. B., Celik, E., Parra, M., Singh, M., & Nicolaides, K. H. (2007). Progesterone and the risk of preterm birth among women with a short cervix. *The New England Journal of Medicine*, 357(5), 462-469. <https://doi.org/10.1056/NEJMoa067815>
- Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J., et al. (2011). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*, 64(4), 383-394. <https://doi.org/10.1016/j.jclinepi.2010.04.026>
- Hassan, S. S., Romero, R., Vidyadhari, D., Fusey, S., Baxter, J. K., Khandelwal, M., et al. (2011). Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: A multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound in Obstetrics & Gynecology*, 38(1), 18-31. <https://doi.org/10.1002/uog.9017>
- Hezelgrave, N. L., Suff, N., Seed, P., Robinson, V., Carter, J., Watson, H., et al. (2024). Comparing cervical cerclage, pessary and vaginal progesterone for prevention of preterm birth in women with a short cervix (SuPPoRT): A multicentre randomised controlled trial. *PLOS Medicine*, 21(7), e1004427. <https://doi.org/10.1371/journal.pmed.1004427>

Vaginal Progesterone in Pregnancies with a Short Cervix: Reassessment of Aggregate Trial Data and Methodological Limitations

- Hezelgrave, N. L., Suff, N., Seed, P., Robinson, V., Carter, J., Watson, H., et al. (2025). [Correction: Comparing cervical cerclage, pessary and vaginal progesterone for prevention of preterm birth in women with a short cervix \(SuPPoRT\): A multicentre randomised controlled trial.](#) *PLOS Medicine*, 22(4), e1004594. <https://doi.org/10.1371/journal.pmed.1004594>
- Higgins, J. P. T., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, 343, d5928. <https://doi.org/10.1136/bmj.d5928>
- Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, 327(7414), 557-560. <https://doi.org/10.1136/bmj.327.7414.557>
- Iams, J. D., Goldenberg, R. L., Meis, P. J., Mercer, B. M., Moawad, A., Das, A., et al. (1996). The length of the cervix and the risk of spontaneous premature delivery. *The New England Journal of Medicine*, 334(9), 567-572. <https://doi.org/10.1056/NEJM199602293340904>
- Norman, J. E., Marlow, N., Messow, C. M., Shennan, A., Bennett, P. R., Thornton, S., et al. (2016). Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): A multicentre, randomised, double-blind trial. *The Lancet*, 387(10033), 2106-2116. [https://doi.org/10.1016/S0140-6736\(16\)00350-0](https://doi.org/10.1016/S0140-6736(16)00350-0)
- Norman, J. E., Marlow, N., Messow, C. M., Shennan, A., Bennett, P. R., Thornton, S., et al. (2018). Does progesterone prophylaxis to prevent preterm labour improve outcome? A randomised double-blind placebo-controlled trial (OPPTIMUM). *Health Technology Assessment*, 22(35), 1-304. <https://doi.org/10.3310/hta22350>
- O'Brien, J. M., Adair, C. D., Lewis, D. F., Hall, D. R., DeFranco, E. A., Fusey, S., et al. (2007). Progesterone vaginal gel for the reduction of recurrent preterm birth: Primary results from a randomized, double-blind, placebo-controlled trial. *Ultrasound in Obstetrics & Gynecology*, 30(5), 687-696. <https://doi.org/10.1002/uog.5158>
- Ohuma, E. O., Moller, A. B., Bradley, E., Chakwera, S., Hussain-Alkhateeb, L., Lewin, A., et al. (2023). [National, regional, and global estimates of preterm birth in 2020, with trends from 2010: A systematic analysis.](#) *The Lancet*, 402(10409), 1261-1271. [https://doi.org/10.1016/S0140-6736\(23\)00878-4](https://doi.org/10.1016/S0140-6736(23)00878-4)
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). [The PRISMA 2020 statement: An updated guideline for reporting systematic reviews.](#) *BMJ*, 372, n71. <https://doi.org/10.1136/bmj.n71>
- Rethlefsen, M. L., Kirtley, S., Waffenschmidt, S., Ayala, A. P., Moher, D., Page, M. J., et al. (2021). [PRISMA-S: An extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews.](#) *Systematic Reviews*, 10(1), 39. <https://doi.org/10.1186/s13643-020-01542-z>
- Romero, R., Conde-Agudelo, A., da Fonseca, E., O'Brien, J. M., Creasy, G. W., Hassan, S. S., et al. (2025). [Vaginal progesterone reduces the risk of preterm birth and adverse perinatal outcomes in singleton gestations with a midtrimester sonographic short cervix \(\$\leq 25\$ mm\): An updated individual patient data meta-analysis.](#) *American Journal of Obstetrics and Gynecology*, 233(1), e1-e5. <https://doi.org/10.1016/j.ajog.2025.03.013>

Vaginal Progesterone in Pregnancies with a Short Cervix: Reassessment of Aggregate Trial Data and Methodological Limitations

- Romero, R., Conde-Agudelo, A., Da Fonseca, E., O'Brien, J. M., Cetingoz, E., Creasy, G. W., et al. (2018). Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: A meta-analysis of individual patient data. *American Journal of Obstetrics and Gynecology*, 218(2), 161-180. <https://doi.org/10.1016/j.ajog.2017.11.576>
- Romero, R., Dey, S. K., & Fisher, S. J. (2014). Preterm labor: One syndrome, many causes. *Science*, 345(6198), 760-765. <https://doi.org/10.1126/science.1251816>
- Romero, R., Nicolaides, K., Conde-Agudelo, A., Tabor, A., O'Brien, J. M., Cetingoz, E., et al. (2012). Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: A systematic review and meta-analysis of individual patient data. *American Journal of Obstetrics and Gynecology*, 206(2), 124.e1-124.e19. <https://doi.org/10.1016/j.ajog.2011.12.003>
- Society for Maternal-Fetal Medicine. (2024). SMFM Consult Series #70: Management of short cervix in individuals without a history of spontaneous preterm birth. *American Journal of Obstetrics and Gynecology*, 231(2), B2-B13. <https://doi.org/10.1016/j.ajog.2024.05.006>
- Sterne, J. A. C., Savovic, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., et al. (2019). RoB 2: A revised tool for assessing risk of bias. *BMJ*, 366, 14898. <https://doi.org/10.1136/bmj.14898>
- Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., Terrin, N., Jones, D. R., Lau, J., et al. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*, 343, d4002. <https://doi.org/10.1136/bmj.d4002>
- Wennerholm, U. B., Bergman, L., Kuusela, P., Ljungstrom, E., Moller, A. C., Hongslö Vala, C., et al. (2025). Corrigendum: Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies-A systematic review and meta-analyses. *Frontiers in Medicine*, 12, 1561413. <https://doi.org/10.3389/fmed.2025.1561413>