e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(6); 201-209

Original Research Article

Oral Dydrogesterone versus Vaginal Micronized Progesterone for Pregnancy Outcomes in Women with Threatened Miscarriage or Recurrent Pregnancy Loss: A Systematic Review and Meta-Analysis

Neha Sharma[1], Sweta Kumari[1], Netali[1], Harshit Agrawal[1]

[1]Tutor/Clinical Instructor, College of Nursing, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, India

Received: 27-04-2026 / Revised: 29-05-2026 / Accepted: 30-05-2026
Corresponding Author: Harshit Agrawal
Conflict of interest: Nil

Abstract:

Background: Progestogen supplementation is commonly used in the management of threatened miscarriage (TM) and recurrent pregnancy loss (RPL). While both oral dydrogesterone and vaginal micronized progesterone are widely prescribed, direct comparative evidence evaluating their relative efficacy remains sparse and has not been systematically synthesized.

Objective: To compare the efficacy of oral dydrogesterone versus vaginal micronized progesterone for pregnancy continuation in women diagnosed with TM or RPL.

Methods: PubMed, Cochrane Library and Google Scholar were searched from inception through January 2026 following a pre-registered PROSPERO protocol (CRD420261287005). Randomised controlled trials (RCTs) comparing oral dydrogesterone to vaginal progesterone were included. Risk ratios (RR) were pooled using inverse-variance random-effects meta-analysis. Risk of bias was assessed using Cochrane RoB 2, and certainty of evidence was graded using the GRADE framework.

Results: Four RCTs (n = 416) met inclusion criteria for the primary analysis. Oral dydrogesterone was associated with significantly higher pregnancy continuation rates compared with vaginal progesterone (RR 1.12, 95% CI 1.02–1.23, p = 0.02; I^2 = 0%; NNT = 10). Sensitivity analysis excluding one high-risk study yielded borderline non-significance (RR 1.10, 95% CI 0.99–1.21, p = 0.07). Secondary analysis from one additional RCT (n = 160) showed no significant differences in late pregnancy outcomes. The overall certainty of evidence was rated LOW.

Conclusions: Low-certainty evidence suggests oral dydrogesterone may improve pregnancy continuation compared with vaginal progesterone in women with TM or RPL. Late pregnancy outcomes appear comparable. Larger, adequately powered, double-blind RCTs with live birth as the primary outcome are needed to confirm these findings.

Keywords: Dydrogesterone; vaginal micronized progesterone; threatened miscarriage; recurrent pregnancy loss; systematic review; meta-analysis.

PROSPERO Registration: CRD420261287005.

DOI: 10.25258/ijcpr.18.6.34

Introduction

Vaginal bleeding during the first trimester in the presence of a confirmed viable intrauterine pregnancy, commonly referred to as threatened miscarriage, is encountered in approximately 15–25% of all recognised pregnancies, making it among the most frequent early-pregnancy complications.[1] Recurrent pregnancy loss (RPL), conventionally defined as two or more consecutive pregnancy losses, affects 1–2% of couples and represents a major source of physical and psychological morbidity.[2] Both conditions constitute significant clinical challenges in obstetric practice and are associated with considerable patient anxiety.

The role of progesterone in sustaining early pregnancy is well established and multifaceted. This steroid hormone drives the transformation of the endometrium into a receptive decidual state, supports the process of embryo attachment and invasion, reduces the contractile activity of the myometrium, and orchestrates a localised shift toward immunological tolerance at the maternal–foetal interface.[3] A relative deficiency of progesterone has been implicated in the pathogenesis of both threatened miscarriage and RPL, thereby providing a biological rationale for progestogen supplementation in affected women.[4]

Among the available progestogen options, two formulations have gained widespread clinical acceptance for pregnancy support: oral dydrogesterone and vaginally administered micronised progesterone. Dydrogesterone, a retro-stereoisomer of endogenous progesterone, is distinguished by its high oral bioavailability, selective progestogenic activity without anti-androgenic or glucocorticoid effects, and the convenience of tablet-based administration.[5] Vaginal micronised progesterone achieves high local uterine tissue concentrations through a first-uterine-pass effect but is frequently associated with local side effects including vaginal discharge and irritation.[6] Leading professional bodies, including ESHRE and RCOG, endorse progesterone supplementation for women with threatened miscarriage and prior losses,[2] but do not specify a preference between these two formulations, reflecting the absence of synthesised head-to-head comparative evidence.

A Cochrane systematic review by Wahabi and colleagues reported low-certainty evidence suggesting that progestogen use may lower miscarriage rates when compared with placebo among women experiencing threatened miscarriage.[7] Findings from the PRISM trial indicated no significant overall reduction in miscarriage with vaginal progesterone, although a subgroup benefit was noted in women with a prior miscarriage history.[8] Nevertheless, these prior reviews compared progestogens with placebo or no treatment, and no rigorous meta-analysis has directly compared oral dydrogesterone against vaginal micronised progesterone for pregnancy outcomes.

Considering the extensive clinical utilisation of both formulations worldwide and the absence of synthesised direct comparative evidence, this systematic review and meta-analysis was undertaken to compare the efficacy of oral dydrogesterone versus vaginal micronised progesterone for pregnancy continuation in women with threatened miscarriage or RPL, conducted in accordance with PRISMA 2020 guidelines [9] and prospectively registered on PROSPERO.

Materials and Methods

Protocol and Registration: Prior to initiating any data collection, a detailed review protocol was drafted and deposited in the PROSPERO international register of systematic reviews under the identifier CRD420261287005. All stages of this review adhered to the reporting framework set forth by the PRISMA 2020 statement. [9]

Eligibility Criteria: Only randomised controlled trials (RCTs) that compared oral dydrogesterone directly against vaginal micronised progesterone in women suffering from threatened miscarriage or recurrent pregnancy loss were considered for inclusion. Pregnancy continuation — meaning an ongoing viable pregnancy at a predefined gestational endpoint without intervening miscarriage — was designated as the primary outcome. Studies were excluded if they (1) used oral micronised progesterone as comparator, which constitutes a pharmacologically different route from vaginal administration; (2) were placebo-controlled trials without a direct dydrogesterone versus vaginal progesterone comparison arm; (3) employed non-randomised or quasi-experimental designs; (4) were protocols, conference proceedings without outcome data, or duplicate publications; or (5) did not report pregnancy continuation or miscarriage as a measured endpoint.

Information Sources and Search Strategy: PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL) and Google Scholar were searched from inception to January 2026. Search terms were built around synonyms and controlled vocabulary for dydrogesterone, progesterone, micronised progesterone, threatened miscarriage, threatened abortion, recurrent pregnancy loss and habitual abortion. No language or geographic restrictions were imposed. Reference lists of all retrieved full-text articles and prior relevant systematic reviews were hand-searched to capture additional studies.

Study Selection and Data Extraction: Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially relevant reports against the pre-established eligibility criteria. Discrepancies were resolved through discussion. Data extraction was performed in duplicate using a standardised form capturing study design, sample size, participant characteristics, intervention details and outcomes. When published reports did not furnish adequate numerical data, values were extracted from graphical presentations using validated digital extraction tools.

Risk of Bias Assessment: The methodological rigour of each included trial was scrutinised using version 2 of the Cochrane risk-of-bias instrument (RoB 2), [10] which probes five separate dimensions: how randomisation was generated and concealed, whether there were departures from the planned interventions, the extent of missing outcome data, the methods used to measure outcomes, and whether the selection of reported results was influenced by the findings. Each domain received a judgement of low risk, some concerns or high risk, and these individual verdicts were aggregated into an overall risk-of-bias rating for each trial following the algorithm prescribed by the RoB 2 developers.

Certainty of Evidence: The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [11] across five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. The starting level of HIGH for evidence derived from RCTs was downgraded as appropriate based on concerns identified across these domains.

Statistical Analysis: Treatment effects for binary outcomes were expressed as risk ratios (RR) with accompanying 95% confidence intervals (CI). Summary effect estimates were generated through meta-analysis using a random-effects model weighted by the inverse of each study's variance (DerSimonian–Laird), an approach that accommodates both sampling error within individual trials and genuine between-study variation in the true effect. Statistical heterogeneity was gauged through the I^2 statistic and Cochran's Q test. As a pre-specified robustness check, a sensitivity analysis was conducted by removing the study with the highest risk-of-bias rating and re-running the pooled analysis to determine whether the direction and significance of the summary estimate remained stable. The number needed to treat (NNT) was calculated from the absolute risk difference. All meta-analyses were performed using Review Manager 5.4 (Cochrane Collaboration).

To evaluate the sufficiency of the accumulated evidence and control for the risk of random error due to sparse data and repetitive testing, trial sequential analysis (TSA) was conducted. The optimal information size (OIS) was calculated using a two-sided α of 5%, a statistical power of 80%, a control-arm event rate of 71.30% (derived from the pooled vaginal progesterone group) and a relative risk increase of 13.60% (corresponding to the observed meta-analytic effect). O'Brien–Fleming-type alpha-spending monitoring boundaries were constructed to determine whether the cumulative evidence had crossed the threshold for a conclusive finding of benefit, harm or futility. TSA was performed using TSA software version 0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research).

Results

Study Selection: Database searching returned 140 records (PubMed 45, Cochrane Library 28, Google Scholar 67), with 20 additional records from citation tracking, yielding 160 records in total. After removing 40 duplicates, 120 records were screened by title and abstract. Twenty-two full-text articles were assessed for eligibility; eighteen were excluded (two wrong comparators, five placebo-controlled, eight non-randomised, two protocols, one not reporting the primary outcome). Four RCTs satisfied all inclusion criteria and entered the primary meta-analysis (Figure 1). [13,14,15,17]

A fifth trial (Pakniat 2021, n = 160) did compare oral dydrogesterone with vaginal progesterone in women with threatened abortion [12] but was excluded from the primary analysis because it did not report pregnancy continuation or miscarriage rates, instead following women who continued pregnancy through to delivery for obstetric outcomes. This study was retained for a pre-specified secondary analysis of late pregnancy outcomes.

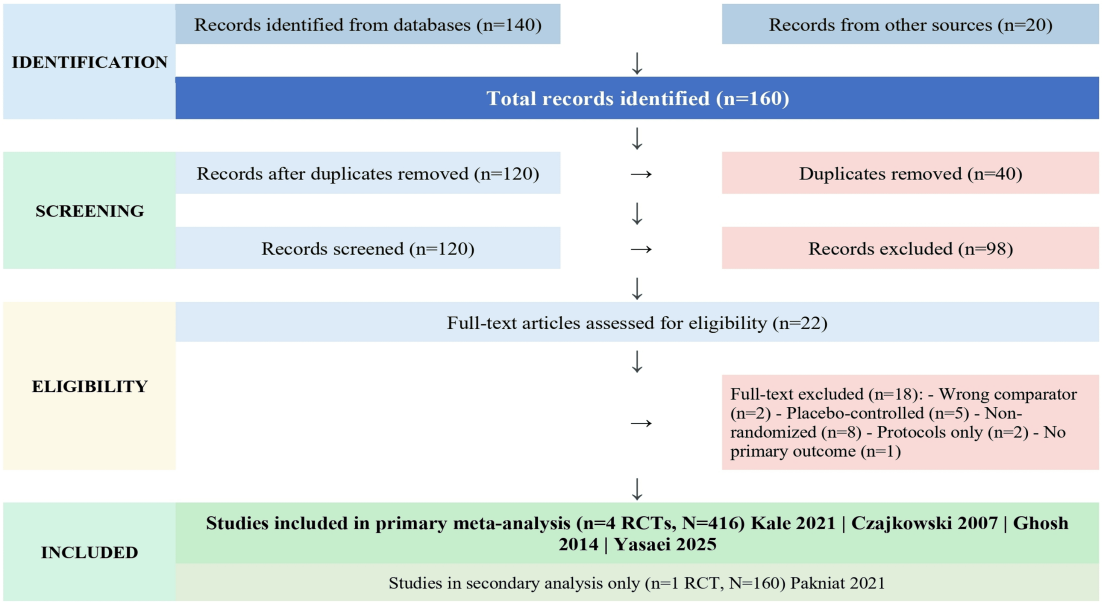


Figure 1: PRISMA 2020 flow diagram showing the study selection process. Four RCTs were included in the primary analysis of pregnancy continuation. One additional RCT (Pakniat 2021) was included in the secondary analysis of late pregnancy outcomes.

Study Characteristics: Collectively, the four trials entering the primary synthesis recruited 416 women across clinical sites in three countries: India, Poland and Iran (Table 1). Half of the studies drew their participants from women presenting acutely with threatened miscarriage, while the other half enrolled women carrying a diagnosis of recurrent pregnancy loss with or without concurrent bleeding. Dydrogesterone doses ranged from 20 to 30 mg/day; vaginal progesterone doses ranged from 300 to 600 mg/day across the studies. Treatment duration extended from the first trimester until 12 to 20 weeks of gestation. One trial employed a double-blind design,13 two were open-label, [14,15] and one (Yasaei 2025) was available only as a published abstract, limiting the amount of methodological detail available for assessment.[17]

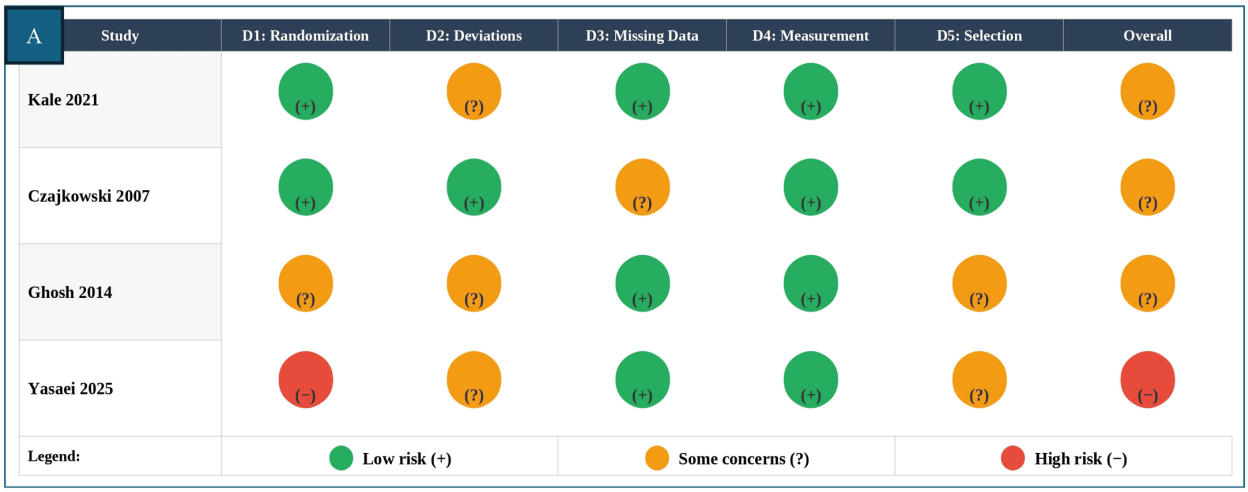
Table 1: Characteristics of included studies in the primary analysis.

Study	Country	Population	N	DYD/VP	DYD dose	VP dose	Duration	Blinding
Czajkowski 2007	Poland	Threatened abortion	53	24 / 29	20 mg/day	300 mg/day	Until 12 wks	Double-blind
Ghosh 2014	India	Idiopathic RSM	101	50 / 51	20 mg/day	300 mg/day	Until 12 wks	Open label
Kale 2021	India	RPL + bleeding	200	100 / 100	30 mg/day	600 mg/day	Until 20 wks	Open label
Yasaei 2025	Iran	Threatened abortion	62	31 / 31	NR	Suppositories	NR	Abstract only

DYD = dydrogesterone; VP = vaginal progesterone; RPL = recurrent pregnancy loss; RSM = recurrent spontaneous miscarriage; NR = not reported.

Risk of Bias

When each trial was run through the RoB 2 checklist, three of the four emerged with a composite judgement of "some concerns" (Figure 2). In the Kale (2021) trial, the primary source of concern resided in the domain of deviations from intended interventions, a predictable consequence of its open-label design whereby both participants and clinicians knew which treatment was being administered.[14] Czajkowski (2007), the only double-blind trial, received some concerns in the domain of missing outcome data due to incomplete reporting of attrition.[13] For Ghosh (2014), concerns arose in the randomisation domain because the method of allocation concealment was insufficiently described, and in the selection-of-results domain because the study appeared to report only selected secondary endpoints.[15] The Yasaei (2025) trial was rated as high risk overall on account of its unclear randomisation process and the unavailability of a full manuscript for detailed methodological scrutiny.[17]



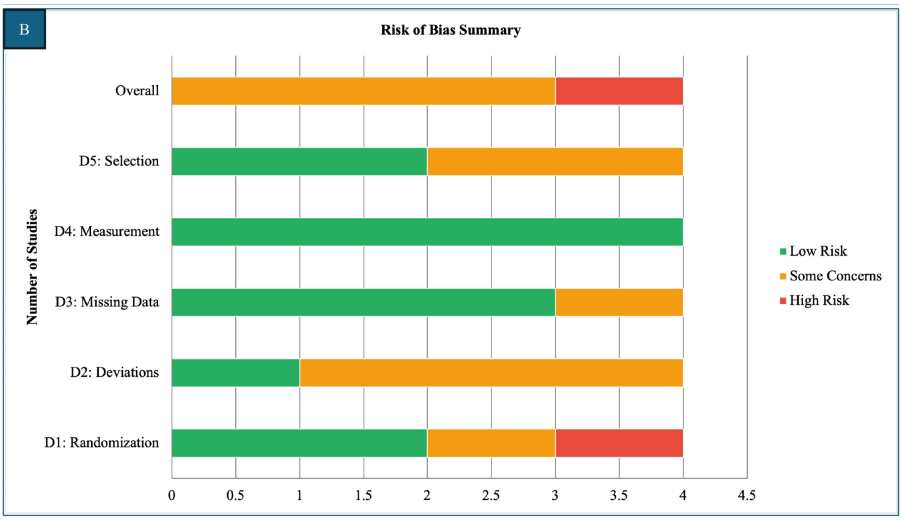


Figure 2: Risk of bias assessment (Cochrane RoB 2). Panel A: Traffic-light plot showing domain-level judgements for each study. Panel B: Summary bar chart showing distribution of risk-of-bias judgements across domains. D1 = randomisation process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of outcome; D5 = selection of reported results.

Primary Outcome: Pregnancy Continuation

When the results of all four eligible trials were combined in meta-analysis, a statistically significant difference emerged in favour of oral dydrogesterone: women assigned to the oral formulation exhibited higher rates of pregnancy continuation than their counterparts receiving vaginal progesterone (pooled RR 1.12, 95% CI 1.02–1.23, p = 0.02; Figure 3). The absolute pregnancy continuation rates were 81.00% (166/205) in the dydrogesterone group versus 71.30% (150/211) in the vaginal progesterone group, yielding an absolute risk difference of 9.60 percentage points and a number needed to treat (NNT) of 10 (Table 2).

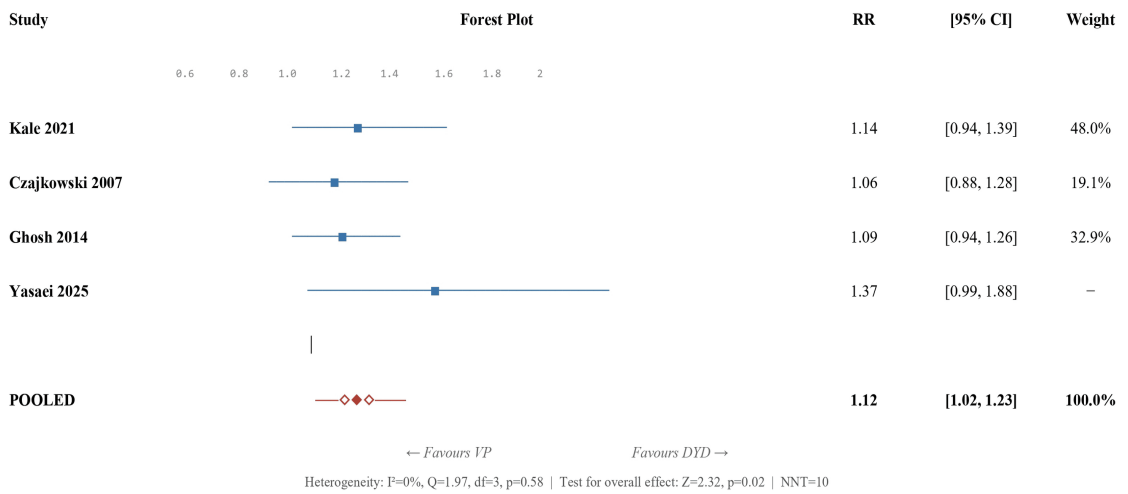


Figure 3: Forest plot comparing oral dydrogesterone versus vaginal micronised progesterone for pregnancy continuation. Risk ratios > 1 favour dydrogesterone. Diamond = pooled effect (random-effects model). ■ = individual study point estimate (size proportional to weight); ◆ = pooled estimate; │ = null line (RR = 1.0); ─ = 95% confidence interval.

Heterogeneity across the four studies was negligible (I^2 = 0%, Cochran's Q = 1.97, df = 3, p = 0.58), indicating consistent results and providing reassurance that the observed effect was not driven by a single outlier study. All four trials showed the same direction of effect favouring dydrogesterone, with individual risk ratios ranging from 1.06 to 1.37.

Table 2: Meta-analysis results for pregnancy continuation (primary outcome).

Study	DYD Events	DYD N	VP Events	VP N	DYD Rate (%)	VP Rate (%)	RR	95% CI	Weigh t (%)
Czajkowski 2007	22	24	25	29	91.67	86.21	1.06	0.88–1.28	19.10
Ghosh 2014	46	50	43	51	92.00	84.31	1.09	0.94–1.26	32.90
Kale 2021	72	100	63	100	72.00	63.00	1.14	0.94–1.39	48.00
Yasaei 2025	26	31	19	31	83.87	61.29	1.37	0.99–1.88	—
POOLED	**166**	**205**	**150**	**211**	**81.00**	**71.30**	**1.12**	**1.02–1.23**	**100.00**
Heterogeneity: $I^2 = 0\%$, $Q = 1.97$, $p = 0.58$. Test for overall effect: $Z = 2.32$, $p = 0.02$. Absolute risk difference = 9.60%. NNT = 10. The pooled row is shown for emphasis.									

Sensitivity Analysis: As pre-specified in the review protocol, the meta-analysis was re-run after removing the trial that had attracted the highest risk-of-bias rating (Yasaei 2025). With this study excluded, the pooled risk ratio dropped slightly to 1.10 (95% CI 0.99–1.21, p = 0.07) — a result that no longer cleared the conventional threshold for statistical significance (Table 3). The direction of effect remained consistent, and heterogeneity continued to be absent ($I^2 = 0\%$). This analysis highlights the fragility of the primary finding: the pooled estimate is sensitive to the inclusion of the one study with the most serious methodological limitations.

Table 3: Sensitivity analysis excluding the high-risk study (Yasaei 2025).

Parameter	Main Analysis (4 studies)	Sensitivity (3 studies)
Number of participants	416	354
Pooled RR (95% CI)	1.12 (1.02–1.23)	1.10 (0.99–1.21)
P-value	0.02	0.07
I^2 (%)	0.00	0.00
Statistically significant?	Yes	No (borderline)
Excluded study: Yasaei 2025 (rated high risk overall in the RoB 2 assessment).		

Secondary Outcomes: Information regarding bleeding duration was reported in two of the four included studies, and both pointed in the same direction. In the trial conducted by Kale (2021), women treated with dydrogesterone stopped bleeding substantially sooner than those on vaginal progesterone, with a mean cessation time of 53.90 ± 9.10 hours compared with 94.60 ± 7.30 hours ($p < 0.001$). [14] The Yasaei (2025) trial reported concordant findings, with bleeding resolving in a mean of 6.30 ± 2.60 days versus 10.70 ± 5.30 days ($p < 0.001$). [17] Patient satisfaction was notably higher with dydrogesterone in the Yasaei study (22.60% versus 3.20%, $p < 0.001$), with vaginal progesterone associated with more drowsiness and local side effects including vaginal discharge and irritation. [17]

Secondary Analysis: Late Pregnancy Outcomes: The Pakniat (2021) trial, which tracked its 160 participants from the first trimester through to delivery, afforded an opportunity to examine whether the choice of early-pregnancy progestogen had any bearing on later obstetric or neonatal events. [12] Across every measured endpoint, the two treatment groups performed comparably: caesarean delivery rates were 31.25% versus 33.75% ($p = 0.736$), prematurity rates 10.00% versus 8.75% ($p = 0.789$), gestational diabetes 8.75% versus 7.50% ($p = 0.771$), hypertensive disorders 6.25% versus 3.75% ($p = 0.447$), and birthweight distributions showed no significant divergence (Table 4). These findings suggest that among women who respond to progestogen therapy and continue their pregnancy, the choice of dydrogesterone versus vaginal progesterone does not appear to influence late pregnancy or neonatal outcomes.

Table 4: Late pregnancy outcomes from Pakniat 2021 (n = 160, secondary analysis).

Outcome	DYD (n = 80)	VP (n = 80)	p-value
Caesarean delivery	31.25%	33.75%	0.736
Prematurity	10.00%	8.75%	0.789
Gestational diabetes mellitus	8.75%	7.50%	0.771
Hypertensive disorders	6.25%	3.75%	0.447
Low birthweight	6.25%	5.00%	0.749
Intrauterine foetal death	1.25%	2.50%	0.560

DYD = dydrogesterone; VP = vaginal progesterone. All comparisons were statistically non-significant. This analysis is based on a single study and includes only women whose pregnancy continued beyond the threatened-abortion episode.

Certainty of Evidence: The overall confidence in the evidence for pregnancy continuation was assessed as LOW within the GRADE framework (Table 5). Two downgrades were applied. The first was for serious risk of bias, reflecting the fact that three out of four trials used non-blinded or partially blinded designs and that one study carried a high overall risk. The second downgrade was for serious imprecision: the total sample of 416 fell substantially below the calculated optimal information size of 598 participants (information fraction 69.60%), and the lower bound of the confidence interval (1.02) grazed the line of no difference. No downgrades were warranted for inconsistency (I^2 = 0%), indirectness (the PICO elements of the included studies matched the review question directly) or publication bias (which could not be formally assessed with fewer than 10 studies using funnel-plot methods).

Table 5: GRADE summary of findings.

Outcome	Studies (n)	Effect (95% CI)	Certainty	Reasons for Downgrading
Pregnancy continuation	4 (n = 416)	RR 1.12 (1.02–1.23)	⨁⨁⨀⨀ LOW	Risk of bias (–1)[a]; Imprecision (–1)[b]
Late pregnancy outcomes	1 (n = 160)	Non-significant for all	⨁⨀⨀⨀ VERY LOW	Risk of bias (–1); Imprecision (–1); Indirectness (–1)[c]

[a] Most studies not double-blind; one high-risk study. [b] Total sample below optimal information size; CI close to null. [c] Single study; women who miscarried excluded, creating selection bias.

Discussion

Drawing together the results of four randomised controlled trials involving 416 women, this systematic review offers preliminary evidence that oral dydrogesterone may hold a modest but potentially meaningful advantage over vaginal micronised progesterone when it comes to sustaining early pregnancy in women with threatened miscarriage or recurrent pregnancy loss. The pooled risk ratio of 1.12 (95% CI 1.02–1.23) translates into an NNT of 10, indicating that for every ten women treated with dydrogesterone instead of vaginal progesterone, one additional pregnancy may be preserved. The negligible heterogeneity (I^2 = 0%) and the consistent direction of effect across all four studies strengthen the credibility of this finding.

Fragility of the Primary Finding: It would be premature to treat these results as definitive. The sensitivity analysis brought into sharp relief the fragility of the evidence: stripping out the one high-risk study pushed the pooled estimate past the boundary of statistical significance (p = 0.07). Moreover, the trial sequential analysis confirmed that the cumulative Z-curve, although crossing the conventional significance threshold, failed to cross the more stringent O'Brien–Fleming monitoring boundary at the current information fraction of 69.60%. This means that despite the nominally significant p-value, the accumulated evidence has not yet reached the threshold needed to exclude a false-positive finding attributable to sparse data. An additional 182 participants in future trials would be required to reach the optimal information size of 598 and allow a conclusive determination.

Comparison with the Broader Progesterone Literature: Placing these results in the broader landscape of progesterone research in early pregnancy helps to contextualise their meaning. The Cochrane review led by Wahabi and colleagues had previously established that progestogens as a class may offer some protection against miscarriage relative to placebo, although the certainty of that conclusion was itself rated as low. [7] The landmark PRISM trial, which randomised over 4,000 women to vaginal progesterone or placebo following early-pregnancy bleeding, reported no significant benefit overall but did observe a subgroup benefit in women with a history of one or more prior miscarriages. [8] The companion PROMISE trial, focusing specifically on women with unexplained RPL, found no advantage for vaginal progesterone over placebo. [18] Against this backdrop, the present review provides a different angle of evidence by comparing two active treatments head-to-head rather than each against placebo.

A prior systematic review by Lee and colleagues [16] also compared oral dydrogesterone with vaginal progesterone but pooled heterogeneous study designs including non-randomised comparisons. The present review advances that work by restricting inclusion to RCTs, applying formal RoB 2 assessment, performing sensitivity analysis, providing GRADE certainty ratings, and incorporating trial sequential analysis to evaluate the sufficiency of accumulated evidence.

Late Pregnancy Safety Signal: The secondary analysis of data from the Pakniat (2021) trial adds a reassuring dimension to the overall picture. Finding no meaningful between-group differences in caesarean delivery, prematurity, hypertensive disorders, gestational diabetes or newborn weight suggests that the choice of early-pregnancy progestogen does not adversely affect downstream maternal or neonatal outcomes.[12] This finding, though drawn from a single study with acknowledged limitations, provides preliminary safety reassurance for both treatment strategies.

Practical Considerations: Several practical considerations flow from these observations. Oral dydrogesterone offers convenience advantages including tablet-based administration, avoidance of local mucosal irritation and leakage associated with vaginal pessaries, and potentially better adherence. Two studies demonstrated significantly faster bleeding cessation with dydrogesterone,[14,17] and patient satisfaction was higher with the oral route[17] — factors that are clinically relevant, particularly in resource-constrained settings. Dydrogesterone's selective progestogenic activity and absence of sedative side effects may offer additional pharmacological advantages.[5]

Strengths: Strengths of this review include prospective PROSPERO registration, comprehensive database searching with no language restrictions, granular domain-by-domain risk-of-bias assessment using RoB 2, GRADE certainty evaluation, trial sequential analysis to quantify the sufficiency of evidence, and transparent separation of primary and secondary analyses for the Pakniat (2021) trial. Adherence to PRISMA 2020 reporting guidelines ensures reproducibility.

Limitations: Counterbalancing these strengths are several limitations. The pool of eligible trials was small — four studies with a combined enrolment of 416 participants, representing only 69.60% of the optimal information size. Most studies were not double-blinded, introducing potential performance and detection bias. One study was available only as a conference abstract, precluding thorough quality assessment. The included studies varied in dosing regimens, treatment duration and clinical indication, although this heterogeneity was not reflected in statistical inconsistency. Geographic concentration in South Asia and the Middle East may limit generalisability.

Research Implications: The trial sequential analysis indicates that an additional 182 participants beyond the currently accrued 416 are needed to reach the optimal information size of 598 and enable a conclusive determination. The single most pressing need is therefore for one or more large, multicentre, double-blind RCTs adequately powered to confirm or refute the treatment difference observed in the present meta-analysis, using live birth — rather than pregnancy continuation — as the primary endpoint. Standardised dosing protocols, rigorous allocation concealment, and extended follow-up through delivery and the neonatal period would substantially enhance the quality and applicability of future evidence. Cost-effectiveness analyses comparing the two formulations in different healthcare settings, along with patient-reported outcome measures capturing treatment acceptability and quality of life, would further enrich the evidence base informing clinical decision-making.

Conclusions

Low-certainty evidence from four randomised controlled trials involving 416 women suggests that oral dydrogesterone may improve pregnancy continuation compared with vaginal micronised progesterone in women with threatened miscarriage or recurrent pregnancy loss (RR 1.12, 95% CI 1.02–1.23, NNT = 10). However, trial sequential analysis demonstrates that the cumulative evidence has not yet crossed the monitoring boundary for conclusive benefit, with the current sample representing only 69.60% of the required optimal information size. Sensitivity analysis further indicates that this finding is fragile when the single high-risk study is excluded. Late pregnancy outcomes appear comparable between the two treatments based on limited data. Larger, adequately powered, double-blind randomised trials recruiting at least 182 additional participants, with live birth as the primary outcome, are needed before definitive clinical recommendations can be made.

Declarations

Author Contributions: All authors contributed to concept and design, acquisition, analysis and interpretation of data, drafting of the manuscript and critical review for important intellectual content. All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Conflicts of Interest: In compliance with the ICMJE uniform disclosure form, all authors declare no financial relationships with any organisations that might have an interest in the submitted work, and no other relationships or activities that could appear to have influenced the submitted work.

Funding: No financial support was received from any organisation for the submitted work.

Ethics Statement: This systematic review and meta-analysis used only previously published data and did not require institutional ethics committee approval.

References

1. Hendriks E, MacNaughton H, MacKenzie MC. First trimester bleeding: evaluation and management. Am Fam Physician. 2019;99(3):166–174.
2. ESHRE Guideline Group on RPL; Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open. 2018;2018(2):hoy004.
3. Szekeres-Bartho J. Progesterone-mediated immunomodulation in pregnancy: its relevance to leukocyte immunotherapy of recurrent miscarriage. Immunotherapy. 2009;1(5):873–882.
4. Coomarasamy A, Devall AJ, Brosens JJ, Quenby S, Stephenson MD, Sierra S, et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol. 2020;223(2):167–176.
5. Schindler AE. Progestational effects of dydrogesterone in vitro, in vivo and on the human endometrium. Maturitas. 2009;65 Suppl 1:S3–S11.
6. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. Obstet Gynecol. 2000;95(3):403–406.
7. Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH. Progestogen for treating threatened miscarriage. Cochrane Database Syst Rev. 2018;(8):CD005943.
8. Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. N Engl J Med. 2019;380(19):1815–1824.
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg. 2021; 88:105906.
10. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
11. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–926.
12. Pakniat H, Ansari I, Kashanipour N, Movahed F. Effect of vaginal progesterone and dydrogesterone on pregnancy outcomes in patients with threatened abortion: a randomized clinical trial. Iran J Obstet Gynecol Infertil. 2021;24(2):18–25.
13. Czajkowski K, Sienko J, Mogilinski M, Bros M, Szczecina R, Czajkowska A. Uteroplacental circulation in early pregnancy complicated by threatened abortion supplemented with vaginal micronized progesterone or oral dydrogesterone. Fertil Steril. 2007;87(3):613–618.
14. Kale AR, Kale AA, Yelikar K. A comparative, randomized control trial in patients of per vaginal bleeding comparing efficacy of oral dydrogesterone versus vaginal progesterone in successful pregnancy outcome for patients with recurrent pregnancy loss. J Obstet Gynaecol India. 2021;71(6):591–595.
15. Ghosh S, Chattopadhyay R, Goswami S, Chaudhury K, Chakravarty B, Ganesh A. Assessment of sub-endometrial blood flow parameters following dydrogesterone and micronized vaginal progesterone administration in women with idiopathic recurrent miscarriage: a pilot study. J Obstet Gynaecol Res. 2014;40(7):1871–1876.
16. Lee HJ, Park TC, Kim JH, Norwitz E, Lee B. The influence of oral dydrogesterone and vaginal progesterone on threatened abortion: a systematic review and meta-analysis. Biomed Res Int. 2017; 2017:3616875.
17. Yasaei F, Nikbakht Dana F. The effects of dydrogesterone tablet vs progesterone suppositories on threatened abortion. Iran J Obstet Gynecol Infertil. 2025; 28:1–8.
18. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, et al. A randomized trial of progesterone in women with recurrent miscarriages. N Engl J Med. 2015;373(22):2141–2148.