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

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Objective: To investigate whether treatment with progestogens in the first trimester of pregnancy would decrease the incidence of miscarriage in women with a history of unexplained recurrent miscarriage.
Design: Systematic review and meta-analysis.
Setting: Not applicable.
Patient(s): Women with a history of unexplained recurrent miscarriage.
Intervention(s): Randomized, controlled trials were identified by searching electronic databases. We included randomized, controlled trials comparing supplementation with progestogens (i.e., intervention group) in the first trimester of pregnancy with control (either placebo or no treatment) in women with a history of recurrent miscarriage. All types of progestogens, including natural P and synthetic progestins, were analyzed.
Main Outcome Measure(s): The primary outcome was the incidence of miscarriage. The summary measures were reported as relative risk (RR) with 95% confidence interval (CI).
Result(s): Ten trials including 1,586 women with recurrent miscarriage were analyzed. Eight studies used placebo as control and were double-blind. Regarding the intervention, two RCTs used natural P, whereas the other eight studies used progestins: medroxyprogesterone, cyclopentylenol ether of progesterone, dydrogesterone, or 17-hydroxyprogesterone caproate. Pooled data from the 10 trials showed that women with a history of unexplained recurrent miscarriage who were randomized to the progestogens group in the first trimester and before 16 weeks had a lower risk of recurrent miscarriage (RR 0.72, 95% CI 0.53–0.97) and higher live birth rate (RR 1.07, 95% CI 1.02–1.15) compared with those who did not. No statistically significant differences were found in the other secondary outcomes, including preterm birth (RR 1.09, 95% CI 0.71–1.66), neonatal mortality (RR 1.80, 95% CI 0.44–7.34), and fetal genital abnormalities (RR 1.68, 95% CI 0.22–12.62).
Conclusion(s): Our findings provide evidence that supplementation with progestogens may reduce the incidence of recurrent miscarriages and seem to be safe for the fetuses. Synthetic progestogens, including weekly IM 17-hydroxyprogesterone caproate, but not natural P, were associated with a lower risk of recurrent miscarriage. Given the limitations of the studies included in our meta-analysis, it is difficult to recommend route and dose of progestogen therapy. Further head-to-head trials of P types, dosing, and route of administration are required. (Fertil Steril® 2017;107:430–8. ©2016 by American Society for Reproductive Medicine.)
Key Words: Abortion, endocrinology, meta-analysis, progesterone, review

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Recurrent miscarriage (or recurrent pregnancy loss) is defined by the American Society for Reproductive Medicine as the loss of two or more pregnancies before 24 weeks (1, 2). It affects approximately 1% to 2% of women who attempt to have a child (1, 2). Unexplained recurrent miscarriage is associated with substantial adverse clinical and psychological consequences for women and their families (1–3). Various therapeutic strategies to increase the rate of live births among these women have been evaluated, but no effective treatment has been identified (1–3).

Progestogens (or progestagens or gestagens), including P, are a class of steroid hormones essential to achieve and maintain a healthy pregnancy.(4) The efficacy of P therapy has been studied in several populations (5, 6), including women with prior preterm birth (7), women with short cervical length (8), women with threatened miscarriage (9), and as maintenance tocolysis in women with arrested preterm labor (10, 11). However, the efficacy of P supplementation in the first trimester of pregnancy among women with a history of recurrent miscarriage is still a matter of debate (1–3, 12).

The aim of this systematic review and meta-analysis of randomized, controlled trials (RCTs) was to investigate whether treatment with progestogens in the first trimester of pregnancy would decrease the incidence of miscarriage in women with a history of unexplained recurrent miscarriage.

MATERIALS AND METHODS

Eligibility Criteria

The review protocol was established by two investigators (G.S., V.B.) before commencement and was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no. CRD42016033721).

Two authors (G.S., V.B.) identified trials by searching independently the electronic databases MEDLINE, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, EMBASE, Scielo, and the Cochrane Central Register of Controlled Trials with the use of a combination of text words: "progesterone," "miscarriage," "progesteron," "recurrent," "pregnancy," "progestogens," "progestagens," "gestagens," "loss," "vaginal," "termination of pregnancy," "17P," "17-OHPC," "hydroxyprogesterone," "caproate," "alpha," "injection" "trial," "gel," "singleton," "multiple," and "habitual" from inception of each databases until January 2016. No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches.

Study Selection

We included RCTs comparing supplementation with progestogens (i.e., intervention group) in the first trimester of pregnancy with control (either placebo or no treatment) in women with a history of recurrent miscarriage, either consecutive or nonconsecutive. The definition of recurrent miscarriage was per the original trial design, which included either two or more or three or more losses. Trials in which recurrent miscarriage was defined as one miscarriage or more were excluded. All progestogens types were included, both natural P and synthetic progestogens (i.e., progestins), including but not limited to 17-α-hydroxyprogesterone-caproate (17-OHPC) and dydrogesterone. Studies in women with threatened miscarriage were excluded.

Data Extraction and Risk of Bias Assessment

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (13). Seven domains related to risk of bias were assessed in each included trial because there is evidence that these issues are associated with biased estimates of treatment effect: [1] random sequence generation; [2] allocation concealment; [3] blinding of participants and personnel; [4] blinding of outcome assessment; [5] incomplete outcome data; [6] selective reporting; and [7] other bias. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias (13).

Two authors (G.S., V.B.) independently assessed inclusion criteria, risk of bias, and data extraction. Disagreements were resolved by consensus. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Differences were reviewed and further resolved by common review of the entire process.

Primary and secondary outcomes were defined before data extraction. The primary outcome was the incidence of miscarriage, as defined by the authors. Secondary outcomes included incidence of live birth, as defined by the authors; preterm birth in women without miscarriage (i.e., preterm delivery $<$37 weeks); neonatal mortality (defined as a death of a live-born baby within the first 28 days of life); and fetal genital abnormalities/virilization. We planned to assess the primary outcome (i.e., incidence of miscarriage) in planned subgroup analyses classifying whole trials by interaction tests as described by the *Cochrane Handbook for Systematic Review of Interventions* (13). The subgroup analyses entailed [1] placebo-controlled trials only; [2] route of administration of progestogen: oral, intramuscular, or vaginal; [3] type of progestogens: natural P or synthetic progestins; [4] type of progestogens: natural P, medroxyprogesterone, cyclopentyl enol ether of P, dydrogesterone, or 17-OHPC; and [5] definition of recurrent miscarriage: two or more or three or more losses.

Only the primary outcome (i.e., incidence of miscarriage) was used in the subgroup analyses.

Data Analysis

The data analysis was completed independently by two authors (G.S., V.B.) using Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014) (13). The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Higgins I^2 statistic (13). In case of statistically significant heterogeneity (moderate ($70\% \leq I^2 \geq 50\%$) to high ($I^2 \geq 70\%$) heterogeneity) the random effect model of

TABLE 1

Studies assessed for the eligibility criteria.

First author and year (reference)	Included/excluded	Reason for exclusion
Swyer 1953 (29)	Included	–
Shearman 1963 (22)	Included	–
Le Vine 1964 (28)	Included	–
Goldzieher 1964 (26)	Included	–
Klopper 1965 (18)	Included	–
Moller 1965 (9)	Excluded	Inclusion criteria: All women with positive pregnancy test
MacDonald 1972 (19)	Included	–
Berle 1980 (15)	Excluded	Inclusion criteria: Women presenting with threatened miscarriage, defined as bleeding up to 20 wk
Tognoni 1980 (23)	Excluded	Inclusion criteria: Women presenting with threatened miscarriage, defined as bleeding up to 14 wk
Gerhard 1987 (17)	Excluded	Inclusion criteria: Women presenting with threatened miscarriage, defined as bleeding up to 20 wk
Reijnders 1988 (21)	Included	–
Corrado 2002 (16)	Excluded	Inclusion criteria: Women undergoing amniocentesis
Nyboe Anderson 2002 (20)	Excluded	Inclusion criteria: All women having undergone assisted reproductive technology
El-Zibdeh 2005 (25)	Included	–
Kumar 2014 (27)	Included	–
Coomarasamy 2015 (24)	Included	–

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DerSimonian and Laird was used to obtain the pooled risk estimate. In cases of no inconsistency in the risk estimate (I^2 <50%) a fixed effect model was managed (13). The summary measures were reported as relative risk (RR) with 95% confidence interval (CI), with an RR <1 indicating treatment benefit. Potential publication biases were assessed graphically by using the funnel plot of the primary outcome and statistically by using Begg's and Egger's tests (13). A *P* value of <.05 was considered statistically significant.

The meta-analysis was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement (14).

RESULTS

Study Selection and Study Characteristics

Supplemental Figure 1 (available online) shows the flow diagram (PRISMA template) of information through the different phases of the review. Sixteen trials were assessed for eligibility (Table 1) (9, 15–29). Six studies were excluded (9, 15–17, 20, 23). Ten randomized trials including 1,586 women with recurrent miscarriage were analyzed (18, 19, 21, 22, 24–29). None of the included studies had high risk of bias in "selective reporting" and "allocation concealment" (selection bias). Eight studies were double-blind (Supplemental Fig. 2) (18, 19, 21, 22, 24, 26–28). Supplemental Figure 3 shows the funnel plot of the primary outcome for assessing publication bias; the symmetric plot suggests no publication bias. Publication bias, assessed using Begg's and Egger's tests, showed no significant bias (*P*=.79 and *P*=.73, respectively).

Table 2 shows the characteristics of the included trials. All studies had incidence of recurrent miscarriage as primary outcome. Only one study excluded women who had experienced a live birth (18). Eight trials only accepted women within the first trimester of pregnancy (18, 19, 21, 22, 24, 25, 27, 29), whereas Le Vine et al. (28) accepted women to the 20th gestational week. It was unclear in the remaining study what gestational cutoff, if any, was used (26).

In one trial participants were excluded from randomization if they had antiphospholipid syndrome or other recognized thrombophilia conditions, as well as uterine cavity abnormalities or other identifiable cause of recurrent miscarriage, such as diabetes, thyroid disease, or systematic lupus erythematous; or if they were currently receiving heparin therapy or had contraindications to P use (24).

Six trials defined recurrent miscarriage as history of three or more miscarriage (24–29), four as history of two or more miscarriage (18, 19, 21, 22). Five RCTs came from the United Kingdom (18, 19, 22, 24, 29), two from the United States (26, 28), one from India (27), one from the Netherlands (21), and one from Jordan (25).

Eight studies used placebo as control (18, 19, 21, 22, 24, 26–28). Regarding the intervention, two RCTs used natural P (24, 29), whereas the other eight studies used progestins (i.e., synthetic progestogens) (18, 19, 21, 22, 25–28). One trial used 6 × 25-mg natural P pellets inserted within the gluteal muscle (29), two used 17-OHPC 500 mg weekly IM (21, 28), one a dosing scale of 17-OHPC (22), two used dydrogesterone 10 mg two times daily orally (25, 27), one used cyclopentyl enol ether of P 50 mg twice daily orally (18), one used 2 × 5-mg tablets of dydrogesterone three times daily (19), and one used medroxyprogesterone 10 mg daily (26), whereas Coomarasamy et al. (24) randomized women to receive twice-daily vaginal suppositories containing either 400 mg of micronized P or matched placebo. In all 10 trials the intervention started soon after the pregnancy was confirmed and not later the first trimester.

Data regarding the use of heparin and/or aspirin were only described in one study (24). Coomarasamy et al. reported the use of aspirin in 75 women (38 in the P group

TABLE 2

Characteristics of the included trials.

First author and year (reference)	Study location	No. of patients at randomization	Inclusion criteria and definition of recurrent miscarriage	Definition of miscarriage	Definition of live birth	GA at randomization	Intervention	Control	Duration of intervention	Primary outcome
Swyer 1953 (29)	United Kingdom	47 (27/20)	Women with three or more prior consecutive miscarriages	Pregnancy loss before 22 wk	Delivery of a live infant after 22 wk	As soon as pregnancy confirmed and not later than 10th wk	6 × 25-mg natural P pellets inserted within the gluteal muscle	No treatment	Unclear	Miscarriage
Shearman 1963 (22)	United Kingdom	50 (27/23)	Women with two or more prior consecutive miscarriages	Pregnancy loss before 21 wk	Delivery of a live infant after 21 wk	As soon as pregnancy confirmed and not later than 12th wk	17P IM Up to 8 wk: 250 mg/wk 8–11 wk: 375 mg/wk 12–16 wk: 500 mg/wk 17–20 wk: 375 mg/wk 21–24 wk: 250 mg/wk	Placebo	Until miscarriage or the 24th wk	Miscarriage
Le Vine 1964 (28)	US	30 (15/15)	Women with three or more prior consecutive miscarriages	Pregnancy loss before 21 wk	Delivery of a live infant after 21 wk	Within the 16th wk	17P 500 mg/wk IM	Placebo	Until miscarriage or the 36th wk	Miscarriage
Goldzieher 1964 (26)	US	18 (8/10)	Women with two or more prior consecutive miscarriages	Pregnancy loss before 22 wk	Delivery of a live infant after 22 wk	Within the 14th wk	Medroxyprogesterone 10 mg/daily oral	Placebo	Unclear	Miscarriage
Klopper 1965 (18)	United Kingdom	33 (18/15)	Women with two or more prior consecutive miscarriages	Pregnancy loss before 22 wk	Delivery of a live infant after 22 wk	As soon as pregnancy confirmed and not later than 10th wk	Cyclopentyl enol ether of P 50 mg BID oral	Placebo	Unclear	Miscarriage
MacDonald 1972 (19)	United Kingdom	40 (20/20)	Women with two or more prior consecutive miscarriages	Pregnancy loss before 22 wk	Delivery of a live infant after 22 wk	Unclear	2 × 5-mg oral tablets of dydrogesterone 3 times daily	Placebo	Unclear	Miscarriage
Reijnders 1988 (21)	Netherlands	64 (32/32)	Women with two or more prior consecutive or nonconsecutive miscarriage	Pregnancy loss before 24 wk	Delivery of a live infant after 24 wk	As soon as pregnancy confirmed and not later than 6th wk	17P 500 mg/wk IM	Placebo	From the 7th wk to the 12th wk	Miscarriage

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TABLE 2

Continued.

First author and year (reference)	Study location	No. of patients at randomization	Inclusion criteria and definition of recurrent miscarriage	Definition of miscarriage	Definition of live birth	GA at randomization	Intervention	Control	Duration of intervention	Primary outcome
El-Zibdeh 2005 (25)	Jordan	130 (82/48)	Women <35 y with three or more prior consecutive miscarriages	Pregnancy loss before 24 wk	Delivery of a live infant after 24 wk	As soon as pregnancy confirmed	Dydrogesterone 10 mg BID oral until 12 wk	No treatment	Until miscarriage or the 12th wk	Miscarriage
Kumar 2014 (27)	India	348 (175/173)	Women with three or more prior consecutive miscarriages	Pregnancy loss before 14 wk	–	As soon as pregnancy confirmed and not later than 10th wk	Dydrogesterone 10 mg BID oral	Placebo	Until miscarriage or the 20th wk	Miscarriage
Coomarasamy 2015 (24)	United Kingdom	826 (398/428)	Women with three or more prior consecutive or nonconsecutive miscarriages	Pregnancy loss before 14 wk	Delivery of a live infant after 24 wk	As soon as pregnancy confirmed	Vaginal natural P 400 mg twice daily	Placebo	Until miscarriage or the 12th wk	Miscarriage
Total	–	1,399 (705/694)			–	–	–	–	–	–

Note: Data are presented as total number (n progestogens group/control group). GA = gestational age.

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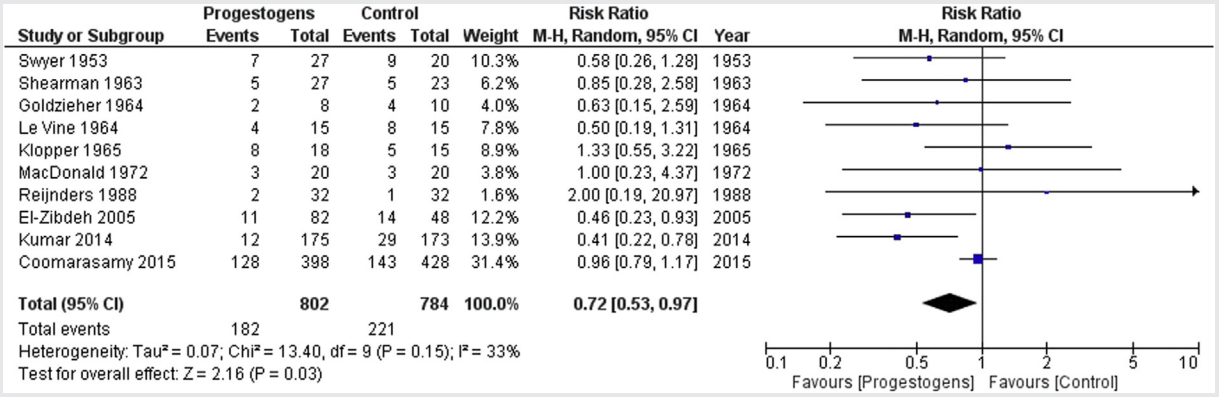
FIGURE 1



Forest plot for the risk of recurrent miscarriage in women with unexplained recurrent miscarriage. df = degrees of freedom; M-H = Mantel-Haenszel.

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and 37 in the placebo group) and explicitly excluded women who were receiving heparin therapy (24). Three studies reported support or sponsorship from pharmaceutical companies (19, 22, 26).

Synthesis of Results

Of the 1,586 women included in the meta-analysis, 802 (50.5%) were randomized to the intervention group, 784 (49.5%) to the control group. The pooled analysis of the primary outcome (i.e., incidence of miscarriage) is shown in Figure 1. Women with a history of unexplained recurrent miscarriage who were randomized to the intervention group had a lower risk of recurrent miscarriage (RR 0.72, 95% CI 0.53–0.97; Fig. 1) and higher live birth rate (RR 1.07, 95% CI 1.02–1.15) compared with those who did not. No statistically significant differences were found in the other secondary outcomes, including preterm birth (RR 1.09, 95% CI 0.71–1.66), neonatal mortality (RR 1.80, 95% CI 0.44–7.34), and fetal genital abnormalities (RR 1.68, 95% CI 0.22–12.62). Statistical heterogeneity within the studies was moderate for the primary outcome and low for the secondary outcomes (Table 3).

Subgroup analysis of placebo-controlled trials (RR 0.80, 95% CI 0.70–0.97) (18, 19, 21, 22, 24, 26–28), oral progestogens (RR 0.61, 95% CI 0.38–0.98) (18, 19, 25–27), IM progestogens (RR 0.54, 95% CI 0.29–0.94) (21, 22, 28, 29), and synthetic progestogens (RR 0.35, 95% CI 0.23–0.52) (18, 19, 21, 22, 25–28) concurred with the overall analysis. However, no statistically significant differences were found in subgroup analyses of vaginal P (RR 0.96, 95% CI 0.79–1.17) (24) or natural P (RR 0.94, 95% CI 0.77–1.13) (24, 29). Five different type of progestogens were used: natural P, medroxyprogesterone, cyclopentyl enol ether of P, dydrogesterone, and 17-OHPC. However, pooled data were available only for two types of progestins, 17-OHPC and dydrogesterone. Subgroup analyses of IM 17-OHPC (either dose scale or 500 mg weekly) (21, 22, 28) and of oral dydrogesterone (either 2 × 5-mg tablet three times daily or 10 mg twice daily) (19, 25, 27) both concurred with the overall analysis (RR 0.69, 95% CI 0.35–0.88; and RR 0.47, 95% CI 0.30–0.73, respectively). Subgroup analysis according to definition of recurrent miscarriage supported the overall analysis for trials in which recurrent miscarriage was defined as a history of three or more prior miscarriages (RR 0.60, 95% CI 0.40–0.91) (24–29) but not for trials in which recurrent miscarriage was defined as a history of two or more prior miscarriages (RR 1.14, 95% CI 0.62–2.09) (18, 19, 21, 22).

DISCUSSION

Main Findings

This meta-analysis from the 10 RCTs, including 1,586 women, showed that progestogens in women with at least two or three prior miscarriages were associated with lower risk of recurrent miscarriages and seemed to be safe to use during the first trimester. Synthetic progestogens therapy but not natural P supplementation was associated with a lower risk of recurrent miscarriage. Notably, progestogens reduced the risk of miscarriage in studies in which recurrent miscarriage was defined as a history of three or more miscarriages but not in studies in which it was defined as a history of two or more miscarriages.

Comparison with Existing Literature

Our meta-analysis supported earlier findings of a Cochrane review (12) of four small trials (25, 26, 28, 29), showing a significantly lower risk of miscarriage among those who received progestogens compared with placebo or no treatment (odds ratio 0.39, 95% CI 0.21–0.72), whereas it did not concur with a new large, well-designed RCT from the United Kingdom (24). Indeed, Coomarasamy et al. (24) showed that P therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births

TABLE 3

Primary and secondary outcomes in the overall analysis.

First author and year (reference)	Miscarriage	Live birth	PTB < 37 wk	Neonatal mortality	Fetal genital abnormalities/ virilization
Swyer 1953 (29)	7/27 (25.9) vs. 9/20 (45.0)	20/27 (74.1) vs. 11/20 (55.0)	2/20 (10.0) vs. 1/11 (9.1)	1/20 (5.0) vs. 0/11	Not reported
Shearman 1963 (22)	5/27 (18.5) vs. 5/23 (21.7)	22/27 (81.5) vs. 18/23 (78.3)	Not reported	Not reported	Not reported
Le Vine 1964 (28)	4/15 (26.7) vs. 8/15 (53.3)	11/15 (73.3) vs. 7/15 (46.7)	6/11 (54.5) vs. 3/7 (42.9)	Not reported	0/11 vs. 0/7
Goldzieher 1964 (26)	2/8 (25.0) vs. 4/10 (40.0)	6/8 (75.0) vs. 6/10 (60.0)	1/6 (16.7) vs. 1/6 (16.7)	Not reported	Not reported
Klopper 1965 (18)	8/18 (44.4) vs. 5/15 (33.3)	10/18 (55.6) vs. 10/15 (66.7)	Not reported	Not reported	Not reported
MacDonald 1972 (19)	3/20 (15.0) vs. 3/20 (15.0)	17/20 (85.0) vs. 17/20 (85.0)	Not reported	Not reported	Not reported
Reijnders 1988 (21)	2/32 (6.3) vs. 1/32 (3.1)	30/32 (93.7) vs. 31/32 (96.9)	1/32 (3.1) vs. 1/32 (3.1)	1/32 (3.1) vs. 0/32	1/32 (3.1) vs. 0/32
El-Zibdeh 2005 (25)	11/82 (13.4) vs. 14/48 (77.8)	71/82 (86.6) vs. 34/48 (22.2)	5/71 (70) vs. 3/34 (8.8)	2/71 (2.8) vs. 1/34 (2.9)	0/71 vs. 0/34
Kumar 2014 (27)	12/175 (6.9) vs. 29/173 (16.8)	Not reported	Not reported	Not reported	Not reported
Coomarasamy 2015 (24)	128/398 (32.2) vs. 143/428 (33.4)	262/398 (68.8) vs. 271/428 (63.3)	27/262 (10.3) vs. 25/271 (9.2)	1/261 (0.4) vs. 0/269	1/266 (0.4) vs. 1/276 (0.4)
Total	182/802 (22.7) vs. 221/784 (28.2)	449/627 (71.6) vs. 405/611 (66.3)	42/402 (10.4) vs. 34/361 (9.4)	5/384 (1.3) vs. 1/346 (0.3)	2/380 (0.5) vs. 1/349 (0.3)
I^2 (%)	33	10	0	0	0
RR (95% CI)	0.72 (0.53–0.97)[a]	1.07 (1.02–1.15)[a]	1.09 (0.71–1.66)	1.80 (0.44–7.34)	1.68 (0.22–12.62)

Note: Data are presented as number (percentage) progestogens group vs. control group except where otherwise noted. PTB = preterm birth.
[a] Statistically significant.

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among women with prior unexplained recurrent miscarriage. However, they studied a vaginal preparation of P, at a dose of 400 mg twice daily, which may be not generalizable to women receiving other doses and preparations. Some studies indeed have suggested that IM preparations of P and synthetic progestins may provide greater therapeutic effect than vaginal and natural preparations, respectively (5, 30–32).

Strengths and Limitations

Our study has several strengths. This meta-analysis included all RCTs published to date on the topic. The number of randomized women was high. To our knowledge, no prior meta-analysis on this issue is as large, up to date, or comprehensive. We assessed the primary outcome in several subgroup analyses, to reduce the clinical heterogeneity among the trials. Intent-to-treat analysis was used, and both random and fixed effects models were used when appropriate. In addition, publication bias was not apparent by statistical analysis. Statistical heterogeneity among the studies was variable but generally not significant. These are key elements that are needed to evaluate the reliability of a meta-analysis (13).

Limitations of our study are inherent to the limitations of the included RCTs. The first and most important limitation is the age of the included studies. Seven of the ten were published before 1990; that is, before the days when randomized trials had any chance of being conducted to any degree of quality. This limitation raises the question of the translation of these data to today's clinical management and of the poor quality of the majority of the studies. The PROMISE trial, the largest and most recent trial, recruited more than the other trials put together and was negative (24). Although this may be due to the use of natural P, the effect may have occurred because synthetic progestogens studies are older, generally smaller, and of lower quality.

Only eight trials were double-blind. The studies span a period of more than 60 years. Search strategies for retrieving RCTs in electronic databases are limited, and this could have influenced our findings. More than half of the women included in the analysis (826 of the 1,586) came from one large trial (24). The literature on P use can be divided into replacement and supplementation. This meta-analysis focuses on supplementation. Further, different preparations, routes, and doses of progestogens, as well as different durations of treatment, were used, so it is unclear which of these should be preferred. This would only be effectively answered with a head-to-head trial of different formulations, dosages, and routes, although it does appear, as stated above, that the synthetic, rather than natural, P preparations would be preferred according to the literature to date. All the trials initiated treatment after pregnancy was confirmed, and therefore our meta-analysis cannot address whether progestogens could be more effective if administered during the luteal phase of the cycle, before the confirmation of pregnancy (33–35). No trial reported long-term follow-up, so the long-term safety of the intervention is still not well known.

Implications

Progesterone is essential to achieve and maintain a healthy pregnancy. It is known to induce secretory changes in the lining of the uterus essential for successful implantation of a fertilized egg (3, 4). It has been suggested that a causative factor in many cases of miscarriage may be inadequate secretion of P during the luteal phase of the menstrual cycle and in the early weeks of pregnancy (1). Therefore, progestogens have been used beginning in the first trimester of pregnancy in an attempt to prevent spontaneous miscarriage (1, 12). Their use is particularly common with assisted reproductive technologies (12, 31, 32). However, notably, it has been estimated that, in more than half of miscarriages, a chromosomal abnormality is present, and this could explain the percentage of nonresponsive women (1, 12).

Progestogens can be classified as natural or synthetic (30, 36). Natural compounds, including natural P, are those with chemical structures similar to those produced by living organisms. Synthetic progestogens (or progestins), including 17-OHPC, are compounds generated in the laboratory whose structures have been modified and do not correspond to a naturally occurring steroid (30, 36). Natural P and 17-OHPC have different physiologic properties and pharmacologic profiles (30, 36) and therefore different indications for their use in obstetrics and gynecology (5, 6, 10, 11, 30, 36–38). Natural P suppresses myometrial contractility in strips that were obtained at time of cesarean delivery, whereas 17-OHPC does not have this effect and at high concentration stimulates myometrial contractility. In pregnant animals and in vitro experimentation, P but not 17-OHPC inhibits cervical ripening. However, the effects of the two compounds are complex and dependent on the route of administration and the vehicle used (36). Luteal phase insufficiency is one of the reasons for implantation failure and has been responsible for miscarriage and unsuccessful assisted reproduction (29, 34). Moreover, IM progestogens result in a higher plasma concentration, and the level is maintained for a longer duration compared with vaginally administered P (32). Progesterone is essential for secretory transformation of the endometrium that permits implantation and maintenance of early pregnancy. Progestins have been shown to stimulate the production of 34-KDa protein P-inducing blocking, which prevents inflammatory reactions toward the trophoblast via blockade of natural killer cells. Recently, several studies showed that deregulation in the numbers of natural killer cells and/or their activity in the blood and in the endometrium is associated with various manifestations of reproductive failure (29, 32, 34).

The fact that progestogens were associated with a lower rate of recurrent miscarriage needs to be correlated also with cost-effectiveness consideration. Unfortunately, none of the included trials reported any cost or cost-effectiveness analysis. The US cost of vaginal P (approximately $11 per day, or approximately $77 per week) (39) is much lower than that of 17-OHPC (approximately >$500 per week) (40).

In conclusion, our findings provide evidence that supplementation with progestogens in the first trimester of pregnancy may reduce the incidence of miscarriages in women with history of unexplained recurrent miscarriages. Synthetic progestogens, including weekly IM 17-OHPC, but not natural P were associated with a lower risk of recurrent miscarriage. Given the limitations of the studies included in our meta-analysis in terms of head-to-head comparisons, it is difficult to recommend a specific preparation, route, and dose of synthetic progestogen therapy. Further head-to-head trials may more fully address this question.

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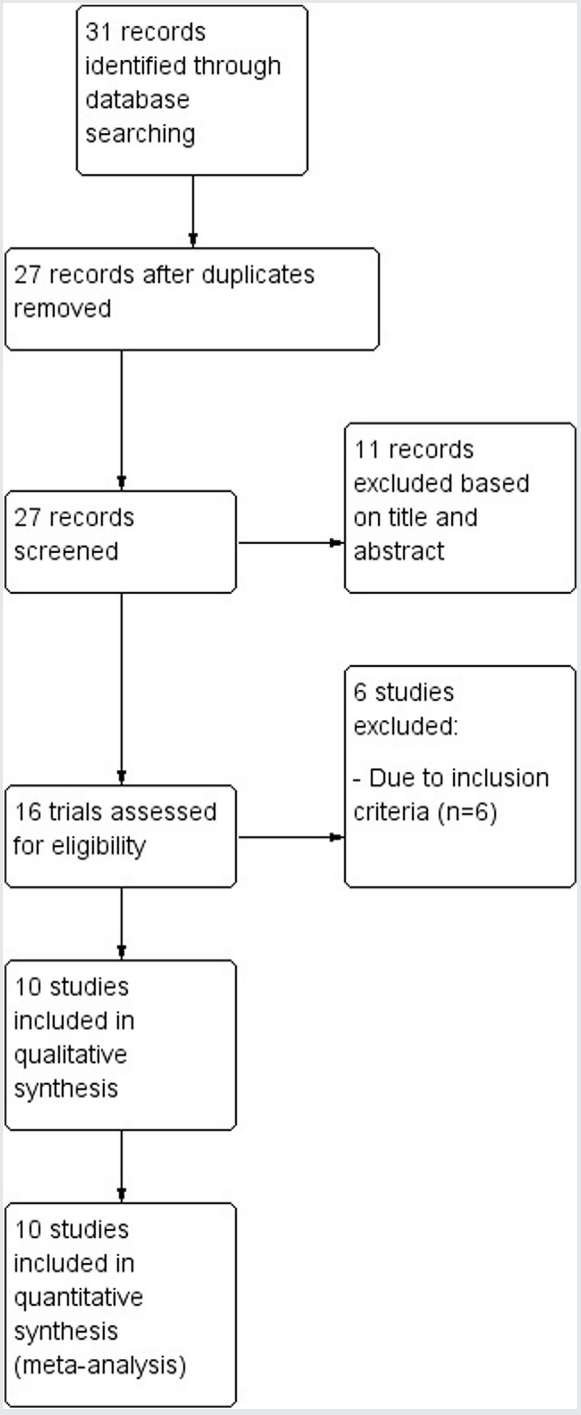
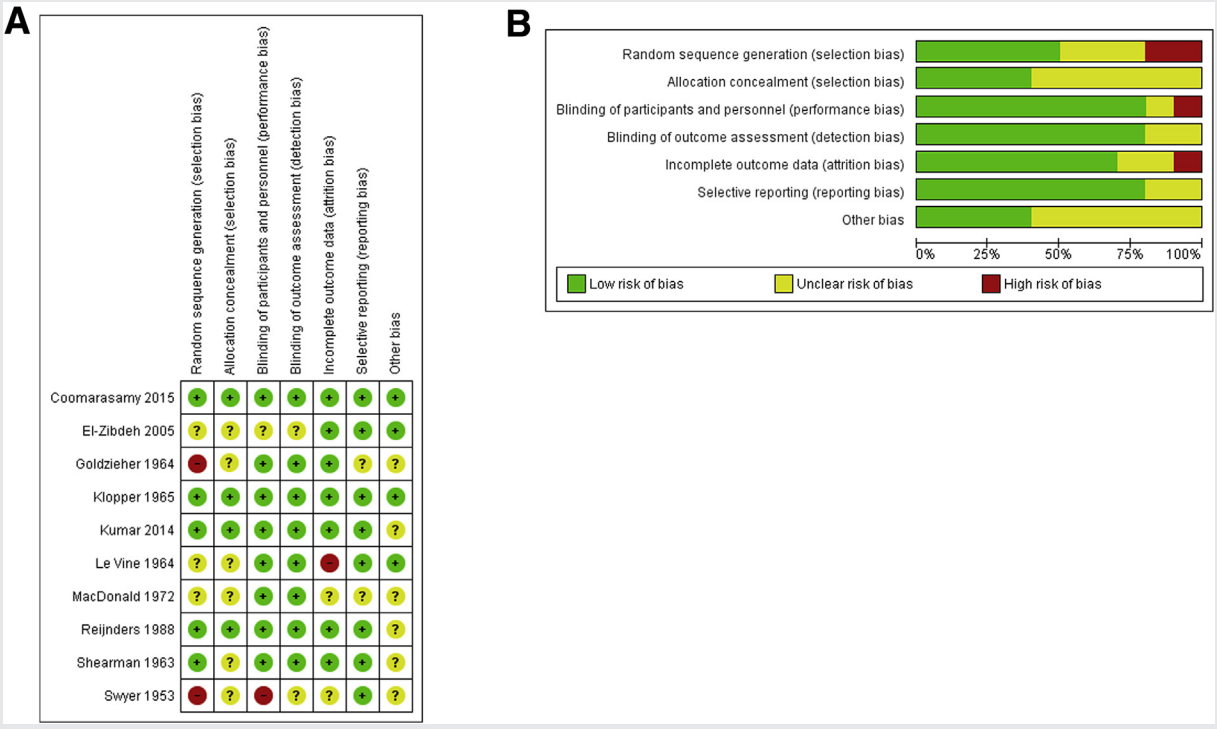
SUPPLEMENTAL FIGURE 1



Flow diagram of studies identified in the systematic review (PRISMA template).

Saccone. Progestogens for miscarriage. Fertil Steril 2016.

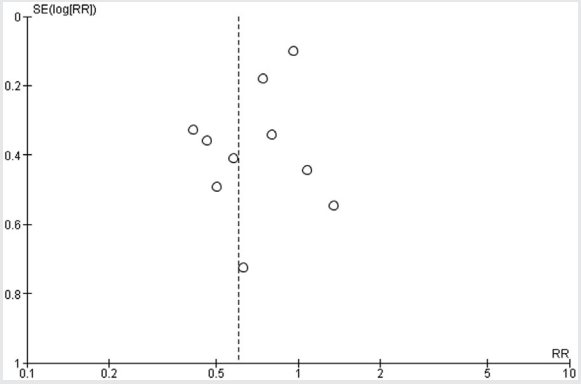
SUPPLEMENTAL FIGURE 2



Assessment of risk of bias. (**A**) Summary of risk of bias for each trial; Plus sign = low risk of bias; minus sign = high risk of bias; question mark = unclear risk of bias. (**B**) Risk of bias graph about each risk of bias item presented as percentages across all included studies.

Saccone. Progestogens for miscarriage. Fertil Steril 2016.

SUPPLEMENTAL FIGURE 3



Funnel plot for assessing publication bias.

Saccone. Progestogens for miscarriage. Fertil Steril 2016.