

Progestogens in Recurrent Pregnancy Loss: After the 'Promise' Trial

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Progesterone was so named in the 1930s due to its physiological role in maintaining pregnancy. Progesterone has been used for the last 50 years to prevent subsequent miscarriages in women with recurrent miscarriage. The first reports in the 1950s and 1960s showed no statistically significant benefit for using progestogens [1-3]. Each study used different progestogens, including medroxy-progesterone acetate, implant and 17-hydroxy-progesterone acetate. When the three reports were combined in a meta-analysis [4], the slight benefit of each study reached statistical significance with a combined odds ratio of 3.09 (confidence interval 1.28–7.52). However, the wide confidence interval left doubt as to the strength of the conclusions. In 2013, a Cochrane Review [5] reported on the efficacy and safety of progesterone use in miscarriage prevention. The authors reported that in a subgroup analysis, women with recurrent miscarriages may benefit from progestogen treatment. There was a significant decrease in the miscarriage rate when compared to placebo or no treatment in this subgroup of patients. The Cochrane Review [5] of 2013 based their conclusions on the same studies [1-3] as Daya did in his 1989 [4] meta-analysis. However, The methodology of the trials was considered to be very poor [5].

In October 2015, the results of the 'Promise' (Progesterone in Miscarriage) trial were published [6] which showed no significant effect of supplementation with vaginal micronized progesterone (Utrogestan®, Bessins, Belgium). The study was a double-blind randomized placebo-controlled and multicenter trial comprising 836 patients. The methodology was well thought out in advance, in order to select the patients considered to derive the maximum benefit from progesterone supplementation. Vaginal micronized progesterone was chosen as the progestogen to be tested since micronized progesterone is the closest progestogen to the physiological hormone. The study was supervised by an independent monitoring committee to ensure safety and quality. Micronized progesterone is the most

widely used progestogen supplement in Israel today. Of 20 new patients presenting to the Recurrent Pregnancy Loss clinic at Sheba Medical Center in December 2014, 12 were failures of progesterone treatment. However, 6 months prior to publication of the 'Promise' trial, Kumar et al. [7] showed in a double-blind randomized trial that progestogen supplementation with dydrogesterone (Duphaston®, Abbott, Netherlands) conferred a statistically significant beneficial effect in recurrent miscarriage. The results of the study by Kumar et al., published in *Fertility and Sterility* [7], claimed to have used all the methodological safeguards that were instituted in the 'Promise' trial.

How are we to reconcile the opposing conclusions of these two trials? There are differences in the inclusion criteria of both trials, and differences in the progestogen used. The 'Promise' trial started treatment as soon as pregnancy was diagnosed, whereas Kumar et al. [7] commenced treatment when a fetal heartbeat was detected. Hence, pregnancies terminating in blighted ova were included in the results of the 'Promise' trial but were excluded from the Kumar trial. Since many blighted ova have a high incidence of embryonic aneuploidy, the results of the 'Promise' trial may have been confounded by fetal aneuploidy. Beginning treatment after detection of a fetal heart leaves less possibility of confounding due to aneuploidy. The 'Promise' trial recruited patients up to age 39 years, compared to up to age 37 in the Kumar study, which thereby excluded the greater risk of fetal aneuploidy in the older age groups. Fetal aneuploidy is a major cause of recurrent miscarriage, and it is unfortunate that embryonic aneuploidy was not assessed in either trial. Although the parents were karyotyped, parental karyotyping, even if normal, does not exclude embryonic aneuploidy [8].

Although both trials showed that age distribution and the mean number of miscarriages were similar in treated and control patients, neither trial specifically analyzed for subgroups such as greater number of miscarriages, nor were patients stratified for age or number of miscarriages. Therefore, treatment may have been effective in a subgroup of patients that remains unidentified. Patients with a larger number of miscarriages have a lower incidence of embryonic aneuploidy [9].

Both trials used different progestogens. The 'Promise' trial used micronized progesterone while Kumar and co-authors used dydrogesterone. Although dydrogesterone is a stereoisomer of progesterone, there are differences in pharmacology.

Dydrogesterone binds the progesterone receptor 50% more strongly than progesterone [10]. Dydrogesterone is more biologically available, and its metabolites are progestogenically active [10] (progesterone is degraded and inactivated in the liver). In order to assess dydrogesterone further, Carp [11] conducted a meta-analysis of three trials of dydrogesterone. The meta-analysis comprised 509 patients and showed that dydrogesterone was associated with a statistically significant less chance of a subsequent miscarriage (combined OR 0.29, CI 0.13–0.65).

Therefore, in the light of the above results, micronized progesterone should not be used as there is no evidence of effect. The current trend of using micronized progesterone for recurrent miscarriage on an empiric basis should cease. Additionally, there is no evidence of effect of intramuscular injections of progesterone in oil, since no trials of intramuscular progesterone have been conducted since Goldzieher's [3] trial of 18 patients in 1964. At present the only progestogen with evidence of effect is dydrogesterone, based on a double-blind randomized and quasi-randomized trial and meta-analysis.

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