Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin

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Exogenous progesterone supplementation is a common element of treatment regimens for infertility, particularly those relating to the assisted reproductive technologies. (Fertil Steril® 2008;90:S150–3. ©2008 by American Society for Reproductive Medicine.)

The modulating effects of progesterone (P) on endometrial structure and function are essential to the success of human reproduction. After ovulation, P produced by the corpus luteum (CL) induces "secretory" maturation of the endometrium, involving a cascade of molecular events that ultimately renders the endometrium receptive to implantation of the embryo. After nidation, continued P stimulation, driven by rapidly increasing concentrations of hCG, decidualizes the endometrial stoma and supports early embryonic development.

Considering the important role that P plays in human reproduction, it is not surprising that exogenous supplemental P is a common element of treatment regimens in infertility, particularly those relating to the assisted reproductive technologies (ART). This document will review the effects of various treatments on endogenous P secretion and the rationale for supplementation, the available forms and routes of administration for exogenous P, and the benefits and the risks of exogenous P supplementation during early pregnancy.

NOMENCLATURE

Progestogens are a class of steroidal compounds having P-like actions that includes natural P and various synthetic progestins derived from P itself (containing 21 carbons; C-21), T (C-19), or aldosterone (C-18) precursors.

THE IMPORTANCE OF PROGESTERONE IN EARLY PREGNANCY

A classic series of studies conducted more than three decades ago demonstrated that P secretion by the CL is absolutely required for the success of early human pregnancy. Surgical excision of the CL ("luteectomy") before 7 weeks' gestation (using traditional methods for dating pregnancy from onset of last menstrual period) uniformly precipitated an abrupt

decrease in serum P concentrations followed by miscarriage (1). When luteectomy was performed more than 27 days after the missed menstrual period (8 weeks' gestation or later), P levels decreased only slightly and transiently, and pregnancy continued (1). Finally, exogenous P replacement after early luteectomy (before 7 weeks' gestation) prevented otherwise inevitable miscarriage. These and other related studies demonstrated clearly that the success of early pregnancy depends on P that derives primarily from the CL before 7 weeks' gestation, almost entirely from the trophoblast after 9 weeks' gestation, and from both sources to varying extent during the time between, known as the luteal–placental shift (2).

MEASURES OF LUTEAL FUNCTION

There are no reliable methods for diagnosis of P deficiency during the luteal phase or early pregnancy. Serum P concentrations range widely during the mid and late luteal phases because P secretion by the CL is pulsatile. Levels as low as 2.3 and as high as 40.1 ng/mL have been observed within the relatively short interval of time spanning a single secretory pulse (60–90 minutes) (3). Consequently, single and even serial serum P measurements have limited clinical utility and may not provide a truly accurate gauge of the quality of luteal function. Progesterone levels in early pregnancy also range widely, particularly when conception follows treatment with ovulation-inducing drugs. Histologic endometrial dating was widely accepted for decades as the gold standard among methods for assessing the quality of luteal function (4), but more recently has been proven invalid (5, 6). Progesterone supplementation necessarily is empiric and has been applied liberally in clinical circumstances wherein the amount or duration of P production is reasonably suspect.

EFFECT OF GONADOTROPIN-RELEASING HORMONE ANALOGS ON LUTEAL FUNCTION

Gonadotropin-releasing hormone analogs, both agonists and antagonists, are used widely to synchronize early follicular development and to prevent premature luteinization and ovulation during controlled ovarian hyperstimulation (COH) with exogenous gonadotropins for superovulation or IVF.

However, their mechanisms of action also threaten the quality of luteal function that follows ovulation or oocyte retrieval.

Long-acting GnRH agonists (e.g., leuprolide, nafarelin, goserelin) have a two-phased action on pituitary gonadotropin secretion. Initially, agonists stimulate gonadotropin release directly, but continued stimulation ultimately down-regulates pituitary GnRH receptors and thereby suppresses gonadotropin secretion. Once down-regulated, pituitary function is slow to recover and does not return to normal until 2–3 weeks after agonist treatment ends (7). Because normal CL function depends on pituitary LH stimulation, some form of luteal phase support is considered prudent, if not essential, to prevent any P deficiency that might jeopardize the success of implantation or early pregnancy (7, 8).

The GnRH antagonists block pituitary GnRH receptors directly. Consequently, their onset of action is immediate and their effects more profound than those of long-acting agonists. Like the GnRH agonists, antagonists often are used to prevent a premature LH surge during stimulation with exogenous gonadotropins for ovulation induction, superovulation, or IVF. Whereas treatment with long-acting agonists typically begins during the luteal phase of the cycle preceding stimulation, antagonists are administered for a shorter interval of days, usually beginning when the lead follicle reaches 13–14 mm in mean diameter. Although the corresponding duration of pituitary suppression is shorter than after treatment with an agonist, GnRH antagonist treatment also predisposes to poor luteal function, regardless of whether recombinant LH, hCG, or a GnRH agonist is used to trigger ovulation (9, 10).

Overall, the weight of available evidence supports using some form of luteal phase support when treatment has included any GnRH analog, agonist or antagonist. A 2002 meta-analysis of randomized controlled trials of IVF cycles using GnRH agonists observed that all luteal phase support regimens (IM or vaginally administered P and hCG) yield significantly higher pregnancy rates (PR), compared with placebo or no treatment (11). A 2004 Cochrane systematic review of 59 studies concluded that in IVF cycles involving down-regulation with a long-acting GnRH agonist, P supplementation (administered vaginally or by IM injections) achieved higher ongoing PRs per embryo transfer compared with placebo or no treatment (odds ratio [OR] 2.38, 95% confidence interval [CI] 1.32–4.29) (12).

METHODS OF LUTEAL SUPPORT

Progesterone can be administered orally, vaginally, or by IM injections. Oral P supplementation is the least common method because two randomized controlled trials observed significantly lower implantation rates and PRs, higher miscarriage rates, or both, in women receiving oral micronized P supplementation, compared with women receiving IM or vaginally administered P (13, 14). Intramuscular P in oil (50 mg/day) generates circulating P concentrations at or above the physiological range. Vaginally administered P yields lower serum levels, but nonetheless achieves endometrial tissue concentrations up to 30-fold greater than those achieved with IM P (15).

Progesterone can be administered vaginally in an 8% gel, compounded suppositories, or in tablets containing micronized P. The effects of treatment with vaginal suppositories or tablets in doses ranging between 200 and 600 mg/day appear comparable to those achieved by administration of a gel containing 90 mg of P, but investigations aimed at comparing the efficacy of the differing forms of vaginally administered P have been limited by relatively small study cohorts.

The relative effectiveness of the vaginal and IM routes of P supplementation has been controversial. A clinical trial involving 250 women in a first IVF cycle, randomized to receive IM P (50 mg/day) or vaginal micronized P supplementation (200 mg/day), observed higher PRs in the group treated with IM P (16). A second open label randomized trial involving 201 women yielded similar results; the age-adjusted odds ratios for clinical PR, implantation rates, and live birth rates all favored the group that received IM P supplementation over the one receiving treatment with a vaginally administered P gel (17). In contrast, another study of IVF outcomes in a group of 262 women supplemented with E_2 valerate in combination with either IM P (50 mg/day) or vaginal micronized P (600 mg/day) observed no differences in clinical PRs between the groups (18). In addition, first trimester miscarriage rates were significantly lower in women receiving vaginal P supplementation, although their plasma concentrations also were lower than in those treated with IM P. The Cochrane systematic review of clinical trials examining outcomes in IVF cycles involving treatment with a long-acting GnRH agonist concluded that [1] clinical PRs per embryo transfer in women receiving vaginal or IM P supplementation were not significantly different (OR 0.82, CI 0.67–1.01), and [2] the optimal route of P administration has not been established (12).

The necessary or optimal duration of supplemental P therapy also has not been established firmly. Evidence derived from the classic luteectomy studies described previously indicates that P supplementation is most important during the first 5 weeks after conception (7 weeks' gestation) and almost certainly unnecessary beyond 7 weeks after conception (9 weeks' gestation) (1, 2).

Luteal support is most commonly provided by treatment with supplemental P but also can be achieved effectively by administration of exogenous hCG. In IVF cycles involving treatment with a long-acting GnRH agonist, hCG stimulation of luteal function and P supplementation have similar effectiveness. In an analysis of combined data from six clinical trials involving a total of 1,038 women, the ongoing PR per embryo transfer in cycles supplemented directly with P was not significantly different from that in cycles supplemented with hCG (OR 0.94, 95% CI 0.70–1.27) (12). However, the risk for ovarian hyperstimulation syndrome (OHSS) was significantly lower for women receiving P supplementation than for those treated with hCG (OR 0.46, 95% CI 0.26–0.81) (12).

RISKS OF PROGESTERONE SUPPLEMENTATION

The weight of available evidence indicates that the most common forms of P supplementation during early pregnancy pose no significant risk to mother or fetus. One retrospective case control study has observed an association between maternal exposure to exogenous progestogens during early pregnancy and an increased risk for hypospadias in their infants (OR 2.2, 95% CI 1.0–5.0) (19). However, for 30 of the 42 cases described in the report, the type and duration of progestogen treatment was not known or specified. Because certain progestogens possess weak androgenic and antiandrogenic properties, it is quite possible that the observed association between early maternal progestogen exposure and the risk of hypospadias may be attributed largely, if not entirely, to use of progestins that bind to the androgen receptor. There is no direct evidence to indicate that supplementation with P itself during early pregnancy poses any significant risk of hypospadias or other types of birth defects. The increased risk for hypospadias observed in infants conceived by intracytoplasmic sperm injection (ICSI) most likely can be attributed to genetic factors related to paternal subfertility (20).

In 1999, the US Food and Drug Administration (FDA) conducted a thorough review of the relevant published scientific data, which yielded the following key findings:

- Controlled studies show no increase in congenital anomalies, including genital abnormalities in male or female infants, resulting from maternal exposure to P or 17α-hydroxyprogesterone (17-OHP) during early pregnancy.
- Analysis of the published literature relating to maternal progestogen exposure during pregnancy and virilization of the genitalia in female infants indicates that most reported cases involved high doses of progestins derived from androgens, particularly ethisterone and norethindrone.
- Most reported cases of masculinized female infants are associated with maternal exposure to methyltestosterone, methandriol, and danazol.

The FDA concluded that class labeling for all progestogens warning of an increased risk of birth defects was inappropriate because it would apply without regard to the indication for which the drug is prescribed. The FDA also noted that use of P for luteal phase support in IVF cycles had become routine and that the agency had itself recently approved a P gel for use in infertile women under treatment with ART (21).

SUMMARY AND RECOMMENDATIONS

- Currently, there is no reliable method for specific diagnosis of P deficiency during the luteal phase of the menstrual cycle or early pregnancy.
- During ovarian stimulation with exogenous gonadotropins, use of a long-acting GnRH agonist or a GnRH antagonist to prevent a premature LH surge frequently results in poor luteal function due to residual suppression of pituitary LH secretion.

- In IVF cycles involving down-regulation with a long-acting GnRH agonist, P supplementation (50 mg/day administered IM or 200–600 mg/day administered vaginally) yields significantly higher PRs, compared with treatment with placebo or no treatment.
- Luteal phase supplementation with hCG is associated with greater risk for OHSS compared with supplementation with P.
- Although maternal exposure to exogenous progestogens during early pregnancy has been associated with an increased risk of hypospadias in their infants, the risk appears to be limited to treatment with progestins that bind to the androgen receptor.
- There is no evidence to indicate that maternal exposure to P or 17-OHP during pregnancy increases risk for birth defects.

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