

Progesterone, Impedance to Blood Flow, and Luteal Inadequacy?

To the Editor:

I read with interest the very provocative manuscript by Strigini et al. (1). They demonstrated that P supplementation in the luteal phase correlated with a significant decrease in uterine pulsatility index compared with both spontaneous cycles and FSH-treated cycles without luteal support. They refer to two previous studies suggesting that a decrease in uterine artery pulsatility index is related to an improved probability of conception (2, 3). Strigini et al. thus hypothesize that their data are consistent with improvement in uterine perfusion, which could lead to improved pregnancy rates (PRs), but they ask for larger studies, which should include a greater number of conception cycles (they only had four) to validate clinically their hypothesis. Several years ago we published a study that randomly compared P in the luteal phase versus follicle-maturing drugs (clomiphene citrate [CC] or hMG) in 100 women with luteal phase defects (4). Six-month PRs found 24 of 31 (77.4%) pregnant with P therapy with only 1 spontaneous abortion (4.1%) compared with only 3 of 27 (11.1%) with 2 abortions (66.6%) for those treated with follicle-maturing drugs. Interestingly, during the second 6 months, 25 previous failures with CC or hMG were supplemented with luteal phase P only and 16 of 25 (64%) conceived and only 1 (6.2%) aborted. In the same study, the PR was the same (70%) for those patients with luteal phase defects related to releasing eggs from immature follicles but 57.1% aborted without P supplementation compared with only 7.1% with P supplementation. In another study (n = 100) where women needing follicle-maturing drugs were randomized to either receiving P support or not, the spontaneous abortion rate in the nonsupplemented controls was 28% compared with only 6% in those supplemented with P (5). Thus, these data certainly support Strigini et al.'s hypothesis. Nevertheless, a double-blinded placebo controlled study with transvaginal color flow Doppler imaging would still be encouraged to provide even more credence to the hypothesis.

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Reply of the Authors:

We are grateful to Dr. Check for his comments and the biologic and pharmacologic data supporting our study (1). The question whether P supplementation is the best therapy for luteal inadequacy has been discussed widely (2). Even more discussed is whether cycles of induction of follicular maturation should receive also a luteal support, especially when the development of multiple follicles is induced (2).

Our paper addressed the study of the vascular effects of luteal support with P in cycles of induction of multiple follicular development with gonadotropins alone in patients without any detectable endocrine abnormality. The observation that P administration was able to decrease the impedance to uterine blood flow may offer a further reason for supporting the luteal phase in these cycles. However, this is not sufficient to conclude that P supplementation has similar effects on uterine blood flow in spontaneous cycles or in cycles treated with different drugs.

We believe that for such studies it is of paramount importance to select homogeneous groups of patients treated according to uniform protocols. The relevance of uterine blood flow on fertility and the factors able to modify its impedance are still very imperfectly known. We excluded cycles treated with clomiphene citrate because it is not known if antiestrogens have any effect on uterine blood flow. On the contrary, an increase in uterine vascular impedance has been described after treatment with GnRH analogues (3), so that the baseline uterine blood flow may be affected when these drugs are used in cycles of induction of multiple follicular development. When gonadotropins or antiestrogens are administered to women with luteal inadequacy, their dose is usually adjusted to induce the development of one follicle only; once again, estrogen levels and uterine

blood flow at the beginning of the luteal phase are probably lower with respect to the cycles of induction of multiple follicular development. Therefore, the modifications of uterine blood flow after P administration should be studied separately in the different clinical conditions before suggesting that in each specific endocrine milieu P has vascular effects besides the well-known direct effect on the endometrium.

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