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# *Use of Gonadotropin-Releasing Hormone Agonist to Cause Ovulation and Prevent the Ovarian Hyperstimulation Syndrome*

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Human menopausal gonadotropins (hMG) have been used successfully since the early 1960s as medications for the stimulation of follicular development in anovulatory patients.[1,2] More recently, this regimen has been used to stimulate the development of follicles in normal ovulatory women in preparation for in vitro fertilization and embryo transfer (IVF/ET) or other assisted reproductive techniques.

In patients treated with gonadotropins, the luteinizing hormone (LH) surge is usually absent or attenuated; therefore, the administration of human chorionic gonadotropin (hCG) is required to induce oocyte maturation and ovulation.[3,4] Whereas acute exposure of hCG appropriately may replace the LH surge for the induction of these periovulatory events, it remains to be determined whether hCG exposure alters the normal patterns of the final stage of follicular development, oocyte maturation, and corpus luteum function.[5,6]

Although similar in action to LH, hCG, because of its longer half-life (> 24 hours versus 60 minutes),[7,8] does not provide a physiologic stimulus that is identical to the endogenous LH surge.[9–11] Furthermore, by

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contrast with the spontaneous normal menstrual cycle, where both LH and follicle-stimulating hormone (FSH) are secreted at midcycle, administration of hCG results in an increase in LH activity only.

Because of its longer half-life compared with that of LH, hCG administration to hMG-treated patients results in a sustained luteotropic effect, development of multiple corpora lutea, and supraphysiologic levels of estradiol (E2) and progesterone (P) throughout the luteal phase. In patients with excessive responses to gonadotropin stimulation, this sustained luteotropic stimulation may result in ovarian hyperstimulation syndrome (OHS), the most serious complication related to gonadotropin therapy.[12] Excessive levels of circulating E2 have been implicated in the relatively high rates of implantation failure and early embryonic loss in stimulated cycles.[13,14]

Until recently, hCG was the only effective therapy available for the induction of oocyte maturation and ovulation in stimulated cycles. The use of gonadotropin-releasing hormone (GnRH) to trigger a midcycle LH surge and ovulation is ineffective because it elicits a transient LH surge for only a few hours, which is physiologically insufficient to initiate meiotic maturation of the oocytes and to trigger ovulation. Previous attempts to trigger ovulation with repeated injections or infusion of GnRH in anovulatory patients after hMG treatment yielded variable results.[15–19]

The potent GnRH analogue (GnRHa) induces a sustained release of LH from the pituitary gland that may last for 24 hours. This initial "flare-up" effect is followed by pituitary desensitization to further GnRH stimulation.[20–23] In 1988, we reported preliminary results demonstrating the efficacy of one or two GnRHa injections to trigger a sustained preovulatory LH/FSH surge that effectively induced oocyte maturation in patients undergoing ovarian stimulation for the purpose of IVF/ET.[24,25] We also have shown that injection of GnRHa instead of hCG provides, for the first time, a means by which the development of OHS in patient at high risk for having this syndrome reliably can be prevented.[24,25] The endocrine basis and the potential clinical applications of GnRHa for ovulation induction and the prevention of OHS are reviewed in this article.

## *The Spontaneous LH/FSH Surge*

Follicle-enclosed oocytes are arrested in the prophase of the first meiotic division until the midcycle LH/FSH surge. The surge initiates a cascade of events that result in germinal vesicle breakdown and reinitiation of meiosis, luteinization of the follicular wall, and eventually, ovulation.

The duration of the normal midcycle LH surge is 48.7 ± 9.3 hours.[26] Its onset occurs abruptly. The normal LH surge can be divided into three phases, a rapidly ascending limb (14 hours), a peak plateau phase (14 hours), and a long descending phase (20 hours, Fig. 1). The rate of increase and decrease in the LH concentration is greater than that of FSH. The dynamics of the changes in ovarian hormones during the periovulatory period of the normal menstrual cycle also have been characterized (Fig. 1).[26] Serum E2 levels reach a peak at about the time of the onset of the LH surge and then decline rapidly. The circulating P level increases exponentially, beginning 12 hours before and continuing until 12 hours after the onset of the LH surge. It then plateaus for approximately 24 hours preceding ovulation. After follicular rupture (36 hours after LH surge onset), a second rise in the P level and a continuous fall in the E2 concentration are observed, reflecting an acute shift in ovarian steroidogenesis in favor of P and the beginning of the luteal phase.

The threshold amplitude and duration of the midcycle LH surge required for the final stage of follicle maturation and its enclosed oocyte have been studied to a limited extent in primates. The temporal relationship between the LH surge and human oo-

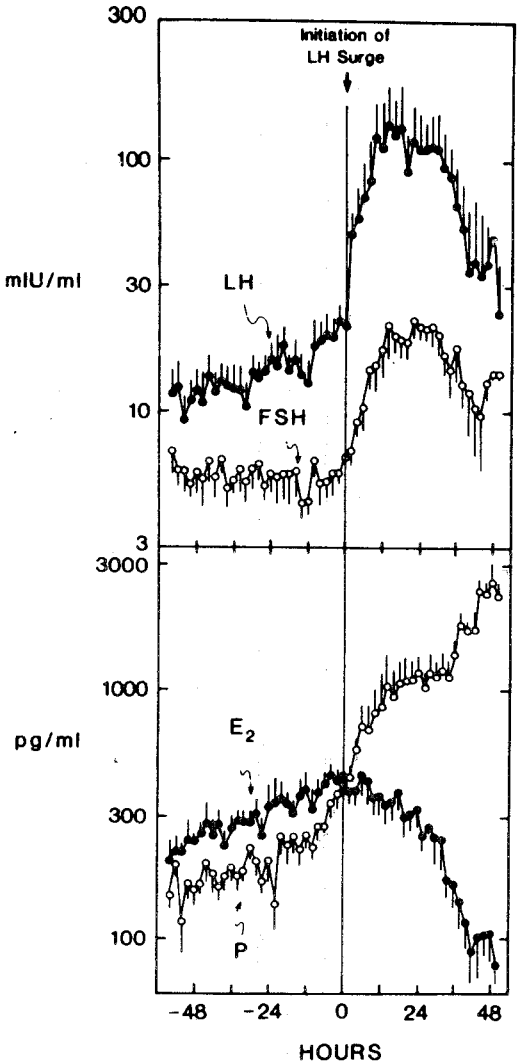


*FIG. 1.* The normal LH/FSH surge. Serum levels of pituitary and ovarian hormones were measured every 2 hours for 5 days at midcycle in seven women. (from Hoff JD, Quigley ME, Yen SSC.[26])

cyte maturation in vivo throughout the human preovulatory period has been studied by Seibel et al.[27] If an oocyte was harvested more than 18 hours after the onset of the LH surge, resumption of meiosis had occurred. Twenty-eight to 38 hours after the onset of the LH surge, preovulatory oocytes in metaphase II were obtained (Fig. 2). Others demonstrated that 14 hours of elevated LH did not elicit the normal periovulatory events in follicles of stimulated monkeys.[28] However, the majority of the oocytes retrieved 27 hours after hCG injection had reentered meiosis. These studies in humans and monkeys suggest that the threshold duration for the LH surge levels required to reinitiate meiosis appears to be 14–18 hours. To obtain metaphase II oocytes at the time of follicle aspiration, a LH surge of more than 28 hours appears to be required.[27]

The threshold amplitude of the midcycle LH surge required for human oocyte maturation and other periovulatory events is not known. Studies in rats suggest that only 5% of the normal LH surge amplitude is necessary for oocyte maturation, whereas 85% of the surge is required for ovulation, suggesting that the threshold of LH exposure varies for different periovulatory events.[29] No comparable information is available for primates.

An endogenous LH/FSH surge occurs infrequently or is attenuated in women treated with gonadotropins, despite persistently elevated levels of E2.[3] Therefore, the administration of hCG is needed to induce oocyte maturation and ovulation. It has been suggested that nonsteroidal factors, gonadotropin inhibin surge-inhibiting factor and inhibin, present in follicular fluid, are secreted from the ovary and block the surge mode of LH and FSH secretion induced by either a bolus of E2 or GnRH.[30,31] However, as discussed subsequently, our data show that GnRHa injection can overcome this block and elicit a LH/FSH surge in ovarian-stimulated patients that is comparable in magnitude to that of the normal menstrual cycle.

## *The GnRHa-Induced LH/FSH Surge*

Several regimens for the induction of a preovulatory LH/FSH surge with GnRHa have been reported and were found to be effective

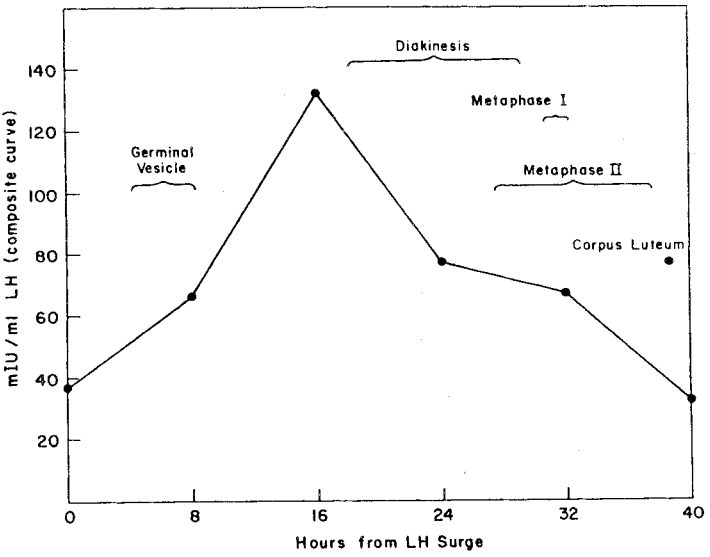


*FIG. 2.* The temporal relationship between oocyte maturation and the LH surge. (from Seibel MM, Smith DM, Levesque L, Borten M, Taymor ML.[27])

in triggering oocyte maturation and ovulation. These include single or repeated injections of GnRHa (100–500 μg) given either subcutaneously or intranasally (Table 1).[25,32–39]

Pituitary and ovarian responses to midcycle GnRHa injections in stimulated cycles are displayed in Figure 3. The injection of GnRHa resulted in an acute release of LH and FSH. The serum LH and FSH levels rose over 4 and 12 hours, respectively, and were elevated for 24–36 hours. The amplitude of the surge was similar to that seen in the normal menstrual cycle, but by contrast with the natural cycle (Fig. 1), the surge consisted only of two phases: a short ascending limb (> 4 hours) and a long descending limb (> 20 hours).

Despite the presence of supraphysiologic concentrations of E2 before the GnRHa in-

*TABLE 1. GnRH-a for the Induction of Preovulatory LH/FSH Surge*

| Reference | Cycle | GnRH-a | Dosage |
|---|---|---|---|
| Itskovitz et al.[24,25] | IVF | Buserelin | 250 μg, 500 μg, 250 μg × 2, 500 μg × 2 (SC, 8-hr interval) |
| Lanzone et al.[32] | Ovulation induction, natural cycle | Buserelin | 200 μg × 3 (SC, 12-hr interval) |
| Gonen et al.[33] | IVF | Leuprolide acetate | 500 μg (SC) |
| Imoedemhe et al.[34,35] | IVF | Buserelin | 100 μg × 2 (nasal spray, 8-hr interval) |
| Tulchinsky et al.[36] | Ovulation induction | Leuprolide acetate | 500 μg × 2 (SC, 16-hr interval) |
| Emperaire et al.[37,38] | Ovulation induction, IVF | Decapeptyl | 100 μg × 3 (SC, 8-hr interval) |
| | | Buserelin | 200 μg × 3 (nasal spray, 8-hr interval) |
| Segal and Casper[39] | IVF | Leuprolide acetate | 500 μg (SC) |

SC, subcutaneous.

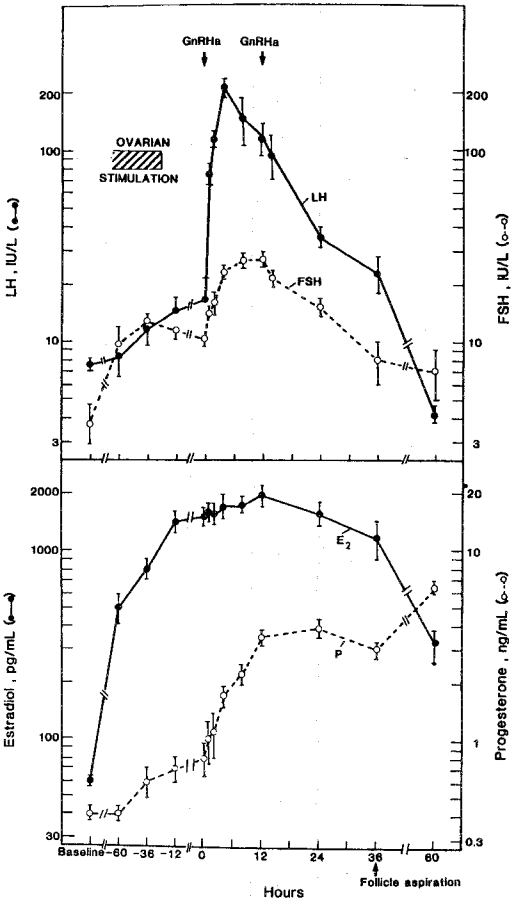


*FIG. 3.* Hormonal levels (mean ± standard error of the mean) before and after the injection of two doses of buserelin acetate, 500 μg, in six IVF patients. Mean serum E2 level: before GnRHa injection was 1,494 ± 422 pg/ml (± standard deviation). The baseline is day 3 of the menstrual cycle. (from Itskovitz J, Boldes R, Levron J, Erlik Y, Kahana L, Brandes JM.[25])

jection, the dynamics and pattern of ovarian hormone changes in the periovulatory period in ovarian-stimulated women were qualitatively similar to the changes observed in the normal natural cycle (Figs. 1, 3). As in the natural cycle, the LH surge was associated with a rapid rise of P and the attainment of peak E2 levels for the first 12 hours after the injection of GnRHa. This was followed by a transient suppression of P biosynthesis and a gradual decline in E2 levels during the 24 hours preceding follicle aspiration. After oocyte retrieval, a second rapid rise of P and a continuous fall of E2 were observed, reflecting an apparently normal transition from the follicular to the luteal phase in ovarian steroidogenesis.

## *The Luteal Phase*

Patients given GnRHa to trigger endogenous LH surge had an apparently normal follicular–luteal shift in ovarian steroidogenesis but had lower circulating luteal E2 and P levels than did patients injected with an ovulatory dose of hCG (Fig. 4).[25] Some of these patients had early luteolysis and a short luteal phase.[25,39] The longer duration of plasma hCG elevation compared with the briefer GnRHa-induced LH elevation may result in higher luteal phase E2 and P levels. After ovulation, the corpus luteum is dependent on pituitary LH.[40,41] It is also possible, therefore, that the prolonged down-regulation of pituitary GnRH receptors after a midcycle injection of high-dose GnRHa results in reduced LH support for the developing corpora lutea, reduced steroidogenesis, and early luteolysis. Further research is needed to study the function of the corpus luteum throughout the luteal phase and early pregnancy and the requirements for luteal support in ovarian-stimulated patients in whom oocyte maturation and ovulation were induced by GnRHa. Currently, patients treated with midcycle GnRHa in our program are given P and E2 to support their luteal phase.

All current protocols use high-dose GnRHa (100–500 μg). The minimal effective dose of GnRHa required to trigger an endogenous midcycle LH surge sufficient to induce oocyte maturation and ovulation, without significantly affecting the normal development and function of the corpus luteum, remains to be established.

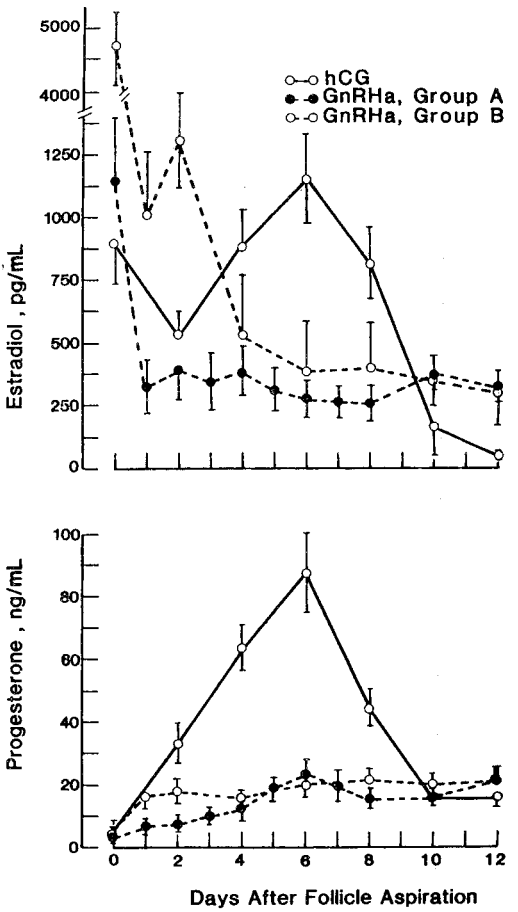


*FIG. 4.* Serum E2 and P levels (mean ± standard error of the mean) throughout the luteal phase in "normal responders" injected with either hCG (O—O, n = 14, E2 on the day of hCG = 1,182 ± 562 pg/ml [± standard deviation]) or GnRHa (group A, ●--●, n = 6, E2 on the day of GnRHa = 1,494 ± 422 pg/ml) and in "high responders" injected with GnRHa (group B, O--O, n = 8, E2 on the day of GnRHa = 7,673 ± 3,028 pg/ml). Control normal responders treated with hCG were supplemented with progesterone in oil 25–50 mg/day from day 2–12. Normal and high responders injected with GnRHa were supplemented with estradiol valerate and progesterone in oil to maintain serum E2 and P levels at approximately 200–400 pg/ml and 15–20 ng/ml, respectively. (from Itskovitz J, Boldes R, Levron J, Erlik Y, Kahana L, Brandes JM.[25])

## *Benefits and Limitations*

The currently available data suggest that GnRHa is an effective alternative to hCG for use in IVF cycles or for the induction of ovulation in anovulatory women. Pregnancy rates in cycles in which oocyte maturation was induced by GnRHa are similar to the rates observed in hCG cycles.

The use of GnRHa instead of hCG for ovulation induction has several potential advantages. Whereas the role of the midcycle LH surge in oocyte maturation, luteinization of the granulosa theca cells, and follicle rupture is well established, it is not known whether the concurrent midcycle FSH surge plays any physiologic role in these periovulatory events in primates. The presence of a midcycle FSH surge is not obligatory because apparently normal oocyte maturation and ovulation do occur after administration of hCG. In rats, however, a role for FSH in the maturation of the oocyte–cumulus complex has been demonstrated.[42] It is not known whether the use of GnRHa, because of its release of endogenous FSH, has any advantage over the use of hCG, which has no FSH-like activity.

A potential advantage for the use of GnRHa instead of hCG for ovulation induction stems from the short (24–36 hours) duration of the LH surge induced by GnRHa, which provides a more physiologic ovulatory stimulus than the extended surge (approximately 6 days) associated with hCG. This time-limited stimulus can be restricted to the few follicles that are more mature, and thus a lower frequency of multiple pregnancies could be expected in patients undergoing ovarian stimulation for the purpose of ovulation induction. As discussed earlier, this GnRHa-induced LH surge is associated with lower luteal E2 and P than that seen after hCG injection. Luteal phase support and the desired concentrations of E2 and P could be managed more accurately, thus avoiding the excessive levels of circulating estrogens and, theoretically, improving the chance for implanta-

tion and increasing pregnancy rates in stimulated cycles.[13,14] As discussed subsequently, GnRHa therapy has been found to be effective for preventing the development of OHS in patients at high risk for having this syndrome.[25] It should be noted that GnRHa would not be effective for triggering an adequate LH surge in women with a low gonadotropic LH reserve (e.g., hypothalamic hypogonadism) or in cycles where GnRHa downregulation was used to prevent a spontaneous LH surge or early luteinization.

## Prevention of OHS

An important benefit emerging from the use of GnRHa, rather than hCG, for ovulation induction, is the ability of this therapeutic regimen to prevent OHS, the most serious complication related to gonadotropin therapy. The full-blown clinical syndrome is characterized by ovarian enlargement with multiple functioning luteal cysts, increased vascular permeability, third-space accumulation of fluid, hemoconcentration, and oliguria. Cases of renal failure, hypovolemic shock, thromboembolism, adult respiratory distress syndrome, and even death have been reported.[12] The pathogenesis of OHS is not known, but it clearly is related to the existence of multiple functioning corpora lutea and to the sustained luteotropic effects of endogenous or exogenous hCG.

Until recently, there has been no means by which OHS could be prevented because withholding hCG administration results in failure to ovulate and conceive. Follicle aspiration and elective cryopreservation of all embryos to minimize the risk of OHS in IVF patients at high risk of having OHS does not eliminate the syndrome.[43] In 78 women with serum E2 levels greater than 3,500 pg/ml (mean approximately 5,000 pg/ml on the day of hCG injection), after pituitary downregulation with buserelin and ovarian stimulation with hMG, all their embryos were cryopreserved, and buserelin was continued in the luteal phase. Twenty-one women (27%) had OHS, and six had the severe form of the syndrome. In 1988, we reported our preliminary results and suggested that midcycle injection of high-dose GnRHa (buserelin, 500 $\mu$g × one dose or 500 $\mu$g × two doses, 8 hours apart) is effective, not only for the induction of oocyte maturation and ovulation, but also for the prevention of OHS in ovarian-stimulated patients.[24,25] We have treated more than 20 women, all of whom had serum E2 levels of 4,000 pg/ml or more on the day of GnRHa injection. None has had any signs or symptoms of OHS despite the presence of extremely high circulating levels of E2, as high as 14,600 pg/ml. In the presence of multiple preovulatory follicles before GnRHa administration, the ovaries containing many luteal cysts were, not surprisingly, enlarged after GnRHa injection, but only a minimal amount of peritoneal fluid was observed ultrasonographically. Given the large number of corpora lutea, serum luteal E2 and P were much lower than expected and were, in some patients, similar or lower than the levels detected in the luteal phase of the normal menstrual cycle. This would suggest that many of these luteal cysts in GnRHa-treated patients were hormonally inactive and could explain the absence of OHS in these patients because the syndrome will not develop unless multiple hormonally active corpora lutea are present.

More studies are required to determine the efficacy and safety of midcycle GnRHa administration in reducing the risk of OHS in patients with exaggerated response to gonadotropin therapy. Furthermore, the possible adverse effects on electrolyte homeostasis and coagulation of the very high circulating periovulatoy plasma E2 levels, even in the absence of frank OHS, remain to be evaluated. The current data strongly suggest that the use of GnRHa in place of hCG permits, for the first time, ovarian stimulation without the risk of OHS.

## Summary

The physiologic basis and clinical applications of the use of GnRHa, rather than

hCG, to induce the final stage of oocyte maturation and ovulation in gonadotropin-treated cycles were reviewed. A single mid-cycle dose of GnRHa is able to trigger a preovulatory LH/FSH surge, leading to oocyte maturation and pregnancy in women undergoing ovarian stimulation for IVF/ET or induction of ovulation in vivo. The limited information currently available suggests there are similar pregnancy rates in patients treated with either GnRHa or hCG.

The potential clinical advantages of GnRHa over hCG in gonadotropin-treated cycles include 1) the ability to titrate the amplitude and duration of the LH surge, 2) better control of luteal steroid hormone levels, 3) a higher implantation rate, 4) a lower rate of multiple pregnancy, and 5) a reduced risk of OHS. To date, the GnRHa regimen has been effective in preventing OHS in patients at high risk for having this complication.

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