ORIGINAL ARTICLE: EARLY PREGNANCY

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® 2016;■:■–■. ©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