Role of gonadotropin-releasing hormone agonists, human chorionic gonadotropin (hCG), progesterone, and estrogen in luteal phase support after hCG triggering, and when in pregnancy hormonal support can be stopped

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Luteal phase support is mandatory in ovarian stimulation cycles in assisted reproductive technology owing to a deficit in LH pulsatility after the effects of exogenous hCG—used for triggering ovulation—vanish. This is classically accomplished by means of exogenous P administration, but emerging new options include microdoses of hCG and exogenous GnRH agonist. Although luteal phase support is commonly continued for up to 10 weeks into pregnancy, there is accumulating evidence that it can be stopped after the first ultrasound or even after a positive pregnancy test. (Fertil Steril® 2018;109:749–55. ©2018 by American Society for Reproductive Medicine.)
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PATHOPHYSIOLOGY OF LUTEAL DYSFUNCTION IN ASSISTED REPRODUCTIVE TECHNOLOGY

The first assisted reproductive technology (ART) birth—Louise Brown—resulted from an in vitro procedure conducted in the menstrual cycle. Soon after, however, ovarian stimulation (OS) was almost systematically adopted in ART to augment the number of oocytes available. In fact, OS has been the single most effective measure ever implemented for increasing ART outcome. Yet, as discussed here and in other papers of this series, OS alters the proper functioning of the corpus luteum (CL), a fact for which several mechanisms have been implicated (Fig. 1).

First among the purported causes of CL dysfunction are the supraphysiologic levels of E_2 encountered in OS. These interfere with the proper functioning of the hypothalamopituitary complex. Elevated E_2 during the follicular phase and P in the early days of the luteal phase impair LH secretion during the luteal phase. In OS, E_2 commonly reaches and exceeds by tenfold the values encountered in the menstrual cycle. Likewise, P levels—produced by multiple CLs under the influence of triggering doses of hCG—greatly exceed the levels normally encountered in the menstrual cycle during the early days of the luteal phase. The result of these hormonal alterations is that CL support by pituitary LH is compromised (1, 2). Therefore, OS per se constitutes an indication for luteal phase support (LPS) (1, 2).

Over the years, numerous changes were added in OS protocols. Most pertinent to pituitary function—and in turn CL support—has been the introduction of GnRH analogues (3–5). In the mid-1980s, agonist analogues of GnRH

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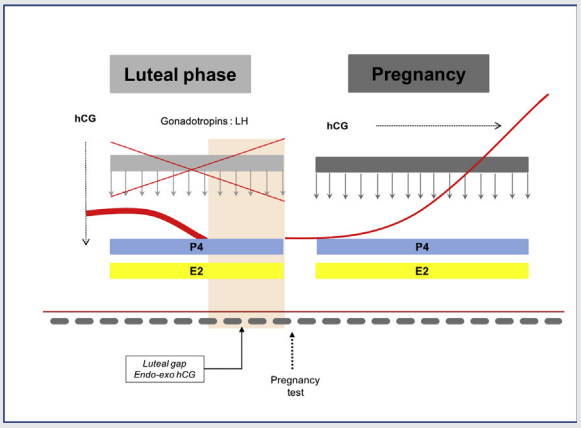
FIGURE 1



Chronologic characteristics of the effects of exogenous hCG and hCG produced by the conceptus. As shown, there is a gap—the luteal gap—between the effects of exogenous hCG on the corpus luteum and the time of takeover by hCG of embryonic origin.

de Ziegler. Luteal phase support indicated in ART. Fertil Steril 2018.

(GnRH-a) became approved for the treatment of prostate cancer and thus freely available to clinicians. The ART—then called IVF—community was swift to adopt GnRH-a in their OS protocols for preventing premature LH elevation (3–6). The use of GnRH-a in ART took place long before any of the GnRH-a preparations were approved for use in ART. The purpose of GnRH-a was to block the anterior pituitary and prevent premature LH and P rise. Although the intended effects of GnRH-a were meant to take place during the follicular phase, their impact on LH pulsatility extends beyond the duration of the follicular phase long into the luteal phase (7). Practically, GnRH-a causes lasting suppression of LH pulsatility during the luteal phase, thereby impeding P production by CL when the stimulatory effects of hCG vanish (7). This sparked the concept of "luteal gap" between the stimulatory effects of exogenous hCG—used for triggering ovulation—and endogenous hCG originating from the conceptus, as illustrated in Figure 1. It is during this luteal gap (Fig. 1) that endogenous P production may drop, thereby causing harm to the potentially developing embryo. Since GnRH-a became routinely used in ART, no one has questioned any more the well founded nature of LPS in OS, with numerous meta-analyses overwhelmingly supporting its use (8).

The introduction of GnRH-a as a routine step in OS greatly increased the risk of ovarian hyperstimulation syndrome (OHSS) for reasons that have not been clearly identified (9). The increased risk of OHSS sparked by the routine use of GnRH-a almost led to abandoning hCG for LPS owing to the several-fold increase in OHSS risk when used at classical LPS doses (10, 11). This principle has remained true until the new low- or microdose hCG approaches were conceived and proposed (see below).

More recently, GnRH-a has been generally replaced by antagonist analogues of GnRH, simply referred today as "antagonists" (12). The primary motivation for the shift toward antagonist protocols has been the substantially lower incidence of OHSS (12). In case of antagonist use in OS, the pituitary disruption is of shorter duration. It is unclear whether antagonists used in the late follicular phase still disrupt the anterior pituitary function during the luteal phase, as seen with GnRH-a (13). Being of competitive nature, the pituitary suppression induced by antagonists can be overridden by GnRH-a, for example, for inducing a LH surge (14). It remains, however, that LPS is needed in OS with the use of antagonist protocols at least for the reasons given above (i.e., the impact of OS itself).

Antagonists are most commonly used in ART today mainly because not only is the risk of OHSS reduced, but also there is the possibility of triggering ovulation with the use of GnRH-a in case of excessive ovarian response to OS (15). Associated with freeze-all and deferred embryo transfer (ET), GnRH-a trigger practically eradicates the risk of OHSS. Options for sustaining the luteal phase during GnRH-a trigger cycles are discussed in a different article of this series.

Finally, one of the seemingly most menial and long ignored step of OS, i.e., the use of "triggering" doses of hCG for replacing the LH surge, is also responsible for impeding CL function (16). The need to replace the endogenous LH surge in OS was already recognized in early pre-ART days. The obligation to artificially trigger ovulation precisely stems from the fact that OS induced by gonadotropins disrupts the functioning of the anterior pituitary function. Notably, the deployment of a positive feedback in response to E_2—despite high levels—impedes the ensuing LH surge (16). Because hCG shares an affinity for the same membrane LH receptor as LH itself and has an extended half-life, triggering doses of hCG have been generally adopted for replacing the LH surge in OS. The high efficacy of hCG at triggering ovulation—evidenced by a high oocyte-to-follicle yield in ART—has eclipsed the experts' interest for this seemingly noninteresting simply mechanical minor step of OS.

Today's knowledge has taught us, however, that ignoring hCG's role in OS was a deplorable oversight for at least two main reasons, one of which is pertinent for LPS. First, hCG through its vascular endothelial growth factor–triggering effects on developing follicles is responsible for the fluid shifts, i.e., extravasation and 3rd-sector fluid accumulation, that are encountered in OHSS (17). Although this effect is not directly related to the topic discussed here, recognized this property of hCG is the primary reason for avoiding its use when the risk of OHSS looms. In these cases, GnRH-a is preferred for triggering ovulation. Yet GnRH-a trigger causes problems of its own in the luteal phase and impedes embryo implantation, which is the subject of discussion in a different article of this series.

Second, hCG—at least at ovulation-triggering doses—exerts lasting alterations of pituitary function and response to endogenous GnRH (16). The use of hCG to replace the LH surge contributes to a chain of events that lead to the need for LPS to palliate to CL dysfunctions encountered in OS.

For several decades, OS and LPS have been intimately linked for the reasons described above (11). The pathophysiology of pituitary alterations encountered in OS—a multifactorial phenomenon that hampers proper CL support—also