Luteal phase support after gonadotropin-releasing hormone agonist triggering: does it still matter?

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Despite the increasing utilization of freeze-only IVF protocols, there is still a need for adequate management of the luteal phase after GnRH agonist trigger for patients who desire a fresh embryo transfer. Two approaches, intensive luteal support with E_2 and P, and the use of adjuvant low-dose hCG either at the time of GnRH agonist trigger (dual trigger) or at the time of oocyte retrieval, have been shown to be effective in maintaining adequate pregnancy outcomes. The addition of low-dose hCG should be used with caution, because it may increase the risk of ovarian hyperstimulation syndrome. For patients with peak E_2 of >4,000 pg/mL, we recommend against adding low-dose hCG, because intensive luteal support alone seems to provide adequate results. (Fertil Steril® 2018;■:■–■. ©2018 by American Society for Reproductive Medicine.)

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The use of a GnRH agonist (GnRH-a) instead of hCG for triggering final oocyte maturation in an effort to prevent ovarian hyperstimulation syndrome (OHSS) during IVF cycles has been advocated since the late 1980s to early 1990s (1–3). However, it was not until GnRH antagonists were introduced for prevention of the LH surge during controlled ovarian stimulation in the late 1990s that GnRH-a could then be used again for the induction of oocyte maturation (4).

Despite several years of research, many questions still exist regarding the effectiveness of GnRH-a in inducing oocyte maturation and the ideal luteal phase supplementation protocol. Early studies reported high early pregnancy loss rates and low clinical pregnancy rates (5, 6). Additional studies were subsequently published in an effort to understand the underlying causes of the suboptimal pregnancy rates and to improve the clinical efficacy of the GnRH-a trigger. Given the initial conflicting results, an international group of investigators met in December 2009 in Copenhagen to evaluate the existing evidence on the use of GnRH-a to trigger final oocyte maturation, share experience, and determine what areas of research were needed (7). The review of the published data suggested that the luteolytic properties of GnRH-a are effective in preventing OHSS but are also likely the cause of low pregnancy rates when standard luteal support is used. In contrast to the natural ovulatory LH surge, the surge after a GnRH-a occurs in two phases, rapid ascent and a moderate descent, lasting 24–36 hours (3). The relatively short duration of the LH surge is capable of inducing oocyte maturation and ovulation but may result in defective formation of the corpus luteum (8). In addition, LH secretion has been shown to deviate significantly from the normal physiologic pattern after GnRH-a trigger, which can also explain the early luteolysis mechanism (9).

Since the Copenhagen Workshop group's report was published, considerable progress has been made in the past few years, which has resulted in a much wider worldwide acceptance of this trigger modality for the prevention of OHSS. Gonadotropin-releasing hormone agonist trigger rapidly has become the treatment of choice for oocyte donors. Another change in IVF practice that has renewed interest in and increased utilization of GnRH-a trigger is freeze-only protocols that may be considered a better option than fresh transfers (10, 11). In addition, the increased utilization of

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preimplantation genetic screening for aneuploidy has resulted in a much greater utilization of freeze-only cycles. Both treatments are followed by a frozen embryo transfer; therefore, the concerns about managing the luteal phase disappear, making GnRH-a trigger a very attractive modality to minimize and virtually eliminate the risk of OHSS. This option also allows for a more aggressive stimulation in an effort to obtain more embryos for cryopreservation or for preimplantation genetic screening.

Despite those changes in the field, we would argue there is still an important role for managing the luteal phase when a fresh embryo transfer is desired. Freeze-only has not been universally accepted as the standard of care at the present time and is not always a viable alternative for all patients. In many states in the United States with a mandate insurance coverage that limits the number of covered cycles, cycle segmentation could result in a reduction in the number of opportunities to achieve a pregnancy for those patients. In addition, not all IVF clinics have established successful embryo cryopreservation programs that can provide the same results reported by the more-experienced centers. By optimizing the luteal phase profile for a fresh transfer after GnRH-a trigger, pregnancy rates can be comparable to those obtained after hCG trigger while reducing or eliminating the risks of OHSS (12–18).

LUTEAL PHASE STEROID PROFILE AFTER NATURAL CYCLE AND GnRH-A TRIGGER

In the luteal phase of a natural menstrual cycle, LH acts as a luteotropic hormone that supports the growth and function of the corpus luteum and steroidogenesis after ovulation (19). If pregnancy does not occur and hCG is not available to continue to support the function of the corpus luteum, withdrawal of LH will result in luteolysis and then menses. In the setting of IVF with GnRH-a trigger, the median duration of the luteal phase may be as short as 9 days, compared with 13 days after hCG trigger (20). Serum levels of P and E_2 throughout the luteal phase are significantly lower with GnRH-a trigger than after an hCG trigger (3, 5, 20). The shortened duration of the LH surge after GnRH-a trigger is enough to induce maturation of oocytes but not sufficient to induce and maintain adequate corpus luteum function (8, 21, 22). After the trigger, GnRH-a may partially down-regulate the pituitary, continuing to inhibit the release of endogenous LH (9, 23). By an additional mechanism common to most IVF protocols, supraphysiologic steroid E_2 levels from ovarian stimulation also suppress LH release from the pituitary (20, 24). All these factors together result in early luteolysis. Even if pregnancy does occur after GnRH-a trigger, the luteolytic process is profound and significant enough that corpora lutea cannot reliably be rescued by the time endogenous hCG from an implanting embryo is detected in the circulation (25).

STRATEGIES FOR SUPPORTING THE LUTEAL PHASE AFTER GnRH-A TRIGGER

After early studies suggested that the luteal phase was suboptimal to achieve optimal live birth rates after GnRH-a trigger (26), numerous strategies have been proposed to modify the standard luteal support, to increase pregnancy rates after fresh embryo transfer without significantly increasing the risk for OHSS. These modifications include intensive exogenous luteal phase steroid support and close monitoring of serum E_2 and P levels (13, 27–29), an adjuvant low dose of hCG given at the time of GnRH-a trigger ("dual trigger") or at the time of oocyte retrieval (14, 15, 17, 29–31), or luteal phase recombinant LH administration (32).

Intensive Luteal Support

After recognizing that the serum levels of E_2 and P after GnRH-a trigger are significantly lower than after hCG trigger, we proposed a strategy to improve the dysfunctional luteal phase, which included a more intensive luteal phase support protocol. This has been described as supplementation with both E_2 and P in addition to close monitoring of serum steroid levels to adjust doses as necessary. The supplementation protocol has been described by Engmann et al. (13) in a randomized controlled study of 66 patients with polycystic ovary syndrome or high-responding patients. Intensive luteal support begins with initiation on the day after oocyte retrieval of P (50 mg IM daily) and three 0.1-mg transdermal E_2 patches replaced every other day. Serum levels of E_2 and P were evaluated at 3 and 7 days after oocyte retrieval and weekly thereafter, with continuation of the hormonal supplementation until approximately 10 weeks' gestational age. On the basis of serum levels, doses of IM P were increased to a maximum of 75 mg daily, with the addition of micronized vaginal P daily as needed to maintain serum P levels above 20 ng/mL. Similarly, E_2 patches could be increased to four 0.1-mg patches every other day, with addition of oral micronized E_2 (2 mg to 8 mg) daily to maintain serum E above 200 pg/mL. This study, which compared intensive luteal phase support after GnRH-a trigger with standard luteal phase support after an hCG trigger, resulted in a 53% ongoing pregnancy rate, compared with 48.3% in the hCG group. Similar favorable results using intensive luteal support have been corroborated by other investigators (27, 31, 33).

The reasons why luteal supplementation regimens using IM P have provided much better outcomes than vaginal P remain speculative. Interestingly, Casper (34) has observed excessive endometrial waves on ultrasound monitoring in women receiving vaginal P for frozen embryo transfer or donor oocyte cycles. His group found that uterine activity ceased or was reduced to one contraction per minute within 24 hours of P in oil injection. He speculated that a high dose of P in oil with constant release may overcome the estrogen effect and suppress uterine contractility. The availability of IM P is not universal and must be considered when planning to provide intensive luteal supplementation. In protocols utilizing an hCG trigger, studies suggest that there is no superiority of IM P over the vaginal route (35); however, IM P administration may be essential after GnRH-a trigger to achieve optimal results.

Adjuvant Low-dose hCG

A number of strategies have been described to restore or replace the function of LH in the luteal phase after use of a