Micronized Vaginal Progesterone to Prevent Miscarriage: A Critical Evaluation of Randomized Evidence

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versus placebo (risk ratio, 1.09; 95% confidence interval, 1.03–1.15; P = 0.003). Among women with 3 or more prior miscarriages and bleeding in the current pregnancy, live birth rate was 72% with progesterone versus 57% with placebo (risk ratio, 1.28; 95% confidence interval, 1.08–1.51; P = 0.004). Guidelines for interpretation of subgroup analyses translate into 11 criteria to assess credibility and therefore clinical applicability; 5 on design, 2 on analysis, and 4 on context. The PRISM trials subgroup analysis meets all 11 criteria in women with dual risk factors of previous miscarriage and current pregnancy

ABSTRACT

Historically, a lack of methodologically strong and generalizable studies has limited policy makers from recommending the use of progesterone supplementation to improve outcomes in women at high risk of miscarriage. The PROMISE and PRISM trials were carried out to rectify this and generate robust evidence on the role of progesterone supplementation to prevent miscarriage. This review aims to evaluate the PROMISE and PRISM trials and their impact on collective academic understanding of the use of progesterone supplementation for miscarriage prevention, as well as to provide recommendations for clinical practice.

The PROMISE trial was a randomized double-blind, placebo-controlled study that included 836 women from 45 hospitals in the United Kingdom and the Netherlands and found a 3% increase in live birth rate with progesterone supplementation; however, the P value associated with this finding was 0.45. A post hoc subgroup analysis was performed with cohorts stratified according to number of previous miscarriages that revealed a trend for greater benefit with increasing number of previous miscarriages. Small sample sizes in this subgroup analysis resulted in a P value of 0.41; however, these results were hypothesis-generating that a biological gradient existed with respect to improved benefit of progesterone treatment among women with an increasing number of prior miscarriages.

The PRISM trial was a randomized, double-blind, placebo-controlled study that involved 4153 women from 48 hospitals in the United Kingdom and noted a 3% increase in live birth rate with vaginal micronized progesterone; however, the P value associated with this finding was 0.08. To follow up on the gradient effect observed in the PROMISE trial, this study included a prespecified subgroup analysis analyzing the number of previous miscarriages with population split into 3 subgroups: women with zero prior miscarriages, women with 1 to 2 prior miscarriages, and women with 3 or more prior miscarriages. Among women with 1 or more prior miscarriages and bleeding in the current pregnancy, the live birth rate was 75% with progesterone versus 70% with placebo (risk ratio, 1.09; 95% confidence interval, 1.03–1.15; P = 0.003). Among women with 3 or more prior miscarriages and bleeding in the current pregnancy, live birth rate was 72% with progesterone versus 57% with placebo (risk ratio, 1.28; 95% confidence interval, 1.08–1.51; P = 0.004). Guidelines for interpretation of subgroup analyses translate into 11 criteria to assess credibility and therefore clinical applicability; 5 on design, 2 on analysis, and 4 on context. The PRISM trials subgroup analysis meets all 11 criteria in women with dual risk factors of previous miscarriage and current pregnancy
bleeding, suggesting the subgroup effect of a gradient existing in the context of improving live birth rate with progesterone treatment is highly plausible.

Given biologic plausibility, lack of short-term safety concerns, and observed positive treatment effect, providers should consider offering women with vaginal bleeding and a history of 1 or more previous miscarriages a course of treatment with vaginal micronized progesterone 400 mg twice daily.

EDITORIAL COMMENT

(Miscarriage is a devastating event for most women, especially for those who have struggled to build their families. The cause of most miscarriages remains unknown, but progesterone plays central role in maintaining pregnancy, so empiric progesterone therapy might prevent unexplained miscarriage. But evidence of benefit remains mixed. The PROMISE and PRISM trials evaluated the effect of progesterone on miscarriage risk. This article reviews these 2 randomized trials with the goal assessing the implications of these trials for clinical practice.

The PROMISE trial randomized 836 women in a double-blind fashion to placebo or progesterone and found a 3% increase in live birth rate in the progesterone group, although this trend was not significant. A post hoc subgroup analysis showed a trend toward greater benefit with increasing number of previous miscarriages, although small sample sizes in the subgroup analysis likely contributed to the nonsignificance of this finding as well. PRISM randomized 4153 women to placebo or progesterone and similarly found a 3% increase in live birth rate, which almost reached statistical significance. PRISM also found a more robust effect in women with 3 or more prior miscarriages—a live birth rate of 72% with progesterone versus 57% (P = 0.004). Given the biologic plausibility, low risk, low cost, and benefits demonstrated by these 2 studies, providers should consider offering women with vaginal bleeding and history of prior miscarriages a course of treatment with vaginal micronized progesterone 400 mg twice daily.—DK)

Psychiatric Comorbidity Among Women With Endometriosis: Nationwide Cohort Study in Sweden

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ABSTRACT

Endometriosis is a major cause of pelvic pain, subfertility, and infertility that affects an estimated 11% of women of reproductive age. It has been reported in literature as a potential risk factor for depression, anxiety, and bipolar disorder in clinical populations, although the quality of evidence is lacking. Given the heritability of endometriosis and psychiatric disorders, it has been hypothesized that this association could be due to shared familial risk factors.

This retrospective longitudinal population-based study aimed to evaluate the bidirectional association between endometriosis and psychiatric disorders while controlling for familial confounding using an applied 2-sibling comparison design. The entire female population of Sweden born between 1973 and 1990 were screened for inclusion using the Total Population Register. The Multi-Generation Register was used to identify a subpopulation of families with at least 2 female children born during the study period. Individuals with a diagnosis of endometriosis in the Sweden National Patient Register between 1987 and 2016 were considered as cases. Individuals with psychiatric diagnoses including bipolar, depressive, and anxiety-related