

Luteal phase estradiol versus luteal phase estradiol and antagonist protocol for controlled ovarian stimulation before in vitro fertilization in poor responders

Luteal phase synchronization of follicular growth has been suggested as a means to improve ovarian response in low responders. We compared luteal E₂ and antagonist (n = 256) with luteal E₂ only (n = 57) before antagonist protocol in low responders. The addition of GnRH antagonist to luteal E₂ for luteal suppression before ovarian stimulation for IVF does not improve IVF outcomes in poor responders. (*Fertil Steril*® 2011;95:324–6. ©2011 by American Society for Reproductive Medicine.)

Key Words: Poor response, controlled ovarian stimulation, GnRH antagonist, luteal estradiol

Low response to controlled ovarian stimulation (COH) is encountered in 9% to 26% of IVF cycles (1). Multiple protocols have been suggested to improve outcomes; however, no specific intervention can claim a consistent increase in ongoing pregnancy rates (PRs). Gonadotropin-releasing hormone antagonist protocols were introduced for ovarian stimulation in low responders to avoid oversuppression of the pituitary gland and the ovary by GnRH agonists.

Because of the variable sensitivity of follicles to FSH, the FSH rise during the late luteal phase may lead to advanced growth of the few, more sensitive follicles and ultimately result in a smaller follicular cohort available for recruitment. Gonadotropin-releasing hormone antagonist protocols do not allow for synchronization of follicles at the time of luteal-follicular transition, before initiation of gonadotropin stimulation (2). Synchronization of early antral follicle growth in the luteal phase before COH in antagonist cycles to increase oocyte yield has been proposed by many investigators (3–6). Estrogen prevents luteal FSH rise and may also increase sensitivity to gonadotropins. GnRH antagonists induce luteolysis, prevent FSH rise, and may increase storage and release of

endogenous gonadotropins (7). Luteal E₂ and/or luteal antagonist have been used as adjuvants before gonadotropin stimulation in antagonist protocols (8–12). However, the optimal regimen for synchronization of follicular growth before COH is not known.

This was a retrospective cohort study in which 313 patients with history of poor response to COH were recruited between January 2006 and December 2008. Approval for the study was obtained from the Institutional Review Board of the University of Connecticut Health Center. Patients included were <43 years old, with five or fewer oocytes retrieved in a prior cycle at a starting dose of gonadotropins of ≥ 300 IU, or previous cycle cancellation because of poor follicular recruitment defined as three or fewer follicles seen on transvaginal ultrasound examination and/or peak E₂ <500 pg/mL. Patients underwent ovarian stimulation with a flexible antagonist protocol, preceded by luteal synchronization with use of either transdermal E₂ or E₂ and GnRH antagonist at their physician's discretion. Primary outcome measure was the delivery rate per started cycle. Secondary outcome measures were the number of oocytes retrieved, clinical PR (defined as the presence of a gestational sac with fetal cardiac activity), cancellation rate, and number of embryos available for transfer.

In the luteal phase ganirelix protocol group (n = 256), a transdermal E₂ patch (0.1 mg) was initiated on day 10 after the LH surge and was replaced every other day. On the 11th day, patients began daily administration of ganirelix acetate (Organon Pharmaceuticals, West Orange, NJ) 0.25 mg SC for 3 days. Patients receiving the luteal phase E₂ protocol (n = 57) underwent a similar regimen without luteal administration of ganirelix. Patients presented on day 2 of their ensuing menses for measurement of FSH, LH, and E₂ levels and a baseline ultrasound examination. The last E₂ patch was removed, and ovarian stimulation was started with use of a high dose of gonadotropins, an average of 600 IU of either recombinant FSH (Gonal-F; Serono Inc., Rockland, MA) alone or in combination with purified urinary hMG (Menopur; Ferring Pharmaceuticals, Tarrytown, NY). Ganirelix was restarted when leading follicles measured ≥ 14 mm or serum E₂ level ≥ 400 pg/mL was reached. Human chorionic gonadotropin was

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TABLE 1

Demographic characteristics and IVF outcomes in the luteal E₂ and luteal E₂ plus GnRH antagonist treatment groups.

Characteristic and outcome	LP (n = 57)	LPG (n = 256)
Age (y) ^a	39.2 ± 0.5	38.3 ± 0.2
BMI (kg/m ²) ^a	25.5 ± 0.8	25.7 ± 0.4
Day 3 FSH (mIU/mL) ^a	10.4 ± 4.6	11.1 ± 3.9
FSH on day 1 of stimulation (mIU/mL) ^a	4.9 ± 2.7	4.2 ± 2.6
Stimulation days ^a	11.4 ± 0.4	11.2 ± 0.2
Total dose of gonadotropins (IU) ^a	6,538 ± 276	6,104 ± 88
Cancellation rate, % (n)	35.1 (20/57)	24.6 (63/256)
Peak E ₂ (pg/mL) ^a	1,494 ± 121	1,509 ± 57
Oocytes retrieved (n) ^a	7.5 ± 0.6	8.8 ± 0.4
Fertilization rate (%) ^a	68 ± 5	74 ± 2
Cleavage stage embryos (n) ^a	3.9 ± 0.5	4.6 ± 0.2
Embryos transferred (n) ^a	2.2 ± 0.3	2.4 ± 0.1
Implantation rate (%) ^a	20.0 ± 5.0	23.0 ± 2.0
CP/initiated cycle, % (n)	22.8 (13/57)	30.1 (77/256)
Live birth/initiated cycle, % (n)	21.1 (12/57)	23.8 (61/256)
CP/transfer, % (n)	43.3 (13/30)	43.3 (77/178)
Live birth/transfer, % (n)	40.0 (12/30)	34.3 (61/178)
Pregnancy loss rate, % (n)	7.7 (1/13)	20.7 (16/77)
Premature LH rise, % (n)	8.8 (5/57)	4.3 (11/256)

Note: P=not significant for all comparisons; BMI = body mass index; CP = clinical pregnancy; LP = luteal phase E₂; LPG = luteal phase ganirelix.

^a Mean ± SD.

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administered SC (5,000–10,000 IU) when at least three leading follicles reached 17 mm mean diameter. Oocyte insemination or intracytoplasmic sperm injection were performed as indicated. The highest morphologic grade embryos were transferred into the uterine cavity 72 hours after retrieval. Luteal phase supplementation was achieved by administering 50 mg P in oil daily IM.

Statistical analyses were performed with use of the Statistical Package for the Social Sciences (release 17.0; SPSS Inc., Chicago). A paired *t*-test was used to compare continuous variables, and the Fisher's exact test was used for categorical variables. A *P* value < .05 was considered statistically significant.

The baseline characteristics of the patients enrolled in this study are shown in Table 1. There were no significant differences between the two groups in mean age, body mass index, or basal FSH and E₂ levels. The two groups were also comparable in duration of ovarian stimulation, total dose of gonadotropins, and E₂ levels on the day of hCG administration. Mean number of prior cycles was 1.9 ± 0.9 in the luteal phase ganirelix group versus 1.9 ± 1.2 in the luteal phase E₂ group, *P*=.9. As predicted, significantly lower FSH levels before initiation of stimulation were noted in both groups when compared with the patients' previous baseline levels (4.2 ± 2.6 vs. 11.1 ± 3.9 mIU/mL, *P*<.003, in the luteal phase ganirelix group and 4.9 ± 2.7 vs. 10.4 ± 4.6 mIU/mL, *P*<.001, in the luteal phase group). Interestingly, there was no significant difference in the baseline FSH levels before initiation of stimulation between both groups, suggesting that a similar level of suppression was achieved.

The mean number of retrieved oocytes was comparable in the luteal phase ganirelix and luteal phase E₂ groups (8.7 ± 0.3 and 7.5 ± 0.6, respectively; *P*=.1). Both groups did not differ in their cancellation rate, premature LH rise (defined as LH >10 mIU/mL), fertilization rate, and mean number of cleavage embryos

available and of embryos transferred. Oocyte retrieval in patients with premature LH surge was cancelled. There were also no differences in the implantation or clinical PRs. Delivery rates per started cycle were also similar for the luteal phase ganirelix and luteal phase E₂ regimens, respectively (23.8% and 21.1%; *P*=.7). Pregnancy loss rate was also similar in both groups (7.7% and 20.7%; *P*=.4).

The initial observations that luteal administration of either E₂ or antagonist can synchronize follicular growth before recruitment prompted several investigators to use either a GnRH antagonist (9, 10), E₂ (11, 12), or both (8–13) in the prior luteal phase to achieve synchronization of follicular growth. The effect of adding luteal E₂ was investigated by Hill et al. (12) in a study comparing 57 infertile women treated with luteal oral E₂ followed by either GnRH antagonist or microflare agonist stimulation versus 228 matched women with no cycle pretreatment. Luteal E₂ was associated with improved embryo development and a trend toward improved delivery rates. Consistent with other studies, the luteal E₂ protocol required a higher dose of gonadotropins with longer stimulation. Yi et al. (14) randomly assigned normal responders to either standard long GnRH agonist protocol or luteal E₂ before GnRH antagonist cycles. There was a significant increase in serum LH levels and in the incidence of premature LH surge with luteal E₂ use (4.6%) but no adverse effects on other IVF parameters. The incidence of premature LH rise in our study was 4.3% in the luteal phase ganirelix group and 8.8% in the luteal phase E₂ group (*P*=.18).

The use of luteal antagonist for synchronization of follicular growth in low responders also was reported (9, 10) with possible improvement in PRs compared with long agonist stimulation. Other investigators subsequently have proposed combining the benefits of the luteal E₂ with the luteal antagonist, suggesting

that both interventions could have a synergistic effect. Dragisic et al. (8) in a crossover study reported that the use of a luteal E₂ patch combined with GnRH antagonist, yielded a lower cancellation rate, higher number of retrieved oocytes, and higher number of embryos transferred in women who had fewer than five oocytes retrieved in a prior cycle, basal FSH >12 mIU/mL, or E₂ <500 pg/mL on the day of hCG administration. Our group (13) in a retrospective analysis compared 45 low-responder patients who underwent stimulation with the luteal phase ganirelix protocol with 76 who were stimulated with a microdose GnRH agonist regimen. The number of retrieved oocytes and available embryos were comparable in both groups. Ongoing PRs per started cycle were 20% in the luteal phase ganirelix group versus 17% in the microdose group. The luteal phase ganirelix group, however, was associated with longer stimulation and required higher doses of gonadotropins.

We found no statistically significant differences in the number of oocytes retrieved, embryos available for transfer, or cancellation rates and PRs. Our study was powered enough (80%) to detect a 15% difference in clinical PRs between the two groups.

Although only patients with poor prognosis were included, the delivery rates per transfer were 40% and 34.3% for the luteal phase and luteal phase ganirelix regimens, respectively, underscoring the potential benefit of synchronizing follicular growth in anticipated poor responders. Both groups showed significantly lower baseline

serum FSH levels compared with the levels obtained during a previous cycle without luteal treatment. Nevertheless, we were not able to demonstrate a difference in the baseline FSH levels observed after luteal E₂ compared with luteal E₂ and GnRH antagonist, suggesting that the combination has no synergistic effect on FSH secretion. At least from a cost-effective standpoint, the use of E₂ alone would reduce the current cost for COH by about \$336 to \$450 (the cost for three injections of ganirelix in Connecticut).

One limitation of this study was the enrollment of patients into treatment groups according to physician's preference. Patients were four times more likely to be recruited to luteal phase ganirelix than to the luteal phase E₂ group. It is possible that this preference may have resulted in a systematic error in recruitment for this study. The two groups, however, were similar in their baseline characteristics, and the majority of patients in both groups had a low response to stimulation in a prior cycle or had a previously cancelled oocyte retrieval. Nevertheless, the possibility of type II error cannot be excluded entirely.

In this study we have shown that synchronization of follicular growth in the luteal phase using E₂ and a GnRH antagonist is not superior to E₂ alone in low responders undergoing ovarian stimulation before IVF. Further randomized studies comparing both protocols prospectively are needed to confirm these findings.

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