14

Debate: Should Progesterone Supplements Be Used? Yes

Jerome H. Check

In the first edition of *Recurrent Pregnancy Loss—Causes, Controversies and Treatment*, the "Role of Using Progesterone Supplementation" was presented as a debate: For—Jerome H. Check, Against—Shazia, Malik, and Lesley Regan.[1–3] There is no debate that completion of a pregnancy is not possible without progesterone (P). Surgical removal of the ovary with the corpus luteum of pregnancy prior to 8 weeks will lead to spontaneous miscarriage.[4] It is clear that a miscarriage will frequently ensue if the effect of progesterone is blocked by treating the woman with 600 mg of the progesterone receptor antagonist mifepristone at 600 mg for one day.[5]

Low levels of P during the first trimester have been found to be associated with a higher risk of miscarriage. Yeko et al. found that 17 of 18 women had a miscarriage with a serum P <15 pg/mL during the first trimester.[6] McCord et al. evaluated P levels in 3674 first trimester pregnancies and found a miscarriage rate of 85.5% with serum P <5 pg/mL, 65.8% with serum P 5 to <10 pg/mL, 31.3% with serum P 10 to 15 pg/mL, 9.8% with serum P levels 15 to <20 pg/mL and 7.7% with serum P 20 to <25 pg/mL.[7] The McCord et al. study did not show the extremely high miscarriage rate reported by Yeko et al. and had much more power but the principle was the same—low levels of P are associated with an increased miscarriage rate.

The association of increased chance of miscarriage with low serum P does not prove that the low P caused the miscarriage. Possibly the low serum P merely reflects a deteriorating placenta. One uncontrolled study aggressively treated women with serum P levels less than 15 pg/mL with P supplementation and produced a 70% live delivery rate.[8] Even women with serum P levels ≤8 pg/mL had a 60% viable rate following aggressive P therapy at the time of detection.[9] These salvage rates compare quite favorably to the high loss rate found by Yeko et al. in women with low serum P levels and even to the study by McCord et al. that did find an association of low serum P and miscarriage but not as high as found by Yeko et al.[6,7]

Evidence that placental deterioration may be the cause of the miscarriage in at least some women was provided by a study comparing serum estradiol (E2) in P supplemented women in those who miscarried versus those who were successful.[10] The serum E2 levels were significantly lower in those who miscarried versus those who were successful despite no difference in the serum P levels.[10] With the assumption that the majority of losses were from chromosomal defects, this study could be interpreted as supporting placental deterioration as a nonremedial cause of depletion of critical hormones during pregnancy. Progesterone supplementation would not be expected to prevent miscarriage if the cause is a failing fetal-placental unit.[10] On the other hand, one could argue that since the corpus luteum makes both P and E2, perhaps supplementing only P in some instances may be insufficient and thus these data could still be consistent with a failing corpus luteum not placental deterioration.[10]

Evidence that P Supplementation Decreases Miscarriage Rates in Women with Threatened Abortion

Women with low serum P frequently have bleeding and/or cramps which improve following P therapy. However, many women with threatened miscarriage deliver a live baby without P therapy. A Cochrane

Collaboration review entitled "Progestogen for treating threatened miscarriage" was published in 2011.[11] In this review the selection criteria included randomized or quasirandomized controlled trials that compared progestogen with placebo, no treatment, or other treatment given in an effort to treat threatened abortion.[11] Four studies met the inclusion criteria and provided the 421 participants for the meta-analysis.[12–15] There was evidence of a reduction in the rate of spontaneous miscarriage with the use of progestogens compared to placebo or no treatment (risk rate 0.53, 95% confidence interval 0.35 to 0.79). For two trials oral dydrogesterone 10 mg twice daily was given; one study only used 25 mg twice daily progesterone vaginal suppositories.[12–15] This Cochrane review also corroborated previous data suggesting no fetal risks by exposure to extra progesterone.[11,16] It is interesting that the benefit was greater for dydrogesterone than for micronized progesterone.

Thus these data suggest that progestogens can reduce the miscarriage rate when there is a threatened abortion. This, however, does not necessarily allow the conclusion that the use of progesterone can prevent miscarriage in women with a tendency for recurrent losses. The possibility exists that, fortuitously in some pregnancies, the corpus luteum of pregnancy may fail before the placenta is making adequate P. However, this may not occur on a repeated basis.

Luteal Phase Deficiency—Diagnosis

One way that recurrent miscarriage could be related to a progesterone insufficiency and be improved by progestogen therapy would be if there existed a recurrent problem of insufficient progesterone effect by the corpus luteum, that is, a luteal phase defect (LPD). An LPD could theoretically cause infertility or recurrent miscarriage. The concept is that if implantation does not occur in an endometrium that has been properly developed, the embryo may not implant at all or eventually result in a miscarriage.

It appears that only a small amount of P is needed to cause an adequate endometrial structure to allow implantation of the conceptus, at least as determined by endometrial biopsy and molecular markers.[17–25] No reliable marker has been identified that could detect a lack of progesterone leading to infertility.[19–25] It was suggested that merely a serum level of 5 pg/mL was needed not only to develop a normal secretory endometrium with normal classical histological changes but also to allow normal endometrial integrins and quantitative reverse transcription–polymerase chain reaction analysis for nine putative biochemical endometrial function markers.[25]

Presently being explored, but so far without any definitive conclusions in humans, is the relationship of the progesterone receptor initiating paracrine signaling within the uterine microenvironment during the preimplantation period.[26–29]

There is now a method for detection of the expression of a cluster of endometrial biomarker genes to assess endometrial receptivity.[30–33] One study failed to identify histological or biomarker abnormalities in women with suspected luteal phase defects but did find altered gene expression.[34]

Is Luteal Phase Deficiency Associated with Infertility or Recurrent Miscarriage?

A recent Practice Committee of the American Society of Reproductive Medicine published their opinion of the clinical relevance of LPD.[35] The committee was composed of 19 experts in the field of reproductive endocrinology. They stated that "No diagnostic test for luteal phase insufficiency has been proven in a clinical setting." They mention that "no treatment for luteal phase insufficiency has been shown to improve outcomes in natural unstimulated cycles."

The practice committee did not acknowledge a key publication that clearly demonstrated that the use of progesterone in the luteal phase could clearly improve pregnancy rates.[36] The study was a randomized drug comparison study comparing follicle maturing drugs in the follicular phase versus

progesterone in the luteal phase in infertile women having an out-of-phase endometrial biopsy in the late luteal phase.[36] The first group compared were those who seemed to achieve a mature follicle (18 mm average diameter with serum E2 >200 pg/mL). For the 31 randomly assigned to P only, there were 24 pregnancies (77%) and only one of 24 (4.1%) miscarried compared to only three of 27 conceiving with clomiphene citrate or human menopausal gonadotropins (hMG) (11.1%) and two of three miscarried.[36] However, during the next six months 16 of 25 women conceived (64%) with P only who had failed with follicle maturing drugs with only one miscarriage (6.2%).[36]

Clinical experience suggests that women treated empirically with follicle maturing drugs achieve a six month pregnancy rate much higher than 11%. Indeed the 58 women with mature follicles were part of a prospective study of 100 consecutive infertile women with regular menses, patent fallopian tubes, and male partners with normal semen parameters. The other 42 women were randomly assigned to exclusive use of follicle maturing drugs (FMD) only or FMD with P luteal phase support versus P supplementation only.[36] For this group exclusive FMD resulted in a 70% clinical pregnancy rate (seven of 10) but with four miscarriages. In contrast for the 70% pregnancy rate with FMD and P (14 of 20) there was only one miscarriage. Progesterone alone resulted in a clinical pregnancy rate of only 25% (three of 12) with no miscarriages.[36] If one empirically placed all these women on follicle maturing drugs irrespective of follicular maturation 43.8% would have conceived with FMD versus 60.4% who would be treated exclusively with P.

The ASRM Practice Committee did not mention any study that refuted the benefits of treating infertility with P. If P deficiency can lead to an embryo that fails to implant causing infertility, it is not hard to envision that a slightly less severe problem could allow implantation but first trimester miscarriage. There actually has been a prospectively randomized placebo-controlled parallel group trial that did in fact find that P supplementation significantly reduced miscarriage rates in women with recurrent miscarriages.[37]

The Role of P in Reducing Immune Rejection of the Fetus

Progesterone enhances the expression by gamma/delta T cells of a unique 34 kDa protein known as the progesterone induced blocking factor (PIBF).[38] The PIBF protein has been found to allow the TH1/TH2 cytokine balance in favor of TH2 cytokines, which provides a more favorable immune environment for the fetus.[39] PIBF has been found to stabilize perforin granules in natural killer (NK) cells and thus inhibit release of perforin from these large storage granules which inhibits the main mechanism for NK cell cytotoxicity.[40]

Initially, both *in vitro* and *in vivo* studies suggested that the allogeneic stimulus of the fetal placental unit may be responsible for a hormone independent upregulation of P receptors by gamma/delta T cells.[41,42] Szekeres-Bartho et al. found significantly lower expression of PIBF in recurrent miscarriage patients compared with those with a healthy pregnancy.[43] Check et al. treated women in the first trimester aggressively with progesterone but found no difference in PIBF expression by lymphocytes.[44] This suggested that the main stimulus for PIBF may be P itself and perhaps whether some causes of miscarriage may be related to inadequate development of P receptors on gamma/delta T cells.[41,42,44,45] Indeed, it has been confirmed following the development of a more sensitive enzyme linked immunosorbent assay (ELISA) rather than the previously used less sensitive immunocytochemistry technique following the development of a monoclonal antibody, that P alone (even in males) is the main stimulus for PIBF expression once there has been adequate estrogen exposure to induce P receptors in the gamma/delta T cells, since there is a very high level of PIBF induced without exposure to a fetus.[46–48]

Progesterone may help to inhibit immune rejection of the fetus through other mechanisms than induction of PIBF and suppression of NK cell cytolysis. Progesterone can act rapidly by epigenetic (nongenomic) interaction with membrane receptors, for example, progesterone receptor membrane 1.[49] One study suggested that P interacting with P receptor 1 membrane may suppress, in an epigenetic manner, T cell rejection of the fetal semiallograft.[50]

Conclusions

One could debate whether there are "sufficient" evidence-based studies to warrant the treatment of women with recurrent miscarriage with progesterone, beginning in the luteal phase and continued throughout the first trimester. Since the good safety record of P has been well established, it makes no sense to withhold such therapy, advising the patient that the present opinion of the treating physician is that there is still an insufficient number of studies to convince that treating physician that the treatment is any better than careful vigilance and benign neglect.

Though the ASRM Practice Committee concluded that there is no evidence of LPD as a cause of miscarriage in lieu of documenting any structural endometrial defects, they failed to consider the effects of P on the immune system.[35] More support that LPD is a cause of infertility (and thus a logical cause of miscarriage with a slightly milder state of P deficiency) was a recent study using P therapy empirically in a group of women age ≤39.9 with over one year of unexplained infertility who were suspected of having LPD related to age (>30) or pelvic pain (suspicious of endometriosis with P resistance).[51,52] In six months 27 of 32 women (84.3%) had a serum beta-hCG (human chorionic gonadotropin) level >100 mIU/mL with luteal phase P as the sole treatment with a low rate of miscarriage.[51] In view of the aforementioned randomized comparison study finding better results with P than follicle maturing drugs when the follicle is mature but vice versa when there is release of the oocyte from an immature follicle, treatment of recurrent miscarriage from suspected LPD should include the use of mild follicular stimulation if there are inadequate mid-cycle estradiol levels attained or inadequate time of exposure to E2 during the follicular phase.[36,53] Estradiol is known to induce P receptors in the endometrium.[54,55] Studies of PIBF in males treated with P or E2 and P suggest that E2 induces P receptors in gamma/delta T cells also.[48]

The treating physician has the obligatory role of suggesting the most effective treatment paradigm with the least risk and least expense. How many erudite members of the ASRM Practice Committee on LPD would have suggested an alternative in lieu of empirical P usage for "unexplained" infertility. They may have suggested *in vitro* fertilization–embryo transfer (IVF-ET), which could be considered an extremely expensive, risky method of providing these women with P therapy from the early luteal phase, or recommended an even more expensive method of treating recurrent miscarriage—IVF-ET with comprehensive chromosome screening for recurrent miscarriage. The latter could be by far the most expensive way to administer P.

Present studies evaluating serum PIBF, now that a sensitive ELISA test has been created, will hopefully determine a discriminatory level below which there is an increased risk of nonconception or miscarriage. There is one caveat however. There is evidence that an intracytoplasmic occupation of PIBF may protect cancer cells from NK cell immune destruction.[56,57] The 90 kDa parent compound of PIBF is found in the cytoplasm of all highly proliferating cells.[58] It is possible that P is needed more for inhibiting the conversion of the intracytoplasmic 90 kDa PIBF form to intracytoplasmic split variants of 34–36 kDa products.[56,58] That, of course, would not allow easy detection of modification of P therapy during a pregnancy if that was the main operative mechanism.

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