Micronized vaginal progesterone to prevent miscarriage

a critical evaluation of randomized evidence

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Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence

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Progesterone is essential for the maintenance of pregnancy. Several small trials have suggested that progesterone supplementation may reduce the risk of miscarriage in women with recurrent or threatened miscarriage. Cochrane Reviews summarized the evidence and found that the trials were small with substantial methodologic weaknesses. Since then, the effects of first-trimester use of vaginal micronized progesterone have been evaluated in 2 large, high-quality, multicenter placebo-controlled trials, one targeting women with unexplained recurrent miscarriages (the PROMISE [PROgesterone in recurrent MIScarriagE] trial) and the other targeting women with early pregnancy bleeding (the PRISM [PRogesterone In Spontaneous Miscarriage] trial). The PROMISE trial studied 836 women from 45 hospitals in the United Kingdom and the Netherlands and found a 3% greater live birth rate with progesterone but with substantial statistical uncertainty. The PRISM trial studied 4153 women from 48 hospitals in the United Kingdom and found a 3% greater live birth rate with progesterone, but with a *P* value of .08. A key finding, first observed in the PROMISE trial, and then replicated in the PRISM trial, was that treatment with vaginal micronized progesterone 400 mg twice daily was associated with increasing live birth rates according to the number of previous miscarriages. Pre-specified PRISM trial subgroup analysis in women with the dual risk factors of previous miscarriage(s) and current pregnancy bleeding fulfilled all 11 conditions for credible subgroup analysis. For the subgroup of women with a history of 1 or more miscarriage(s) and current pregnancy bleeding, the live birth rate was 75% (689/914) with progesterone vs 70% (619/886) with placebo (rate difference 5%; risk ratio, 1.09, 95% confidence interval, 1.03—1.15; *P*=.003). The benefit was greater for the subgroup of women with 3 or more previous miscarriages and current pregnancy bleeding; live birth rate was 72% (98/137) with progesterone vs 57% (85/148) with placebo (rate difference 15%; risk ratio, 1.28, 95% confidence interval, 1.08—1.51; *P*=.004). No short-term safety concerns were identified from the PROMISE and PRISM trials. Therefore, women with a history of miscarriage who present with bleeding in early pregnancy may benefit from the use of vaginal micronized progesterone 400 mg twice daily. Women and their care providers should use the findings for shared decision-making.

Key words: bleeding, luteal phase deficiency, meta-analysis, recurrent miscarriage, threatened miscarriage, vaginal micronized progesterone

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Progesterone is essential for the establishment and maintenance of a pregnancy.[1] Withdrawal of progesterone in early pregnancy typically results in a miscarriage, and antiprogesterone drugs are powerful inducers of abortion. The central role of progesterone in early pregnancy led clinicians and researchers to hypothesize that progesterone deficiency could be a cause of some miscarriages. This hypothesis has resulted in numerous clinical trials of progesterone supplementation in women at high risk of miscarriage. The 2 groups of women at particular risk of miscarriage are those who have a history of recurrent miscarriage and those who are bleeding in early pregnancy. The first randomized trial in women with recurrent miscarriage was published in 1953, and 11 trials followed in the subsequent decades.[2] The first trial in women with threatened miscarriage was published in 1987, and since then 7 further trials have been conducted.[3] However, these trials used different progestogens and were small and methodologically weak, producing heterogenous and unreliable results. Policy makers have therefore been unable to make evidence-based recommendations on the use of progestogen supplementation to improve outcomes in these cohorts of women. For instance, the American College of Obstetricians and Gynecologists reviewed the evidence in 2015 and concluded that "For threatened early pregnancy loss, the use of progestins is controversial, and conclusive evidence supporting their use is lacking. Women who have experienced at least three prior pregnancy losses, however, may benefit from progesterone therapy in the first trimester."[4] Similarly, in the United Kingdom, the National Institute for Health and Care Excellence concluded in 2012 that "a very large multicentre randomised controlled trial of women receiving treatment with either progesterone/progestogen or placebo for threatened miscarriage should be conducted."[5] The PROMISE (PROgesterone in recurrent MIScarriagE) and PRISM (PRogesterone In Spontaneous Miscarriage) trials were conducted to generate robust evidence on the role of progesterone therapy to prevent miscarriage and increase the live birth rate.

In this review, we critically evaluate the results from the PROMISE and PRISM trials to assess what they add to our existing knowledge. We move beyond statistical inference to provide a full scientific inference by taking into account the context, biological rationale, biological gradient, external evidence, and consistency across the studies.[6] We assess the evidence for key prespecified subgroup effects using robust guidelines.[7–9] Finally, we provide our recommendations for clinical practice.

Statistical and Scientific Inferences

The *New England Journal of Medicine* article on the PRISM trial noted a 3% increase in live birth rate with vaginal micronized progesterone, but suggested it was a negative result, as the *P* value associated with this finding was .08.[10] However, our interpretation of the PRISM trial in this review takes into account the totality of available evidence, suggesting a potential role for progesterone for women at high risk of a miscarriage. We propose the apparent discordance between the published *New England Journal of Medicine* manuscript[10] and our interpretation relates to the issue of statistical inference vs scientific inference. Statistical inference focuses on hypothesis testing. Scientific inference, in contrast, not only considers any statistical uncertainty in the findings but in addition takes into account the full extent of all other evidence, to make a considered judgemnt. The American Statistical Association (ASA) has issued a series of 44 instructive articles on drawing scientific inferences from studies.[11] Appreciation of the key messages from these ASA articles is essential for making clinical sense of the PROMISE and PRISM trials.

The ASA's statements recommend that "scientific conclusions or policy decisions should not be based on only whether a *P*-value passes a specific threshold" and "no single index should substitute for scientific reasoning."[11] Further, the ASA states that "practices that reduce data analysis or scientific inference to mechanical 'bright-line' rules (such as $P<.05$, or equivalent confidence intervals) for justifying scientific claims or conclusions can lead to erroneous beliefs and poor decision making."[11] The ASA notes "a conclusion doesn't immediately become 'true' on one side of the divide ($P<.05$) and 'false' on the other," and the ASA recommends that phrases such as "statistically significant" and "statistically nonsignificant" are no longer used. Instead, the ASA recommends that researchers bring many contextual factors into play to derive scientific inferences, including the design of the study, replicability, and other external evidence.

The PROMISE Trial

The PROMISE Trial[12] is a well-powered randomized trial in women with recurrent miscarriage (Table 1). It is a high-quality trial, with computer-generated third-party randomization, allocation concealment, double-blinding, placebo-control, excellent follow-up rate, and a prespecified statistical analysis plan that was diligently implemented.

The primary analysis of the PROMISE trial found the live birth rate was 66% (262/398) in the progesterone group vs 63% (271/428) in the placebo group (risk ratio [RR], 1.04, 95% confidence interval [CI], 0.94−1.15, $P=.45$). There was a 3% greater live birth rate with progesterone, but the trial finding was reported as not statistically significant due to the large *P* value ($P=.45$) and the consequent statistical uncertainty. We then performed a prespecified subgroup analysis by the number of previous miscarriages; the study population was split into 2 subgroups; one included women who had 3 previous miscarriages and the other included women who had $\geq$4 miscarriages. We also performed a post-hoc subgroup analysis by 3, 4, 5, and $\geq$6 previous miscarriages. We understood that the post-hoc analysis would be underpowered and could only be used for hypothesis generation but considered that such an analysis would still be useful for assessing a biological gradient in these subgroups. The findings (Figure 1) appeared to suggest a

TABLE 1
PROMISE trial: vaginal micronized progesterone in women with unexplained recurrent miscarriages

Population	Women with unexplained recurrent miscarriages (≥3 consecutive or nonconsecutive miscarriages), trying to conceive naturally
Intervention	400 mg of micronized progesterone taken vaginally twice daily from no later than 6 weeks until 12 weeks of gestation
Comparison	Placebo
Primary outcome	Live birth beyond 24 weeks
Sample size and power	836 patients randomized; 90% power to detect a 10% difference in live births
Hospitals and countries	36 hospitals in the United Kingdom and 9 hospitals in the Netherlands

PROMISE, PROgesterone in recurrent MIScarriagE.

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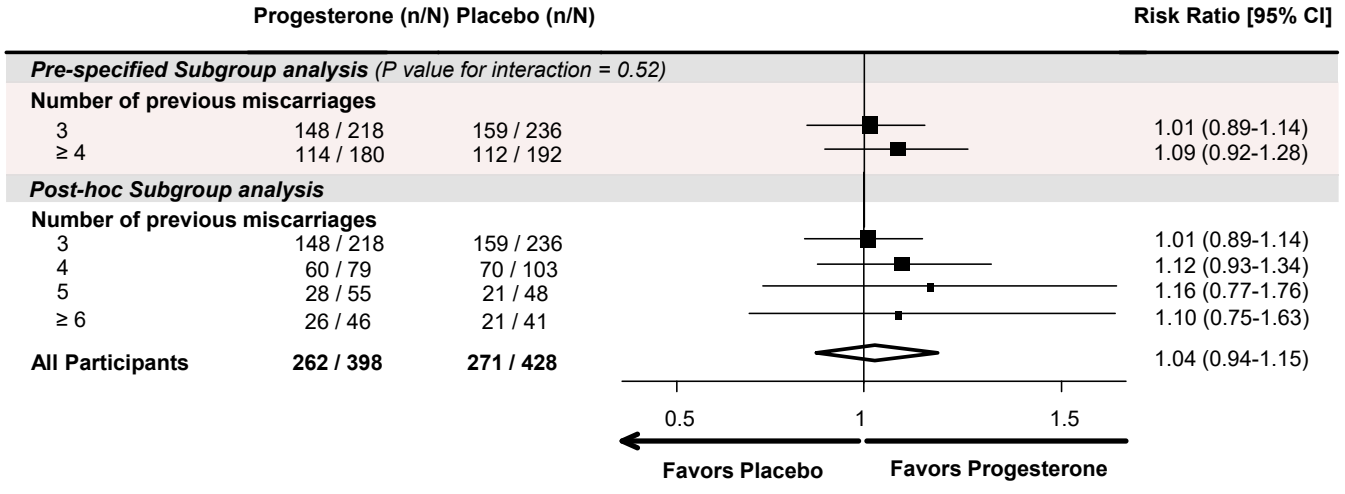
trend for greater benefit with increasing number of previous miscarriages. Although the small sample sizes in the subgroups and the large *P* value for test of subgroup interaction (*P*=.41) suggested an inconclusive subgroup effect, the findings generated a hypothesis that a subgroup effect existed with a biological gradient related to the increasing number of previous miscarriages. As Rothwell published, "The best test of validity of subgroup-treatment effect interactions is their reproducibility in other trials."[7] We were able to assess the reproducibity of this subgroup effect by the increasing number of previous miscarriages in the PRISM trial.[10]

The PRISM Trial

The PRISM trial is a well-powered randomized trial in women with threatened miscarriage (Table 2). It was designed and conducted with methodologic rigor, with appropriate randomization, allocation concealment, double-blinding with placebo control, excellent follow-up rate, and analysis according to a prespecified statistical analysis plan.

The primary analysis of PRISM trial found that the live birth rate was 75% (1513/2025) in the progesterone group vs 72% (1459/2013) in the placebo group (RR, 1.03; 95% CI, 1.00−1.07, *P*=.08). For the prespecified subgroup analysis by the number of previous miscarriages, the study population was split into 3 subgroups: women without a history of miscarriage; women with 1 or 2 previous miscarriages; and women with ≥3 previous miscarriages, as shown in Figure 2. There were 2 post-hoc subgroup analyses: the first grouping women into those who had no previous miscarriage or those who had any number of previous miscarriages; and the second grouping women by 0, 1, 2, ≥3 previous miscarriages, to explore in detail for a possible biological gradient (Figure 2). The *P* values for "subgroup by treatment" interactions were consistent with differential subgroup effects. The live birth rate was 75% (689/914) with

FIGURE 1
PROMISE trial data on live birth >24 weeks by the number of previous miscarriages



CI, confidence interval; *PROMISE*, PROgesterone in recurrent MIScarriagE.

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TABLE 2
PRISM trial: vaginal micronized progesterone in women with threatened miscarriages

Population	Women with vaginal bleeding during the first 12 weeks of pregnancy
Intervention	400 mg of micronized progesterone taken vaginally or rectally twice daily from randomization until 16 weeks of gestation
Comparison	Placebo
Primary outcome	Live birth ≥34 weeks
Sample size and power	4153 patients randomized, 90% power to pick up a 5% difference in live births
Hospitals	48 hospitals in the United Kingdom

PRISM, PRogesterone In Spontaneous Miscarriage.

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progesterone vs 70% (619/886) with placebo (RR, 1.09; 95% CI, 1.03−1.15; *P*=.003) for the subgroup of women with 1 or more previous miscarriage(s) and bleeding in the current pregnancy (number needed to treat = 20; 95% CI, 19−22). The benefit was even greater for the subgroup of women with 3 or more previous miscarriages and current pregnancy bleeding; live birth rate was 72% (98/137) with progesterone vs 57% (85/148) with placebo (RR, 1.28; 95% CI, 1.08−1.51; *P*=.004; number needed to treat = 8, 95% CI, 7−10).

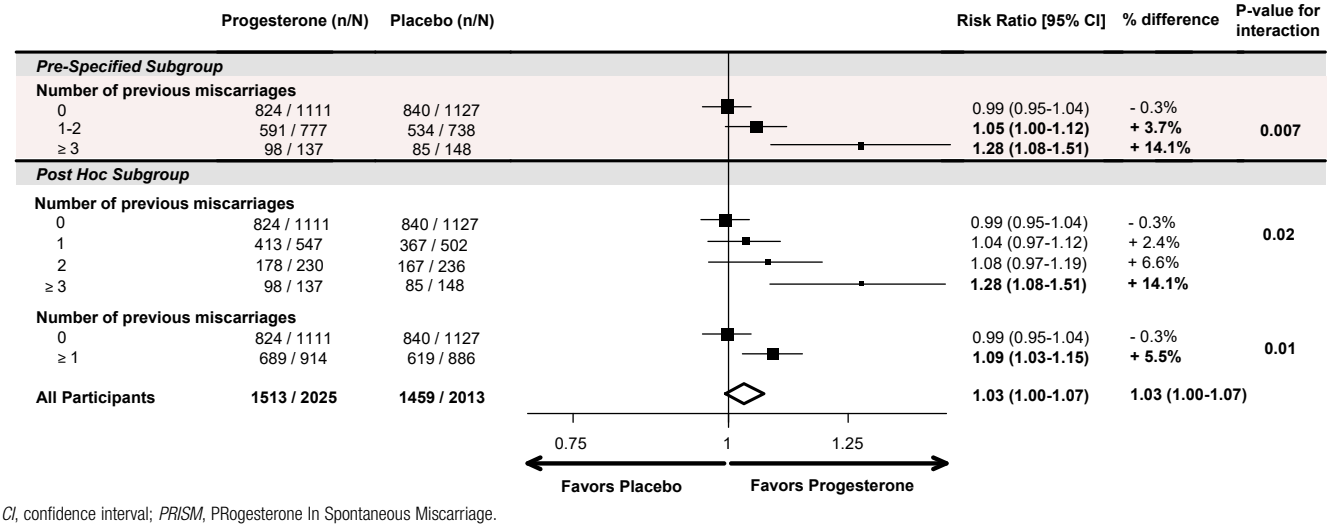
The findings of the post-hoc subgroup analyses were in line with the prespecified subgroup analyses. Whether we consider the prespecified or the post-hoc subgroup analyses, in all of these analyses there is a relationship between the number of previous miscarriages and the effect of progesterone, as was already observed in the PROMISE trial (see Supplemental Materials and Methods).

The PRISM Trial Subgroup by Number of Previous Miscarriages: Credibility

When should one believe a subgroup analysis? Subgroup analyses can suffer from false-positive results because of multiple comparisons or false-negative results from inadequate power. So, robust guidelines have been developed to aid in the interpretation of subgroup analysis.[7–9] These guidelines translate into 11 criteria, 5 on design, 2 on analysis, and 4 on the context.[8] We applied these 11 criteria to the PRISM trial subgroup analysis by number of previous miscarriages to assess the credibility of the subgroup findings.

1. *Is the subgroup variable a characteristic measured at baseline?* Subgroups can be defined by features measured at baseline before randomization, or by features emerging after randomization. As postrandomization features can be influenced by the intervention itself the validity of findings from subgroups that rely on postrandomization features can be compromised. For our subgroups, the number of miscarriages is known at baseline, before randomization, thus this criterion is fulfilled.

FIGURE 2
PRISM trial data on live birth >34 weeks by the number of previous miscarriages



CI, confidence interval; *PRISM*, PRogesterone In Spontaneous Miscarriage.

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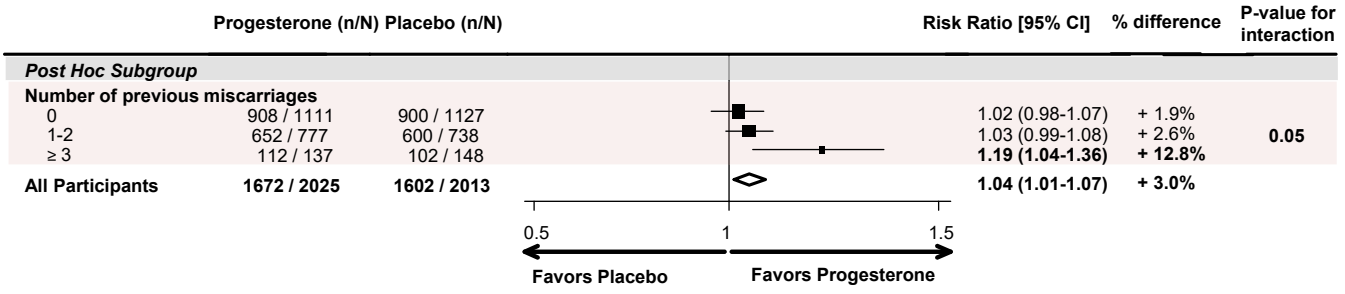
2. *Is the effect suggested by comparisons within rather than between studies?* A subgroup effect observed only between studies, and not within a study, is unreliable as the subgroup effect may be due to the heterogeneity that is often present between various studies. A subgroup effect found within an individual study is more credible. The subgroup effect we identified was within the PRISM study itself, so this criterion is met.
3. *Was the hypothesis specified a priori?* The hypothesis was prespecified in date-stamped presentations, before the allocation codes were unblinded for the PRISM trial (on June 28, 2018).
4. *Was the direction of the subgroup effect specified a priori?* The direction of the effect was indicated in date-stamped presentations before the allocation codes were unblinded (on June 28, 2018).
5. *Was the subgroup effect one of a small number of hypothesised effects tested?* There were 10 prespecified subgroup analyses in the PRISM protocol, but only one was considered to be of special clinical interest; the remaining subgroup analyses were useful for consistency checking across the subgroups. The distinction between subgroups of "special interest" and subgroups for "consistency checking" was not addressed in the PRISM study protocol but was documented in date-stamped presentations, predating the unblinding of PRISM Trial results on June 28, 2018.
6. *Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?* The interaction test *P* value for the subgroups by the number of previous miscarriages was .007, suggesting that it is unlikely that chance explains the observed subgroup effect. In contrast, the subgroup interaction *P* value was larger than .1 for all the other prespecificed subgroups, suggesting a subgroup effect was unlikely for all the other subgroup analyses.
7. *Is the significant subgroup effect independent?* Two, or more, subgroup effects may be related to each other in such a way that one common factor explains the subgroup findings. We adjusted for confounding by key prognostic variables, such as female age, presense of fetal heart activity at presentation, estimated gestation at presentation, and amount of (patient-reported) bleeding, and this did not result in any material change in the interaction test *P* value.
8. *Is the size of the subgroup effect large?* The relative risk for those with 1 or 2 miscarriages was 1.05 (95% CI, 1.00−1.12) and a 5% difference was considered important in a survey of clinicians before the PRISM trial was conducted. For those with 3 or more miscarriages, the RR was 1.28 (95% CI, 1.08−1.51). The effect size is larger for those with a greater number of previous miscarriages.
9. *Is the interaction consistent across the studies?* Increasing benefit with increasing number of prior miscarriages was noted in the PROMISE trial (Figure 1) and the PRISM trial (Figure 2). The replication of the subgroup effect (along with the presence of a biological gradient) among 2 independent, high-quality trials gives confidence to the finding of this subgroup effect.
10. *Is the interaction consistent across closely related outcomes within the study?* We explored this question by conducting subgroup analyses on the outcomes of ongoing pregnancy at 12 weeks, and miscarriage at gestations less than 24 weeks; these 2 outcomes are closely related to live birth. A subgroup effect by the number of previous miscarriages was observed for the outcomes of ongoing pregnancy and miscarriage. We observed an increase in ongoing pregnancies and a decrease in miscarriages according to the number of previous miscarriages; these findings are consistent with the observed live birth subgroup effect (Figures 3 and 4).
11. *Is there indirect evidence that supports the hypothesized interaction (biological rationale)?* There is very good biological reasoning to expect greater effect from progesterone in those with increasing numbers of previous miscarriages. Euploid miscarriage is more likely with increasing number of previous miscarriages (Figure 5).[13] As one of the causes of euploid miscarriage is hypothesized to be luteal phase defect, progesterone can be expected to have greater benefit in those with greater number of previous miscarriages. Furthermore, luteal phase defect is likely to present with vaginal bleeding, thus greater benefit from progesterone use can be expected in women with early pregnancy bleeding.

Guidelines on the interpretation of subgroup effects note that "Debates about subgroup effects may be framed in terms of absolute acceptance or rejection"[8] but such "yes versus no polarised approach is undesirable and destructive, mainly because it ignores the uncertainty that is inevitably part of such judgments."[8] Furthermore, "An approach that is more productive and more realistic is to place the likelihood that a subgroup effect is real on a continuum from 'highly plausible' to 'extremely unlikely'.... the question is then a decision of where on this continuum a putative subgroup effect lies."[8] We propose the subgroup effect first suggested in the PROMISE trial, and then confirmed in the PRISM trial is highly plausible.[14]

Synthesis of External Evidence

There are several studies of micronized vaginal progesterone and other progestogens. Most of these studies are small and of limited methodologic quality. We synthesized the evidence from the PROMISE and PRISM studies first (Figure 6), following which we added the external evidence from other studies of progesterone or progestogens (Figure 7) to check for consistency in the findings across the various studies. The studies were broadly consistent in showing a benefit on live birth or ongoing pregnancy rate from the first-trimester use of progesterone or progestogens, giving further confidence in our findings.

FIGURE 3
Ongoing pregnancy at 12 weeks by the number of previous miscarriages



CI, confidence interval.

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Discussion

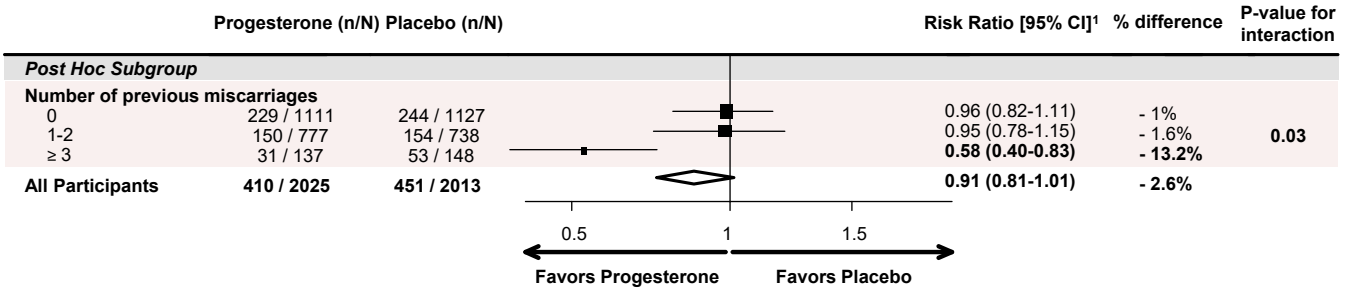
The role of first-trimester progesterone supplementation in the treatment of pregnancies at high risk of miscarriage is a long-standing research question that has been debated in the medical literature for more than 60 years. The PROMISE and PRISM trials are 2 very high-quality trials that have addressed the effects of first-trimester use of vaginal micronized progesterone treatment in women at risk of a miscarriage.

Biologic plausibility

Approximately one half of all miscarriages, including pregnancy losses in women with recurrent miscarriage, are due to numeric chromosome errors with trisomy being the most frequent, especially with advancing maternal age, followed by polyploidy and monosomy X.[15] Such "aneuploid" miscarriages are thought to occur on a random basis, meaning that the risk of subsequent miscarriage is not increased. "Euploid" miscarriages, in contrast, are more frequently diagnosed with increasing number of previous miscarriages, as shown in Figure 5.

A progesterone-related problem, often given the name "luteal phase defect" (LPD), is considered to be one of the causes of a euploid miscarriage. The corpus luteum in the ovary produces progesterone during early pregnancy. Progesterone is essential for maintaining the decidua, and it is hypothesized that a defect in the function of the corpus luteum can result in low progesterone levels which in turn may increase the risk of miscarriage.[15] However, there is no clear definition for LPD, and there are certainly no reliable tests to identify patients who may have the condition. Serum and salivary progesterone have been used[16,17]; however, the diagnostic and prognostic value of the progesterone level has remained unclear.[17,18] Furthermore, direction of causality confounds interpretation of a progesterone result, ie, if the progesterone level is found to be low in early pregnancy, we cannot know whether the low progesterone is the cause or effect of a miscarriage. Histologic assessment of the endometrium, initially proposed by Noyes et al. in 1950,[19] has been shown to have high interobserver and intraobserver variation and poorly discriminates between fertile and infertile women; therefore, molecular-based alternatives, in addition to histologic assessment, are being developed. The endometrium is a dynamic

FIGURE 4
Miscarriage <24 weeks by the number of previous miscarriages



CI, confidence interval.

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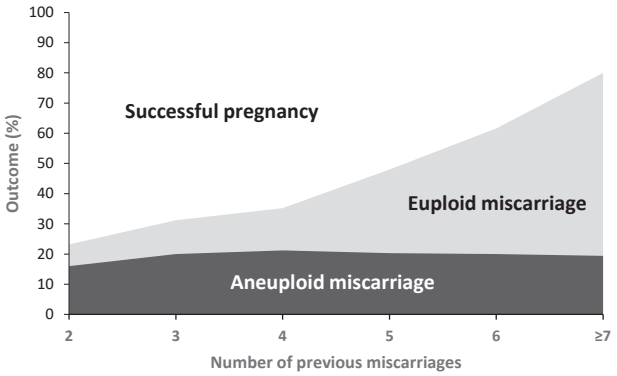
mixture of cells, primarily glandular and stromal, that undergo cycles of proliferation, differentiation, and menstruation. Timed evaluation of the endometrium, particularly in the luteal phase, is being evaluated critically to identify "endometrial factors" associated with recurrent pregnancy loss.

A study by Stephenson et al. reported on 116 women with a history of recurrent early pregnancy loss who were evaluated in the mid-luteal phase with an endometrial biopsy for histologic and immunohistochemical staining for nuclear CyclinE expression of the endometrial glands.[20,21] Luteal phase start vaginal micronized progesterone 100 mg every 12 hours was prescribed based on elevated nuclear CyclinE expression, with a repeat endometrial biopsy recommended on the first treatment cycle, and with increased dosage of progesterone if CyclinE expression did not normalize. The live birth rate was greater in women prescribed luteal phase start vaginal micronized progesterone compared with controls, 68% vs 51%; OR, 2.1 (95% CI, 1.0–4.4). From a biological plausibility perspective, serial endometrial biopsies showed the use of vaginal micronized progesterone resulted in decreased or normalization of nuclear CyclinE expression in 84% of women with initially elevated expression of this molecular marker.

FIGURE 5
Miscarriage risk by the number of previous miscarriages



Redrawn, with permission, from Ogasawara et al.[13]

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Target populations for progesterone therapy

The absence of a meaningful test for LPD left researchers with the challenge of not knowing which patients to target with progesterone treatment. Researchers over the past 6 decades responded to this challenge by targeting "enriched" populations, in whom the overall risk of miscarriage is greater than the unselected population, and any pathology causing miscarriage, including LPD, could reasonably be expected to be more prevalent. The 2 key populations targeted for enrichment were women with previous recurrent miscarriages and women with early pregnancy bleeding, the 2 target populations for the PROMISE and PRISM trials, respectively.

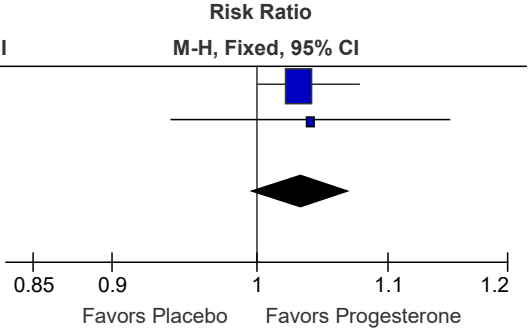
A history of previous miscarriage identifies those at risk of a future miscarriage, and the risk of a future miscarriage increases with the increasing number of previous miscarriages (Figure 8). Specifically, it is the risk of euploid miscarriages that increases with increasing number of previous miscarriages; meanwhile, the risk of miscarriage from sporadic aneuploidies remains broadly constant (Figure 5). This biological gradient increases our

FIGURE 6
Live birth outcome of PROMISE and PRISM trial data

Study or Subgroup	Progesterone Events	Progesterone Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
PRISM 2019 (a)	1513	2025	1459	2013	84.9%	1.03 [1.00, 1.07]
PROMISE 2015 (b)	262	398	271	428	15.1%	1.04 [0.94, 1.15]
Total (95% CI)		**2423**		**2441**	**100.0%**	**1.03 [1.00, 1.07]**
Total events	1775		1730			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%

Test for overall effect: Z = 1.78 (P = 0.08)



Footnotes

(a) Live birth after 34 weeks of gestation; adjusted for minimization variables. (b) Live birth after 24 weeks of gestation.

CI, confidence interval; *PRISM*, PRogesterone In Spontaneous Miscarriage; *PROMISE*, PROgesterone in recurrent MIScarriagE.

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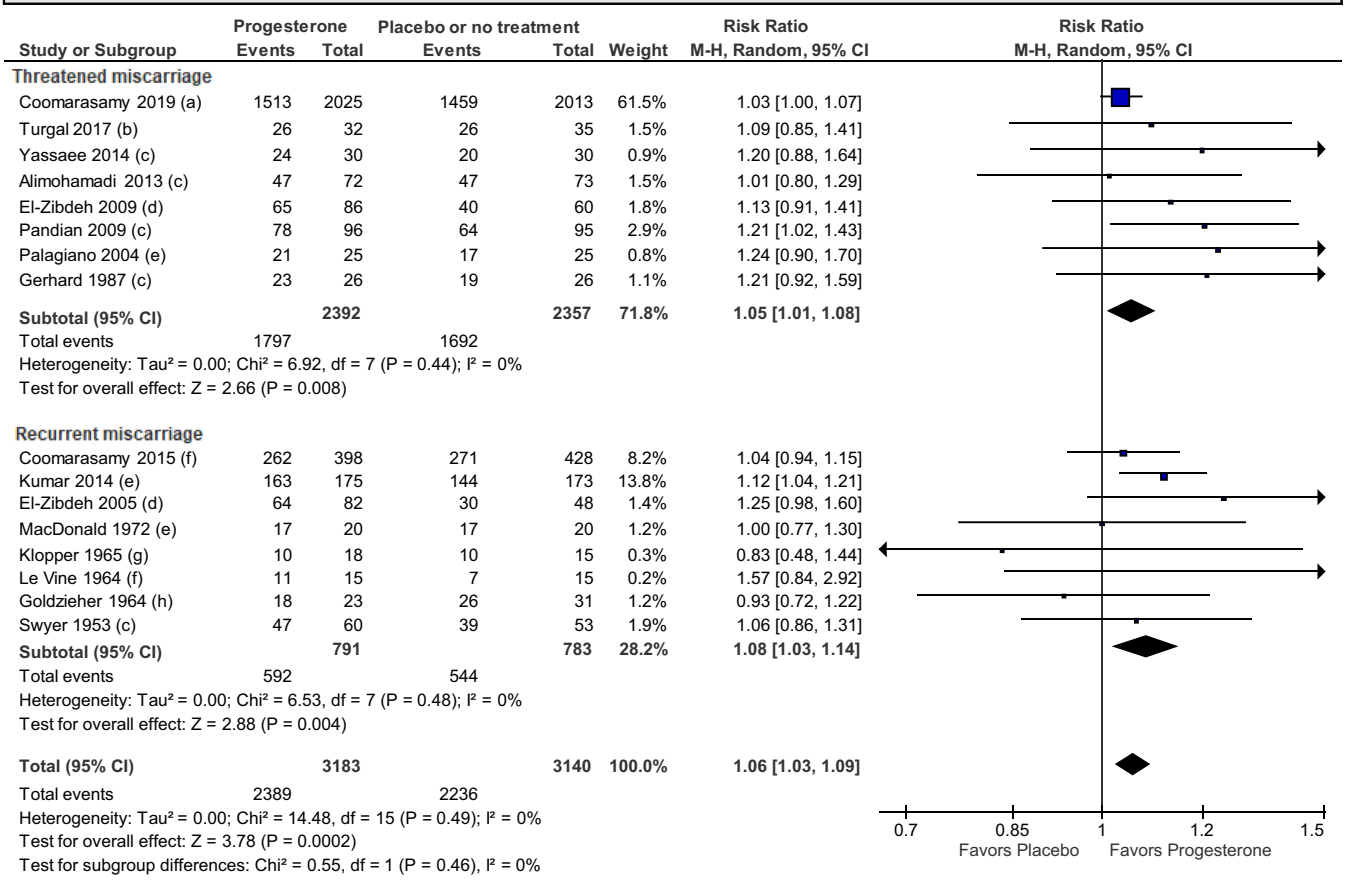
FIGURE 7
Live birth or ongoing pregnancy outcome for all progesterone and progestogen studies



Footnotes
(a) Live birth after 34 weeks of gestation; adjusted for minimization variables. (b) Term live births. Re-included 11 miscarriages that were excluded after randomisation. (c) Term live births. (d) Quasi-randomised trial; term live births. (e) Ongoing pregnancies not clearly defined by the authors. (f) Live birth after 24 weeks of gestation. (g) Ongoing pregnancies over 18 weeks of gestation. (h) Term births.

CI, confidence interval.

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confidence that the history of previous miscarriage is a valid prognostic marker for future miscarriage. If one of the causes of miscarriage is LPD, then the prevalence of LPD can be expected to increase with the increasing number of previous miscarriages. Given this biological understanding and the hypothesis generated from the PROMISE trial findings, we considered the number of previous miscarriages as the most important subgroup in the PRISM study.[10]

Type of progestogen used in the PROMISE and PRISM trials

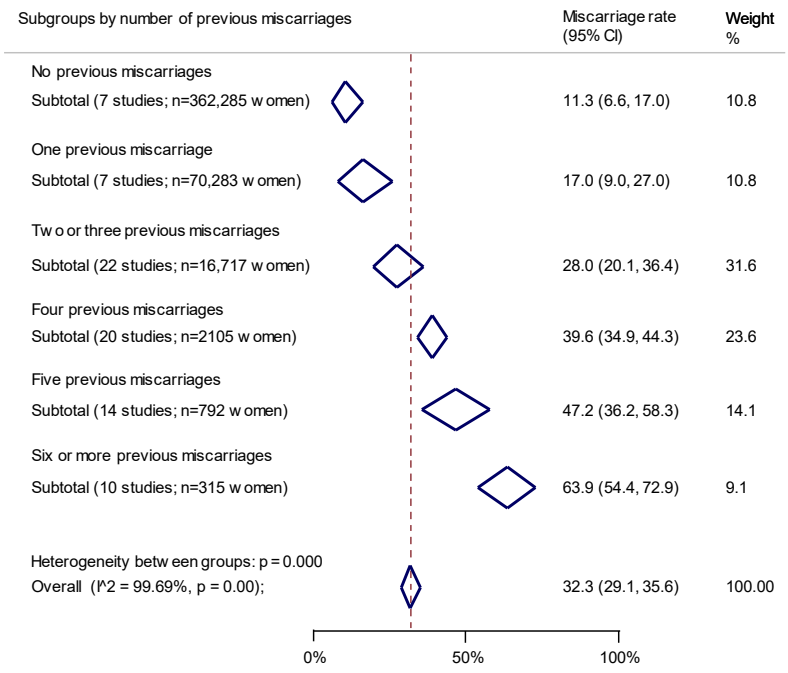
We used vaginal, micronized progesterone in the PROMISE and PRISM trials. The results from these trials are not necessarily generalizable to progestogens such as dydrogestone or 17-hydroxyprogesterone. The natural progesterone used in the PROMISE and PRISM trials is derived from soybeans and Mexican yam roots and has an identical chemical structure to physiological progesterone synthesised in the human body.[22] Synthetic progestogens, which include dydrogesterone and 17-hydroxyprogesterone, have a different molecular structure, pharmacodynamics and pharmacokinetics, as well as a different safety profile.[23] We have restricted our analysis to progesterone, and our data do not support or refute the role of other progesterone-like compounds.

Implications for clinical practice

In summary, the PRISM and PROMISE trials found a small but positive treatment effect that seems to be dependent on the number of miscarriages. Our analysis did not suggest any benefit from progesterone therapy for women with early pregnancy bleeding but no history of miscarriages. We believe that the dual risk factors of early pregnancy bleeding and a history of one or more previous miscarriage(s) identify high-risk women in whom progesterone is of benefit. The question is how this should affect clinical practice. We recommend that the information should be communicated to women at high risk of miscarriages to enable shared decision-making. Our

suggestion is to consider offering to women with vaginal bleeding and a history of 1 or more previous miscarriage(s) a course of treatment with vaginal micronized progesterone 400 mg twice daily, started at the time of presentation with vaginal bleeding and continued to 16 completed weeks of gestation. In the United Kingdom, we estimate that implementing this treatment strategy would result in an additional 8450 live births per year. We believe that a woman at high risk of having a miscarriage may not need absolute scientific certainty to choose to have a treatment. If she is informed about the uncertainty around treatment effects and available safety data, then she could decide for herself the right course of action. Policy makers and guideline developers will need to consider the evidence carefully to make a balanced recommendation.

FIGURE 8
Risk of miscarriage by the number of previous miscarriages



Systematic review methods: Databases: MEDLINE, EMBASE, CCTR, CDSR, DARE; Search period: From respective database inception to June 2019; Search terms (MESH): Recurrent miscarriage (habitual abortion, pregnancy loss, fetal loss, foetal loss, fetal demise, foetal loss) AND prediction and prognosis (significance, score, marker, role, index, indicator, nomogram, forecast, goal, calculate, estimate, project, likelihood, extrapolate, implication or prototype); Review Outcome: Miscarriage categorised by previous number previous pregnancy losses.

Systematic review methods: Databases: MEDLINE, EMBASE, CCTR, CDSR, DARE; Search period: From respective database inception to June 2019; Search terms (MeSH): Recurrent miscarriage (habitual abortion, pregnancy loss, fetal loss, foetal loss, fetal demise, foetal loss) AND prediction and prognosis (significance, score, marker, role, index, indicator, nomogram, forecast, goal, calculate, estimate, project, likelihood, extrapolate, implication or prototype); Review Outcome: miscarriage categorised by previous number previous pregnancy losses.

CCTR, Cochrane Controlled Trials Register; *CDSR*, Cochrane Database of Systematic Reviews; *CI*, confidence interval; *DARE*, Database of Abstracts of Reviews of Effectiveness; *MeSH*, Medical Subject Headings.

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Implications for research

Further research is required to enhance our understanding of LPD and develop and validate tests to identify women with LPD-related pregnancy losses. The increased effectiveness of progesterone with increasing number of miscarriages indicates that endometrial defects are a major driver of higher-order miscarriages. Yet, even after multiple miscarriages, the live birth rate and cumulative live birth rate in these patients remain high. Presumably this means that the underlying endometrial defect is intermittent rather than persistent; and that its frequency (ie, number of "normal" vs "abnormal" cycles) determines the likelihood of miscarriage. This disease model is compatible with emerging biology demonstrating that the tissue homeostasis in the cycling endometrium is dependent on recruitment of bone marrow–derived stem cells and uterine natural killer cells. Both "homeostatic" mechanisms are perturbed in recurrent miscarriage.[24–26] A "dynamic" disease model may help to explain the failure of current diagnostic approaches, such as screening for luteal-phase defects.

Currently, we rely on clinical history to profile patients who may have a high risk of progesterone-related problems. However, this is imprecise. Accurate endometrial tests may allow more precise targeting of patients who may benefit from progesterone treatment. Karyotyping all pregnancy losses may also help to better risk-stratify women who may benefit from progesterone therapy; the role of routine karyotyping using modern genetic analysis needs further research, including the health economic implications of such an approach. Our research focused on first-trimester use of progesterone; research is also needed to explore the effects of luteal phase progesterone use. Development and validation of tests, and therapeutic trials to determine the efficacy of luteal phase progesterone and other potential inteventions, are needed. Finally, the PROMISE and PRISM trials did not find any evidence of an increase in congenital abnormalites or short-term harm. The PROMISE trial, involving 836 participants, found no difference between the treatment and the placebo group for the outcomes of "any congenital anomaly"

(8/266 progesterone arm, 11/276 placebo arm, P=.54) and "genital congenital anomaly" (1/266 progesterone arm, 1/276 placebo arm, P=.98).[12] The PRISM study, involving 4153 women, found no difference between women treated with vaginal micronized progesterone and those receiving placebo for the outcome of "congenital, familial, and genetic disorders" (23/2025 progesterone arm, 22/2013 placebo arm, P=.90).[10] However, we recommend long-term follow up studies of babies exposed to first-trimester progesterone. ■

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