Received: 13 August 2023 | Revised: 26 February 2024 | Accepted: 27 February 2024

DOI: 10.1111/aogs.14829

SYSTEMATIC REVIEW

Progestogens in women with threatened miscarriage or recurrent miscarriage: A meta-analysis

Yunli Zhao[1,2,3] | Rohan D'Souza[4,5] | Ya Gao[4,6] | Qiukui Hao[4,7] | Lucas Kallas-Silva[8] | Jeremy P. Steen[9] | Gordon Guyatt[4]

[1]Department of Geriatric Medicine, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China

[2]Chongqing Municipality Clinical Research Center for Geriatrics, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China

[3]The Center of Gerontology and Geriatrics (National Clinical Research Center for Geriatrics), West China Hospital, Sichuan University, Chengdu, China

[4]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

[5]Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada

[6]Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Lanzhou, China

[7]School of Rehabilitation Science, McMaster University, Hamilton, Ontario, Canada

[8]Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, Brazil

[9]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

Correspondence
Yunli Zhao, Department of Geriatric Medicine, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China.
Email: yunlizhao948@outlook.com

Abstract

Introduction: Clinical practice guidelines provide inconsistent recommendations regarding progestogen supplementation for threatened and recurrent miscarriage. We conducted a systematic review and meta-analysis to assess the effectiveness and safety of progestogens for these patients.

Material and methods: We searched Medline, Embase, and Cochrane Central Registry of Controlled Trials up to October 6, 2023 for randomized control trials (RCTs) comparing progestogen supplementation to placebo or no treatment for pregnant women with threatened or recurrent miscarriage. We assessed the risk of bias using a modified version of the Cochrane risk-of-bias tool and the certainty of evidence using the GRADE approach.

Results: Of 15 RCTs (6616 pregnancies) reporting on threatened or recurrent miscarriage, 12 (5610 pregnancies) reported on threatened miscarriage with or without a prior history of miscarriage. Results indicated that progesterone probably increases live births (relative risk (RR) 1.04, 95% confidence interval (CI) 0.99–1.10, absolute increase 3.1%, moderate certainty). Of these RCTs, three (1973 pregnancies) reporting on threatened miscarriage with a prior history of miscarriage indicated that progesterone possibly increases live births (RR 1.06, 95% CI: 0.97–1.16, absolute increase 4.4%; low certainty), while four (2540 pregnancies) reporting on threatened miscarriage and no prior miscarriage left the effect very uncertain (RR 1.02, 95% CI: 0.96–1.10, absolute increase 1.7%; very low certainty). Three trials reporting on 1006 patients with a history of two or more prior miscarriages indicated progesterone probably increases live births (RR 1.08, 95% CI: 0.98–1.19, absolute increase 5.7%, moderate certainty). Six RCTs that reported on 2979 patients with at least one prior miscarriage indicated that progesterone probably increases live births (RR 1.07, 95% CI: 1.01–1.13, absolute increase 5.0%; moderate certainty). Progesterone probably has little or no effect on congenital anomalies (RR 1.06, 95% CI: 0.76–1.48, absolute increase 0.1%; moderate

Abbreviations: BMI, body mass index; CI, confidence intervals; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCTs, randomized controlled trials; RR, relative risk.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2024 The Authors. *Acta Obstetricia et Gynecologica Scandinavica* published by John Wiley & Sons Ltd on behalf of Nordic Federation of Societies of Obstetrics and Gynecology (NFOG).

certainty), and other serious adverse pregnancy events (RR 1.07, 95% CI: 0.83–1.40, absolute increase 0.2%, moderate certainty).

Conclusions: In women at increased risk of pregnancy loss, progestogens probably increase live births without increasing adverse maternal and neonatal events. It remains possible that the benefit is restricted to those with prior miscarriages.

KEYWORDS
live birth, meta-analysis, progestogens, recurrent miscarriage, threatened miscarriage

1 | INTRODUCTION

Miscarriage, the spontaneous loss of a fetus/pregnancy, is variably defined as a pregnancy under a certain period of gestation (most commonly 20, 24 or 28 weeks) or under a certain birthweight (most commonly under 500 g).[1–3] Miscarriages complicate 15% of all clinically recognized pregnancies, which translates to approximately 23 million miscarriages per year worldwide.[3,4] A miscarriage can result not only in maternal morbidity and mortality from excessive bleeding and the development of sepsis, especially in regions where access to timely clinical care is limited, but may also increase the risk of preterm birth in subsequent pregnancies and long-term physical and mental health risks.[4]

Risk factors for miscarriage include extremes of maternal reproductive age, lifestyle factors such as smoking and alcohol use, infections, certain medications, radiation treatment, uterine structural abnormalities, cervical incompetence, and medical conditions such as autoimmune disease, severe kidney disease, diabetes, and heart disease.[4] Some of these risk factors are modifiable and may present opportunities for primary prevention. Two groups of individuals that might benefit from early pregnancy interventions include those presenting with early pregnancy bleeding, a closed cervix and a live fetus (threatened miscarriage),[5] and those with a history of more than one prior miscarriage (recurrent miscarriage).

The hormone progesterone, secreted during early pregnancy from the ovary by the corpus luteum, and subsequently by the placental syncytiotrophoblast, plays an important role in maintaining early pregnancies.[5,6] A decrease in endogenous progesterone during the functional transition (luteoplacental shift),[5] may result in early pregnancy bleeding and a subsequent miscarriage.[6,7] Therefore, it is plausible that pregnancy supplementation with natural or synthetic progestogen may reduce the risk of a miscarriage.

Despite this biological plausibility, systematic reviews and meta-analyses of randomized controlled trials (RCTs) assessing the effectiveness of progestogen supplementation in pregnant women with threatened miscarriage,[8–12] recurrent miscarriage[13,14] or both,[15] have generated inconsistent summary estimates and inferences ranging from a probable decrease in the incidence of miscarriage[8,9,12,14] and a probable increase in live births,[12,14] to no difference in live birth rates.[15] Differences can in part be explained by variations in eligibility criteria, the timing of conduct of reviews and thus the omission of some relevant RCTs, inconsistencies in addressing the quality of the evidence, and the probably misguided assumption regarding differences in the impact of the available progestogens.

Key message

In women with threatened or prior miscarriage our meta-analysis that included pooled data from 15 trials including 6616 pregnancies established an increase in the likelihood of a live birth with progestogen supplementation, most convincing in those with prior miscarriage.

The rationale for this meta-analysis was to address the limitations of prior systematic reviews and re-evaluate the potential benefits and harms of progestogen supplementation on pregnant women with threatened or recurrent miscarriage.

2 | MATERIAL AND METHODS

The protocol for this meta-analysis adheres to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement.[16] We registered the protocol with PROSPERO (CRD42022344054).

2.1 | Search strategy

In collaboration with a research librarian, we undertook a comprehensive literature search on EMBASE, MEDLINE, and the Cochrane Central Registry of Controlled Trials from the date of their inception to October 6, 2023, without language restrictions. We searched for all relevant RCTs comparing progestogens with placebo or no treatment in pregnant women with threatened miscarriage or recurrent miscarriage. Supporting Information S1 presents details of the search. We scanned the reference lists of included studies and relevant systematic reviews to identify additional eligible studies.

2.2 | Eligibility criteria and study selection

The eligible RCTs met the following criteria:

Participants: pregnant women experiencing a threatened miscarriage as specified by the authors, and with a history of recurrent miscarriage, defined as two or more prior spontaneous consecutive or nonconsecutive miscarriages.

Intervention: natural or synthetic progestogens—micronized progesterone, dydrogesterone, and 17-OH progesterone caproate (17-OHPC) treatment for up to 24 weeks of gestation; Medroxyprogesterone acetate and Quingestrone were not included.

Comparison: placebo or no treatment.

Outcomes: live birth, congenital anomalies, and severe adverse pregnancy events specified by the authors.

Studies: randomized and quasi-randomized clinical trials.

Reviewers (YZ, YG, SL, JS), using standardized forms, worked independently to screen titles, abstracts and full texts of potentially eligible studies in duplicate. When discrepancies existed, reviewers resolved disagreements by discussion or by consultation with a third reviewer (GG).

2.3 | Data extraction

For each eligible study, reviewers (YZ, YG, LK, JS) worked independently to extract data in duplicate with resolution of disagreements by discussion or adjudication by a third reviewer (GG). Extracted data included study characteristics (author, year of publication, country, sample size, type of funding, whether the study protocol had been previously published); participant characteristics (age, country, gestational age at enrollment, body mass index (BMI), proportion of multiple pregnancies); type of miscarriage (threatened, recurrent or both); characteristics of interventions; follow-up time and all outcomes of interest, which included the number of:

1. Live births;
2. Newborns with congenital anomalies;
3. Maternal and neonatal severe adverse events.

When included studies reported pregnancy loss (induced abortions, miscarriages and stillbirths) and not live births, we calculated live births by subtracting the number of pregnancy losses from the total number of pregnancies. As the incidence of stillbirth is extremely low,[17,18] in studies that did not report stillbirths, we assumed pregnancy loss to include all induced abortions and miscarriages.

2.4 | Risk of bias assessment

Reviewers (YZ, YG, LK, JS) worked independently to evaluate the risk of bias in duplicate, on an outcome-by-outcome basis using a modified version of the Cochrane risk-of-bias tool.[19–22] The tool comprises eight domains, including the random sequence generation; allocation concealment; blinding of participants, healthcare providers, data collectors, and outcome assessors; missing outcome data (if the rate of missing data was lower than 10%, we judged it as having a low risk of bias); and other potential sources of bias (eg early trial discontinuation).

2.5 | Statistical analyses

To ensure independent observations, we used the number of pregnant women as the denominator for all outcomes.[23] We considered studies that included twin pregnancies as having only a single event and, as long as one baby experienced a live birth, counted that event as a live birth. Similarly, if either infant experienced a congenital anomaly or severe adverse event, we counted these as a single event.

We analyzed data using R 4.0.2. When there were fewer than five or more than 20 studies included, we used DerSimonian and Laird (DL) random effects model for pooled analysis data; otherwise, we used the Hartung, Knapp, Sidik and Jonkman (HKSJ) random effects model.[24] We presented results as relative risks (RR) and associated 95% confidence intervals (CI) and risk differences calculated by applying the relative effects to the best estimates of baseline risk (the median absolute risks of the control group of included studies).[25] For the impact of progestogens on live birth, we calculated the number needed to treat (NNT) by using the formula ($NNT = 1/|RD|$).[22]

We applied the research integrity assessment (RIA) tool[26] to assess the trustworthiness of included trials. When trials had more than three domains of insufficient information, we conducted a sensitivity analysis by excluding these trials. If the primary outcome's result was close to the sensitivity analysis, we included these trials in the subsequent analyses. Otherwise, we removed these trials with more domains of insufficient information. In addition, we conducted a sensitivity analysis for live births by excluding the trial that only reported miscarriages and not live births.

2.6 | Heterogeneity and subgroup analysis

In addition to visual inspection of the forest plots, the χ^2 test for heterogeneity and the I^2 statistic informed assessment of heterogeneity between studies.

When there were at least two eligible studies in each subgroup, we explored effect modification by conducting a subgroup analysis of relative effects in sequence, with results determining subsequent analyses.

When there were at least two within-study comparisons providing relevant evidence, we conducted within-trial comparisons (using STATA); otherwise, we performed between-trial comparisons. When few within-trial comparisons and an appreciable number of additional between-trial comparisons were available, we used both approaches.

For all subgroup analyses, if *p*-values for heterogeneity were greater than 0.1, we concluded that a true subgroup effect was implausible and did not explore further. If interaction *p*-values were 0.1 or less, we planned to evaluate the credibility of the subgroup hypotheses using the Instrument for the Credibility of Effect Modification Analyses (ICEMAN).[27]

We assessed the effect of progesterone intervention on live birth from pregnancies with or without threatened miscarriage. We addressed the following patient groups:

1. (a) Threatened miscarriage with or without prior miscarriage, (b) threatened miscarriage with one or more prior miscarriages and (c) threatened miscarriage without a prior miscarriage;
2. Two or more prior miscarriages without threatened miscarriage (recurrent miscarriage);
3. Recurrent miscarriage with or without threatened miscarriage OR one or more prior miscarriage with a threatened miscarriage.

Next, we examined the potential impact of risk of bias, focusing on the concealment of randomization (the key risk of bias issue that differentiated high and low risk of bias studies). Our plan was that if there was only low credibility, of a subgroup effect, all subsequent analyses would include all studies. If we found a moderate or high credibility of a subgroup effect, subsequent analyses would use only studies at low risk of bias.

For the overall results including patients with either threatened or recurrent miscarriage, we examined the type of treatment (hypothesizing that vaginal micronized progesterone was more effective than other progestogens). Our plan was that if there was only low credibility of a subgroup effect, all subsequent analyses would include all progestogens. If we found a moderate or high credibility of a subgroup effect, subsequent analyses would separate the two groups.

Subsequent subgroup analyses addressed the following issues:

- Age of patients (we hypothesized that progestogens would be more effective in younger than older participants using thresholds of 30, 35 or 40 years as specified by authors);
- Gestational age (we hypothesized that progestogens would be more effective when commenced earlier in pregnancy than later, using thresholds of 5, 6 or 7 weeks as specified by authors);
- BMI (we hypothesized that progestogens would be more effective in patients with lower BMI than higher BMI using a threshold of 30 kg/m^2 for higher BMI, as specified by authors).

2.7 | Publication bias

When there were more than 10 eligible studies, we used funnel plots and Harbord test to rule out publication bias.[28] If results suggested publication bias (asymmetric funnel plot and/or *p*-value of Harbord's test <0.05), we planned to use the trim-and-fill method to evaluate the impact of publication bias on our results.[29]

2.8 | Certainty of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence, evaluating certainty on whether the true effect was greater or less than the minimally important difference (MID). We rated certainty as very low, low, moderate or high, by assessing risk of bias, imprecision, inconsistency, indirectness, and publication bias.[30–32] We set the MID threshold for live birth, congenital anomalies and severe adverse events as 1%. When studies reported missing outcome data, we used complete case analysis as the primary analysis.

When, for any outcome, the results of the primary analysis suggested a statistically significant treatment effect, we evaluated the robustness of the results by performing a plausible worst case sensitivity analysis for each outcome.[33] If the effect remained significant in the plausible worst-case analysis, we did not rate down the certainty of evidence for risk of bias of missing information; otherwise, we rated down certainty.

We developed summary of findings tables using optimal formats[34] in MAGIC.app (https://app.magicapp.org), presenting both relative and absolute effects and including plain language summaries with wording following GRADE guidance.[35]

2.9 | Patient involvement

No patients were involved in the design, or conduct, or reporting, or dissemination plans of our research.

3 | RESULTS

Figure S1 presents the study selection process. Fifteen studies proved eligible.[36–50] Table S1 presents reasons for excluding studies that previous meta-analyses deemed eligible.

The characteristics of the 15 eligible studies are presented in Table 1, with sample sizes ranging from 42 to 4153, enrolling a total of 6616 pregnancies.[36–50] Two trials were quasi-RCTs.[36,48] Eight studies were conducted in Asia,[36–42,48] five in Europe[43–46,49] and two in Oceania.[47,50] Eleven trials included patients with a gestational age less than 12 weeks[36,37,40,42–49] and four trials included some patients with a gestational age greater than 12 weeks.[38,39,41,50] The proportion of pregnancies lost to follow-up ranged from 0%[35,36,40,41,46–48] to 19.28%.[42]

3.1 | Risk of bias

Figure S2 summarizes the risk of bias among included studies. Considering each outcome was objective and had the same denominator, we judged all studies and all outcomes to have the same risk of bias. We judged all studies at low risk of bias in blinding

TABLE 1 Characteristics of included studies and participants.

Studies	Type of miscarriage	Country	Age mean, range (years)	Gestational age mean, range (weeks) at enrollment	Number of patients (intervention/control)	History of prior miscarriage	Loss to follow-up (%)	Intervention	Outcomes
Alimohamadi et al. 2013[38]	Threatened miscarriage	Iran	30.1 25–40	13 ≤20	160 (80/80)	Unclear	11.25	Vaginal suppository containing 200 mg of micronized progesterone twice a day for 1 week	Miscarriage
Chan et al. 2021[37]	Threatened miscarriage	China	31.1 18–40	NR 5–12	406 (203/203)	Mixed population	3.98	Dydrogesterone 40 mg orally, followed by 10 mg orally three times a day. Women were followed up with weekly pelvic ultrasound and blood tests until 12 weeks of gestation were completed, or 1 week after the bleeding stopped, whichever was later	Live birth, congenital abnormalities
Coomarasamy et al. 2015[49]	Recurrent miscarriage	UK, The Nertherlands	32.6 18–39	NR ≤6	836 (404/432)	All patients	1.21	400 mg vaginal micronized progesterone twice daily from confirmation of pregnancy (and no later than 6 weeks of gestation) through 12 completed weeks of gestation (or earlier if an ectopic pregnancy was diagnosed or miscarriage occurred before 12 weeks)	Live birth, congenital abnormalities, serious adverse pregnancy events
Coomarasamy et al. 2019[43]	Threatened miscarriage	UK	30.6 16–39	NR ≤12	4153 (2079/2074)	Mixed population	2.85	400 mg vaginal micronized progesterone twice daily, from the time of randomization through 16 completed weeks of gestation (or earlier if pregnancy ended before 16 weeks)	Live birth, congenital abnormalities, serious adverse pregnancy events
El-Zibdeh 2005[48]	Recurrent miscarriage	Jordan	NR 20–34	NR ≤12	130 82/48	All population	0	Oral dydrogesterone 10 mg b.i.d.; as soon as pregnancy was confirmed by serum levels of βhCG and continued until the 12th gestational week	Live birth, congenital abnormalities
El-Zibdeh & Yousef 2009[36]	Threatened miscarriage	Jordan	NR ≥30	NR ≤12	146 86/60	Mixed population	0	Oral dydrogesterone 10 mg b.i.d.; from presentation with bleeding and continued for 1 week after the bleeding had stopped	Live birth, congenital abnormalities

(Continues)

TABLE 1 (Continued)

Studies	Type of miscarriage	Country	Age mean, range (years)	Gestational age mean, range (weeks) at enrollment	Number of patients (intervention/control)	History of prior miscarriage	Loss to follow-up (%)	Intervention	Outcomes
Gerhard et al. 1987[44]	Threatened miscarriage	Germany	29.0 NR	NR ≤12	60 (28/32)	Mixed population	7.14	25 mg vaginal micronized progesterone twice daily until abortion or 14 days of being symptom free	Live birth
McLindon et al. 2023[47]	Threatened miscarriage	Australia	30.6 18.2–44.3	7.4 6.4–8.6	269 (136/133)	Mixed population	3.2	400 mg vaginal micronized progesterone nightly until 12 weeks of gestation or earlier if pregnancy ended before 12 weeks	Live birth, congenital abnormalities
Omar et al. 2005[40]	Threatened miscarriage	Japan	29.5 NR	8.5 6–12	154 (74/80)	No patients	0	40 mg oral dydrogesterone stat, followed by 10 mg twice a day until the bleeding stopped (no more than 20 weeks of gestation)	Miscarriage
Palagiano et al. 2004[45]	Threatened miscarriage	Italy	31.2 21–40	8.1 6–12	50 (25/25)	Unclear	0	90 mg vaginal micronized progesterone once a day for 5 consecutive days	Miscarriage
Pandian 2009[41]	Threatened miscarriage	Malaysia	NR NR	NR ≤16	191 (96/95)	Unclear	0	40 mg oral dydrogesterone stat, followed by 10 mg twice daily until 16 weeks of gestation	Live birth, congenital abnormalities
Shearman & Garrett 1963[50]	Recurrent miscarriage	Australia	NR NR	NR 5–14	50 (27/23)	All patients	0	Injection 17-hydroxyprogesterone: up to 8th week, 250 mg/week; 8th to 11th week, 375 mg/week; 12th to 16th week, 500 mg/week; 17th to 20th week, 375 mg/week; 21st to 24th week, 250 mg/week. No treatment was given after the 24th week	Miscarriage
Sondergaard et al. 1985[46]	Threatened miscarriage	Denmark	25.4 18–39	NR ≤12	42 (23/19)	Unclear	0	200 mg vaginal micronized progesterone three times daily to 12 weeks or abortion	Live birth
Turgal et al. 2017[42]	Threatened miscarriage	Turkey	28.7 NR	7.9 6–8	83 (42/41)	Mixed population	19.28	400 mg oral micronized progesterone daily for 4 weeks	Live birth
Yassaee et al. 2014[39]	Threatened miscarriage	Iran	27.0 18–37	9.5 ≤20	60 (30/30)	Unclear	0	400 mg vaginal progesterone suppository daily until bleeding stopped for several days, mostly less than 1 week	Live birth

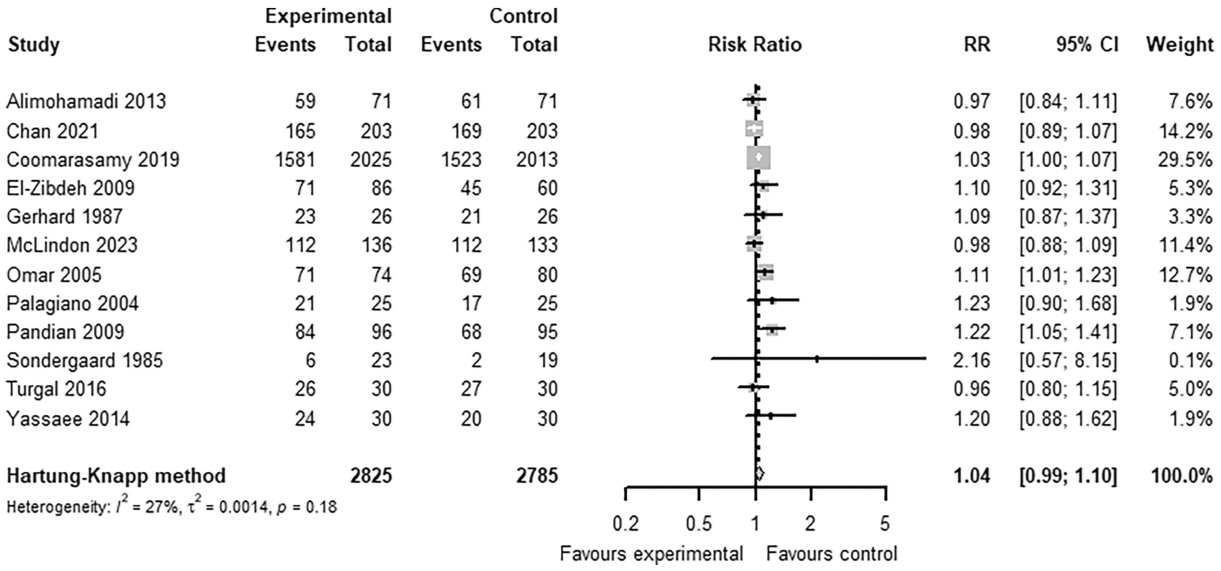

FIGURE 1 Forest plot for relative risk of live birth for progestogens compared with placebo or no treatment for threatened miscarriage patients with or without prior miscarriage.

participants, healthcare providers, data collectors and outcome assessors; seven studies at high risk of bias in random sequence generation[36,40,44–46,48,50]; seven studies at high risk of bias in allocation concealment[36,40,42,44,46,48,50]; and two studies at high risk of bias in missing outcome data.[38,42]

3.2 | Outcomes

3.2.1 | Live birth

Eleven studies explicitly reported live births[36–38,41–44,46–49]; we inferred the number of live births from data on miscarriages and stillbirths in the remaining four studies.[39,40,45,50] Among the eligible trials, 12 studies enrolled 5610 patients with threatened miscarriage,[36–47] and three studies focused on recurrent miscarriage patients.[48–50] Of the studies that focused on threatened miscarriage, three studies reported live births for pregnancies with or without prior miscarriage separately,[43,44,47] one study for pregnancies without prior miscarriage,[40] and the remainder of the trials either did not report or did not present data separately based on a prior history of miscarriage.[36–39,41,42,45,46]

In patients with threatened miscarriages, supplementation with progestogens probably improves live births (RR 1.04, 95% CI: 0.99–1.10, absolute increase 3.1%, NNT 32; moderate certainty; Figure 1; Table 2). Among these trials, one trial had three domains of insufficient information[40] and three trials only reported miscarriages and not live births.[38,40,45] Sensitivity analyses excluding these trials did not significantly influence the observed effects (Figure S3a,b). The symmetrical funnel plot (Figure S4) and Harbord test ($p = 0.19$), suggest no publication bias.

Three studies reported 1973 threatened miscarriage patients with one or more prior miscarriages.[43,44,47] In this population, supplementation with progestogens possibly improves live births among threatened miscarriage patients with one or more prior miscarriages (RR 1.06, 95% CI: 0.97–1.16, absolute increase 4.4%, NNT 23; low certainty; Figure 2; Table 2).

Four studies reported on 2540 threatened miscarriage patients without prior miscarriage.[40,43,44,47] In this population, due to the extremely serious imprecision, we were uncertain whether progestogens improve or worsen live births (RR 1.02, 95% CI: 0.96–1.10; absolute increase 1.7%, NNT 59; very low certainty; Figure 3; Table 2). Sensitivity analyses excluding the trial[40] with three domains of insufficient information and a trial[40] that only reported miscarriage and not live births did not significantly influence the observed effects (Figure S3c).

Three eligible trials included 1006 pregnant women with two or more prior miscarriages without threatened miscarriage.[48–50] In this population, progestogens likely improve live births for pregnant women (RR 1.08, 95% CI: 0.97–1.19, absolute increase 5.7%, NNT 18; moderate certainty; Figure 4; Table 2). Sensitivity analyses excluding one trial[50] with three domains of insufficient information and one trial[50] that only reported miscarriages and not live births did not significantly influence the observed effects (Figure S3d).

Six studies enrolled 2979 patients with at least one prior miscarriage (including those with recurrent miscarriage and threatened miscarriage with one or more prior miscarriages).[43,44,47–50] In this population, supplementation with progestogens probably improved live births (RR 1.07, 95% CI: 1.01–1.13, absolute increase 5.0%, NNT 20; moderate certainty; Figure 5; Table 2). Sensitivity analyses excluding one trial[50] with three domains of insufficient information and one trial[50] that only reported miscarriages and not live births, did not significantly influence the observed effects (Figure S3e).

Figure S5 shows the association between progestogen intervention and live birth in patients with threatened miscarriage or recurrent miscarriage. Compared to the control group, supplementation

TABLE 2 GRADE summary of findings tables for outcomes in review of progestogens vs placebo or no treatment in patients with threatened miscarriage or recurrent miscarriage.

Outcomes	Study results and measurements	Absolute risk difference		Certainty of evidence	Plain language summary
		Placebo or no treatment[a]	Progestogens		
Live birth: threatened miscarriage with or without prior miscarriage[36–47]	Relative risk: 1.04 (CI: 95% 0.99–1.10) Based on data from 5610 participants in 12 studies	782 per 1000	813 per 1000 Absolute increase: 31 more per 1000 (CI: 95% 8 fewer –78 more)	Moderate Due to serious imprecision	Progestogens probably improve live birth for patients with threatened miscarriage with or without prior miscarriage
Live birth: threatened miscarriage with one or more prior miscarriage[43,44,47]	Relative risk: 1.06 (CI: 95% 0.97–1.16) Based on data from 1973 participants in 3 studies	733 per 1000	777 per 1000 Absolute increase: 44 more per 1000 (CI: 95% 22 fewer –117 more)	Low Due to very serious imprecision	Progestogens possibly improve live birth for patients with threatened miscarriage with prior miscarriage
Live birth: threatened miscarriage without prior miscarriage[40,43,44,47]	Relative risk: 1.02 (CI: 95% 0.96–1.10) Based on data from 2540 participants in 4 studies	851 per 1000	868 per 1000 Absolute increase: 17 more per 1000 (CI: 95% 34 fewer–85 more)	Very low Due to extremely serious imprecision	We are uncertain whether progestogens improve or worsen live birth for threatened miscarriage patients without prior miscarriage.
Live birth: pregnancies with two or more prior miscarriage without threatened miscarriage[48–50]	Relative risk: 1.08 (CI: 95% 0.98–1.19) Based on data from 1006 participants in 3 studies	708 per 1000	765 per 1000 Absolute increase: 57 more per 1000 (CI: 95% 14 fewer–135 more)	Moderate Due to serious imprecision	Progestogens probably improve live birth for patients with two or more prior miscarriage without threatened miscarriage
Live birth: pregnancies with at least one prior miscarriage (including those with recurrent miscarriage and threatened miscarriage with one or more prior miscarriages)[43,44,47–50]	Relative risk: 1.07 (CI: 95% 1.01–1.13) Based on data from 2979 participants in 6 studies	721 per 1000	771 per 1000 Absolute increase: 50 more per 1000 (CI: 95% 7 more–94 more)	Moderate Due to serious imprecision	Progestogens probably improve live birth for pregnancies with one or more prior miscarriages regardless of threatened miscarriage
Congenital abnormalities[36–38,42,44,47,48]	Relative risk: 1.06 (CI: 95% 0.76–1.48) Based on data from 6015 participants in 7 studies	22 per 1000	23 per 1000 Absolute increase: 1 more per 1000 (CI: 95% 5 fewer–11 more)	Moderate Due to serious imprecision	Progestogens probably have little or no difference on congenital abnormalities
Serious adverse events[43,49]	Relative risk: 1.07 (CI: 95% 0.83–1.40) Based on data from 4684 participants in 2 studies	27 per 1000	29 per 1000 Absolute increase: 2 more per 1000 (CI: 95% 5 fewer–11 more)	Moderate Due to serious imprecision	Progestogens probably have little or no difference on serious adverse pregnancy events

Abbreviation: CI 95%, 95% confidence intervals.

[a]The median absolute risks of the control group of included studies.

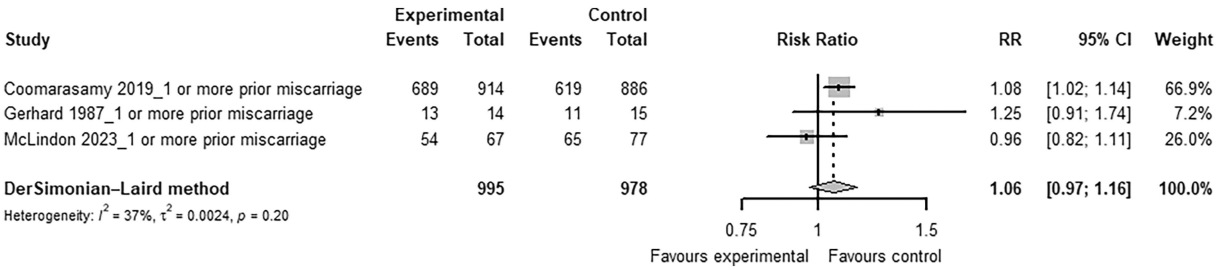

FIGURE 2 Forest plot for relative risk of live birth for progestogens compared with placebo or no treatment for threatened miscarriage patients with prior miscarriages.

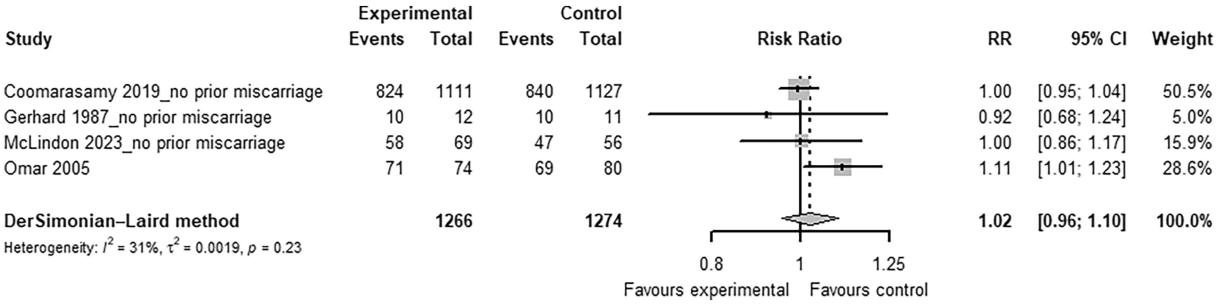

FIGURE 3 Forest plot for relative risk of live birth for progestogens compared with placebo or no treatment for patients without prior miscarriage.

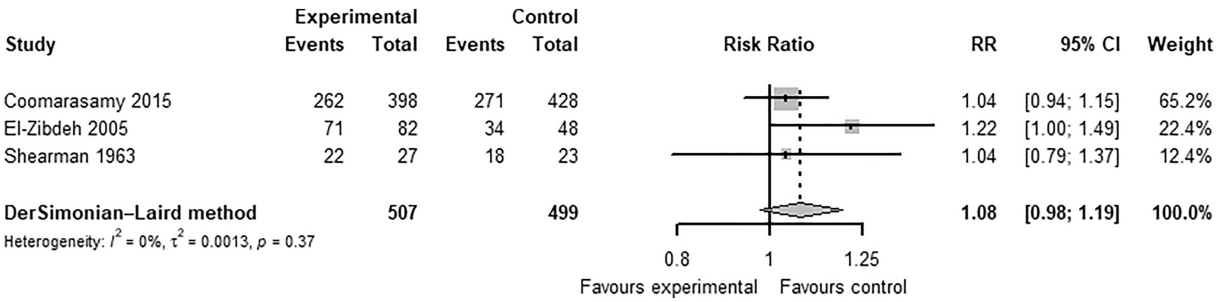

FIGURE 4 Forest plot for relative risk of live birth for progestogens compared with placebo or no treatment for pregnancies with two or more prior miscarriages without threatened miscarriage.

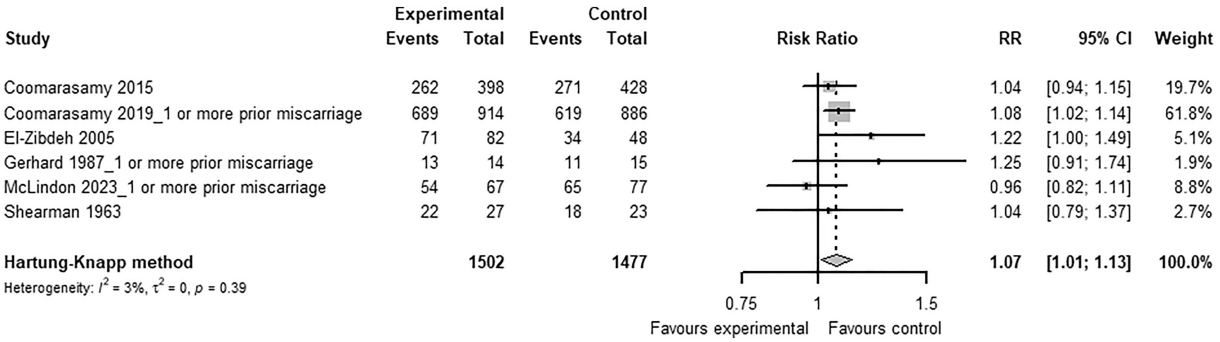

FIGURE 5 Forest plot for relative risk of live birth for progestogens compared with placebo or no treatment for pregnancies with at least one prior miscarriage (including those with recurrent miscarriage and threatened miscarriage with one or more prior miscarriages).

with progestogens improved live births (RR 1.05, 95% CI: 1.0–1.09, absolute increase 3.8, NNT 26; Figure S5; Table S2). Sensitivity analyses excluding trials with more than three domains of insufficient information[40,50] did not significantly influence the observed effects (Figure S6). The plausible worst case sensitivity analyses indicated that missing data did not significantly influence the observed effects

(Figure S7). The symmetrical funnel plot (Figure S8) and Harbord test ($p = 0.11$), suggest no publication bias. Overall, we found serious imprecision, and therefore rated the certainty of evidence of live birth as moderate (Table S2).

Figure S9 shows the subgroup analysis according to the risk of bias for allocation concealment among the pregnancies with threatened miscarriage or recurrent miscarriage. The interaction *p*-value of 0.06 suggested a possible difference between trials with high and low risk of bias for allocation concealment. However, applying ICEMAN criteria, the between-trial comparison, the plausibility of chance as an explanation, and five effect modifiers tested in the analysis, established low credibility of the subgroup effect (Text S2).

With regard to the type of progesterone, seven trials used vaginal micronized progesterone,[38,39,43–45,47,49] five used oral dydrogesterone,[36,37,40,41,50] two used oral micronized progesterone,[42,46] and one used 17-OHPC.[48] The interaction *p*-value of 0.19 failed to support a hypothesis of a subgroup effect according to the type of progestogens (Figure S10).

Five studies reported the association between progestogen intervention and live birth separately for younger and older pregnant women.[37,43,44,47,48] The within-trial comparisons provided no support for a subgroup effect among younger and older pregnant women (test of interaction $p = 0.12$; Figure S11).

Four studies reported the association between progestogen intervention and live birth separately for earlier or later gestation age at enrollment.[43,44,47,48] The within-trial comparisons of earlier gestation age and later gestation age provided no support for a subgroup effect (test of interaction $p = 0.75$; Figure S12).

Two studies separately reported the association between progestogen intervention and live birth according to BMI.[43,48] The within-trial comparisons of higher and lower BMI provided no support for a subgroup effect according to BMI (test of interaction $p = 0.14$; Figure S13).

3.2.2 | Congenital anomalies

Based on data from seven studies that reported on congenital anomalies,[36–38,42,44,47,48] progestogens probably have little or no effect on congenital anomalies (RR 1.06, 95% CI: 0.83–1.40, absolute increase 0.1%, NNT 1000; moderate certainty due to serious imprecision; Figure S14; Table 2).

3.2.3 | Serious adverse pregnancy events

Two studies reported the number of maternal and neonatal serious adverse events.[43,49] Progestogens probably result in few if any serious adverse events (RR 1.07, 95% CI: 0.83–1.40, absolute increase 0.2%, NNT 500; moderate certainty due to serious imprecision; Figure S15; Table 2).

4 | DISCUSSION

Our review provides moderate certainty evidence that progestogens probably improve live births in those with two or more prior miscarriages without threatened miscarriage, and those with at least one prior miscarriage (including those with recurrent miscarriage and threatened miscarriage with one or more prior miscarriages). We also found moderate certainty evidence that progestogens increase live births among the pregnancies with threatened miscarriages, though the inclusion of patients with prior pregnancy loss may be responsible for this benefit. The meta-analysis also provides low-certainty evidence that progestogens possibly improve live births in those with threatened miscarriages with one or more prior miscarriages (Table 2). We found that progestogens have little or no impact on serious adverse pregnancy events and have little or no difference in congenital anomalies among pregnancies with threatened miscarriages or recurrent miscarriages.

We did not find credible subgroup differences according to trials' risk of allocation concealment, the type of progestogens, patients' age, gestational age, BMI, or history of prior miscarriages for progestogens on live births. Nevertheless, results do not exclude the possibility of a subgroup effect according to history of prior miscarriages, and studies restricted to patients with prior miscarriages provided moderate certainty evidence of benefit while studies restricted to patients with threatened miscarriages who had not experienced a prior miscarriage provided only very low-certainty evidence of benefit (Table 2).

This meta-analysis represents the most comprehensive summary thus far of the impact of progestogen supplementation on threatened and recurrent miscarriage patients. Strengths of this review include a comprehensive search for eligible studies and duplicate reviewer selection, data extraction, and risk of bias assessment. We examined results in a number of subpopulations based on status regarding threatened and recurrent abortion, including on analysis with one or more prior abortions. We conducted a limited number of preplanned subgroup analyses to explore the possible effect modification according to the type of progestogens, a prior history of miscarriage, patients' age, gestational age and BMI. When possible, we assessed the subgroup effect and presented results using both relative and absolute effects (Table 2). In addition, we used the GRADE approach to assess the certainty of evidence addressing the efficiency and safety of progestogens for patients with threatened miscarriages or recurrent miscarriages (Table 2). Finally, we included both methodological and clinical considerations when presenting the evidence: although formal application of credibility criteria suggests that chance can explain apparent differences in effect between women with and without a prior history of miscarriage, we nevertheless present both overall results and results or these subgroups.

Our review also had limitations. First, only six of the 15 eligible studies presented results separately for those with and without a

prior miscarriage. Although chance easily explains differences in effects seen in the two subgroups, results do not exclude a subgroup effect which remains possible. In particular, it remains possible that benefit is restricted to those with a prior miscarriage.

Second, in studies that did not report live births or stillbirths, we regarded miscarriages and induced abortions as all pregnancy loss. In these studies, we are at risk of counting stillbirths as live births. However, the number of stillbirths, when reported, was very low, suggesting that our assumption is unlikely to have introduced appreciable bias. In addition, we conducted a sensitivity analysis for live births by excluding the trials that only reported miscarriages and not live births, and we did not find a significant difference in our outcomes.

Third, despite some of the included studies being at high risk of bias because of failure to conceal allocation, we did not rate down for risk of bias in our GRADE rating of overall quality. Support for this decision comes from our post hoc subgroup analysis demonstrating that trials that did and did not conceal allocation showed similar results.

Compared to previous systematic reviews,[8–15,51–53] we included all eligible RCTs and quasi-RCTs, used the GRADE approach, and specified a MID (1% difference in all key outcomes) as the threshold to rate the certainty of evidence. Unlike some previous reviews, we regarded live birth, rather than miscarriage, as our primary outcome.[8–10,51,53] In contrast to prior reviews, we conducted robust subgroup analyses for prior history of miscarriage, the type of progestogens,[11–15] and those with and without prior miscarriage.[54] Where possible, we conducted both within- and between-trial subgroup analyses, and acknowledged the lack of power in addressing the presence of prior miscarriage as a possible subgroup effect. Inferences from our review are consistent with those of a prior Cochrane review in which authors concluded high certainty evidence of a benefit in patients presenting with threatened abortion who had experienced a prior miscarriage.

The authors of the two largest and best conducted randomized trials appropriately concluded that results did not show a statistically significant benefit of progesterone in either the recurrent or threatened abortion population.[43,49] Results did not, however, exclude such a benefit. Indeed, the trial results are completely consistent with our pooled estimates (in the threatened abortion trial: RR 1.04, 95% CI: 0.99–1.10 [Figure 1; Table 2] in our result, RR 1.03, 95% CI: 1.00–1.07 in the previous trial[43]; in the recurrent abortion trial: RR 1.08, 95% CI: 0.98–1.19 [Figure 4; Table 2] in our result, RR 1.04, 95% CI: 0.94–1.15 in the previous trial).[49] The difference is in the interpretation: when confidence intervals cross the null only slightly, authors concluded no effect, whereas we concluded a probable or possible effect.[35]

Pregnancy loss is a common complication during pregnancy. Increasing live births without increasing the risk of congenital anomalies or severe adverse pregnancy events is the most important goal for families and clinicians. Clinical practice guidelines remain inconsistent with recommendations on progestogens supplementation for threatened and recurrent miscarriage: some guidelines suggest insufficient evidence demonstrating the benefit of progestogens for recurrent miscarriage,[55–57] whereas others suggest they may be of help.[1,7,58–60] The latest National Institute for Health and Care Excellence (NICE) guideline, based on one of the trials we found eligible,[43] recommends offering vaginal micronized progesterone twice daily only in those with early pregnancy bleeding in the setting of a previous miscarriage.[58]

In this review, we found that progestogen supplementation probably improves live births in those with two or more prior miscarriages without threatened miscarriage, at least one prior miscarriage (recurrent miscarriage and threatened miscarriage with one or more prior miscarriages) (moderate certainty of evidence), and possibly improves live births in pregnant miscarriage without prior miscarriage (low certainty of evidence). We also found moderate certainty evidence that progestogens increase live births among the pregnancies with threatened miscarriage, though the inclusion of patients with prior pregnancy loss may be responsible for this benefit. For the population with two or more prior miscarriages without threatened miscarriage, the best estimate of the absolute increase in live births is 5.7%; thus, we would need to treat 18 women with progesterone to result in a single additional live birth. For the population with at least one prior miscarriage (recurrent miscarriage and threatened miscarriage with one or more prior miscarriages), the best estimate of the absolute increase in live births is 5%; we would need to treat 20 women with progesterone to result in a single additional live birth. For the population with threatened miscarriage regardless of prior miscarriage, the best estimate of the absolute increase in live births is 3.1%; we would need to treat 32 women with progesterone to result in a single additional live birth. Given these results and the apparent absence of serious adverse effects of progestogens, and the moderate certainty evidence of benefit, most women with threatened pregnancy loss are likely to choose to receive progesterone.

Where uncertainty remains is in women who present with threatened abortion and who have not had a prior miscarriage. While our subgroup analysis failed to provide compelling evidence that the benefit would not be present in such women, neither did it exclude the possibility that women in this group would not benefit from progestogens. Thus, the most compelling question for further research would be testing progestogens in these women.

5 | CONCLUSION

Moderate certainty evidence demonstrates that progestogens probably improve live birth in those with prior pregnancy loss, have little or no difference in congenital anomalies, and have little or no impact on serious adverse pregnancy events.

AUTHOR CONTRIBUTIONS

Yunli Zhao, Gordon Guyatt and Rohan D'Souza conceived and designed the study. Yunli Zhao, Ya Gao, Lucas Kallas-Silva, Jeremy P. Steen acquired data. Yunli Zhao, Ya Gao and Qiukui Hao analyzed

the data. Yunli Zhao, Gordon Guyatt, Rohan D'Souza, Ya Gao and Qiukui Hao interpreted the data. Yunli Zhao drafted the article. Gordon Guyatt and Rohan D'Souza critically revised the article. All authors reviewed the submitted version of manuscript and approved the final version of the manuscript on behalf of all of the authors.

ACKNOWLEDGMENTS

We thank Rachel Couban (librarian at McMaster University; email: rcouban@mcmaster.ca) for assisting with developing the search strategy and Kristen Eckler for interpreting the data. Yunli Zhao and Ya Gao acknowledge funding from the China Scholarship Council.

CONFLICT OF INTEREST STATEMENT

The authors confirm there are no conflicts of interest.

ORCID

Yunli Zhao https://orcid.org/0000-0002-2621-8740

REFERENCES

1. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril*. 2012;98:1103-1111.
2. Carranza-Lira S, Blanquet J, Tserotas K, Calzada L. Endometrial progesterone and estradiol receptors in patients with recurrent early pregnancy loss of unknown etiology—preliminary report. *Med Sci Monit*. 2000;6:759-762.
3. WHO. Why we need to talk about losing a baby. Accessed September 26, 2022. https://www.who.int/news-room/spotlight/why-we-need-to-talk-about-losing-a-baby
4. Quenby S, Gallos ID, Dhillon-Smith RK, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet*. 2021;397:1658-1667.
5. Schindler AE. First trimester endocrinology: consequences for diagnosis and treatment of pregnancy failure. *Gynecol Endocrinol*. 2004;18:51-57.
6. Schindler AE. Progestogens for treatment and prevention of pregnancy disorders. *Horm Mol Biol Clin Invest*. 2010;3:453-460.
7. Schindler AE, Carp H, Druckmann R, et al. European Progestin Club Guidelines for prevention and treatment of threatened or recurrent (habitual) miscarriage with progestogens. *Gynecol Endocrinol*. 2015;31:447-449.
8. 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.
9. Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH. Progestogen for treating threatened miscarriage. *Cochrane Database Syst Rev*. 2018;8:CD005943.
10. Wang XX, Luo Q, Bai WP. Efficacy of progesterone on threatened miscarriage: difference in drug types. *J Obstet Gynaecol Res*. 2019;45:794-802.
11. Yan Y, Chen Z, Yang Y, et al. Efficacy of progesterone on threatened miscarriage: an updated meta-analysis of randomized trials. *Arch Gynecol Obstet*. 2021;303:27-36.
12. Li L, Zhang Y, Tan H, et al. Effect of progestogen for women with threatened miscarriage: a systematic review and meta-analysis. *BJOG*. 2020;127:1055-1063.
13. Saccone G, Schoen C, Franasiak JM, Scott RT Jr, Berghella V. Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials. *Fertil Steril*. 2017;107:430-438.e3.
14. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database Syst Rev*. 2019;2019:CD003511.
15. Devall AJ, Papadopoulou A, Podesek M, et al. Progestogens for preventing miscarriage: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;4:CD013792.
16. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
17. BORN Ontario. Number of Live Births and Stillbirths among Infants born in Ontario, by COVID-19 Vaccination Status. Accessed September 26, 2022. https://www.bornontario.ca/en/news/number-of-live-and-stillbirths-among-infants-born-in-ontario-by-covid-19-vaccination-status.aspx
18. CDC (US). Data and Statistics. Stillbirth is more common than people may realize. Read below for CDC's scientific findings on stillbirth. Accessed September 26, 2022. https://www.cdc.gov/ncbddd/stillbirth/data.html
19. Gordon H, Guyatt JWB. Risk of bias in randomized trials 2016. Accessed March 7, 2024. http://growthevidence.com/gordon-h-guyatt-md-msc-and-jason-w-bussedc-phd/
20. Chang Y, Kennedy SA, Bhandari M, et al. Effects of antibiotic prophylaxis in patients with open fracture of the extremities: a systematic review of randomized controlled trials. *JBJS Rev*. 2015;3:01874474-201503060-00002.
21. Spencer FA, Lopes LC, Kennedy SA, Guyatt G. Systematic review of percutaneous closure versus medical therapy in patients with cryptogenic stroke and patent foramen ovale. *BMJ Open*. 2014;4:e004282.
22. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions version 5.1.0* [updated March 2011]. The Cochrane Collaboration; 2011.
23. Bryant D, Havey TC, Roberts R, Guyatt G. How many patients? How many limbs? Analysis of patients or limbs in the orthopaedic literature: a systematic review. *J Bone Joint Surg Am*. 2006;88:41-45.
24. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol*. 2014;14:25.
25. Newcombe RG, Bender R. Implementing GRADE: calculating the risk difference from the baseline risk and the relative risk. *Evid Based Med*. 2014;19:6-8.
26. Weibel S, Popp M, Reis S, Skoetz N, Garner P, Sydenham E. Identifying and managing problematic trials: a research integrity assessment tool for randomized controlled trials in evidence synthesis. *Res Synth Methods*. 2023;14:357-369.
27. Schandelmaier S, Briel M, Varadhan R, et al. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ*. 2020;192:E901-E906.
28. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006;25:3443-3457.
29. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455-463.
30. Zeng L, Brignardello-Petersen R, Hultcrantz M, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. *J Clin Epidemiol*. 2021;137:163-175.
31. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383-394.

32. Hultcrantz M, Rind D, Akl EA, et al. The GRADE working group clarifies the construct of certainty of evidence. *J Clin Epidemiol*. 2017;87:4-13.
33. Guyatt GH, Ebrahim S, Alonso-Coello P, et al. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. *J Clin Epidemiol*. 2017;87:14-22.
34. Carrasco-Labra A, Brignardello-Petersen R, Santesso N, et al. Improving GRADE evidence tables part 1: a randomized trial shows improved understanding of content in summary of findings tables with a new format. *J Clin Epidemiol*. 2016;74:7-18.
35. Santesso N, Glenton C, Dahm P, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol*. 2020;119:126-135.
36. El-Zibdeh MY, Yousef LT. Dydrogesterone support in threatened miscarriage. *Maturitas*. 2009;65(Suppl 1):S43-S46.
37. Chan DMK, Cheung KW, Ko JKY, et al. Use of oral progestogen in women with threatened miscarriage in the first trimester: a randomized double-blind controlled trial. *Hum Reprod*. 2021;36:587-595.
38. Alimohamadi S, Javadian P, Gharedaghi MH, et al. Progesterone and threatened abortion: a randomized clinical trial on endocervical cytokine concentrations. *J Reprod Immunol*. 2013;98:52-60.
39. Yassaee F, Shekarriz-Foumani R, Afsari S, Fallahian M. The effect of progesterone suppositories on threatened abortion: a randomized clinical trial. *J Reprod Infertil*. 2014;15:147-151.
40. Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. *J Steroid Biochem Mol Biol*. 2005;97:421-425.
41. Pandian RU. Dydrogesterone in threatened miscarriage: a Malaysian experience. *Maturitas*. 2009;65(Suppl 1):S47-S50.
42. Turgal M, Aydin E, Ozyuncu O. Effect of micronized progesterone on fetal-placental volume in first-trimester threatened abortion. *J Clin Ultrasound*. 2017;45:14-19.
43. Coomarasamy A, Devall AJ, Cheed V, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med*. 2019;380:1815-1824.
44. Gerhard I, Gwinner B, Eggert-Kruse W, Runnebaum B. Double-blind controlled trial of progesterone substitution in threatened abortion. *Biol Res Pregnancy Perinatol*. 1987;8:26-34.
45. Palagiano A, Bulletti C, Pace MC, Ziegler DE, Cicinelli E, Izzo A. Effects of vaginal progesterone on pain and uterine contractility in patients with threatened abortion before twelve weeks of pregnancy. *Ann N Y Acad Sci*. 2004;1034:200-210.
46. Søndergaard F, Ottesen BS, Detlefsen GU, Pedersen SC, Schierup L, Lebech PE. Treatment with progesterone in threatened abortion and low level of serum progesterone. A double-blind randomized trial. In: Harrison RF, Bonnar J, Thompson W, eds. *Vitro Fertilizátion, Embryo Transfer and Early Pregnancy. Studies in Fertility and Sterility*. Vol 1. Springer; 1985.
47. McLindon LA, James G, Beckmann MM, et al. Progesterone for women with threatened miscarriage (STOP trial): a placebo-controlled randomized clinical trial. *Hum Reprod*. 2023;38:560-568.
48. El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. *J Steroid Biochem Mol Biol*. 2005;97:431-434.
49. Coomarasamy A, Williams H, Truchanowicz E, et al. A randomized trial of progesterone in women with recurrent miscarriages. *N Engl J Med*. 2015;373:2141-2148.
50. Shearman RP, Garrett WJ. Double-blind study of effect of 17-hydroxyprogesterone caproate on abortion rate. *Br Med J*. 1963;1:292-295.
51. Carp H. A systematic review of dydrogesterone for the treatment of recurrent miscarriage. *Gynecol Endocrinol*. 2015;31:422-430.
52. Guo H, Lu Q. Efficacy of dydrogesterone on treating recurrent miscarriage and its influence on immune factors: a systematic review and meta-analysis. *Ann Palliat Med*. 2021;10:10971-10985.
53. Zhao H, He W, Yang Z. A pairwise and network meta-analysis comparing the efficacy and safety of progestogens in threatened abortion. *Int J Gynaecol Obstet*. 2022;156:383-393.
54. Coomarasamy A, Devall AJ, Brosens JJ, et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. *Am J Obstet Gynecol*. 2020;223:167-176.
55. Royal College of Obstetricians and Gynecologists. *The Investigation and Treatment of Couples with Recurrent First-Trimester and Secondtrimester Miscarriage*. Royal College of Obstetricians and Gynaecologists; 2011.
56. ESHRE Recurrent Pregnancy Loss Guideline Development Group: Regan L, Rai R, Saravelos S, Li TC, Royal College of Obstetricians and Gynaecologists. *Recurrent pregnancy loss*. Recurrent Miscarriage. Green-top Guideline No. 17. BJOG; 2023.
57. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Gynecology. ACOG practice bulletin no. 200: early pregnancy loss. *Obstet Gynecol*. 2018;832:e197-e207.
58. American College of Obstetricians and Gynecologists. ACOG practice bulletin no. 200: early pregnancy loss. *Obstet Gynecol*. 2018;132:e197-e207.
59. Northern Ireland Public Health Agency. *Recurrent Pregnancy Loss Care Pathway for Northern Ireland*. Public Health Agency Belfast; 2020.
60. *Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management*. National Institute for Health and Care Excellence (NICE); 2021.

SUPPORTING INFORMATION

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

How to cite this article: Zhao Y, D'Souza R, Gao Y, et al. Progestogens in women with threatened miscarriage or recurrent miscarriage: A meta-analysis. *Acta Obstet Gynecol Scand*. 2024;103:1689-1701. doi:10.1111/aogs.14829