

# Efficacy of Gonadotropin-Releasing Hormone Agonists to Induce Ovulation Following Low-Dose Human Menopausal Gonadotropin Stimulation

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## I. Introduction

Conventional human menopausal gonadotropin (hMG) therapy requires the use of an additional injection of human chorionic gonadotropin (hCG) because the high levels of estradiol ( $E_2$ ) generated by gonadotropin therapy suppress the endogenous luteinizing hormone (LH) surge. Through the use of pelvic sonography to determine timed collapse of the dominant follicle, failure to release any oocyte from the follicle(s) known as the luteinized unruptured follicle (LUF) syndrome was found to be a frequent complication of hMG therapy despite hCG injection, thus reducing subsequent pregnancy rates (PRs) (Check *et al.*, 1990). Failure to release oocytes in cycle one is usually associated with LUF in the second cycle if the same therapy is used.

Oocyte release is not only preceded by the LH surge, but also a smaller rise in follicle-stimulating hormone (FSH). Among other functions, FSH may be important in converting plasminogen to plasmin which may help to detach the oocyte from the follicle wall. Gonadotropin-releasing hormone agonists (GnRHa) used in a short-term manner may release both LH and FSH and may prove to be superior to hCG in releasing oocytes following hMG stimulation. In fact, data demonstrate that the GnRHa leuprolide acetate (LA) resulted in a lower incidence of LUF than hCG in hMG-treated cycles and was effective despite several previous failures with hCG (Check *et al.*, 1993).

The use of ultralow dose gonadotropin therapy has been found to be as effective and possibly superior to conventional dosages despite the

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induction of fewer follicles (Buvat *et al.*, 1989; Sagle *et al.*, 1991; Hamilton-Fairley *et al.*, 1991). We hypothesized that the higher PR, even with fewer follicles, may be related to a lower incidence of LUF syndrome; the lower sera  $E_2$  levels generated may have less adverse effects on the endogenous FSH surge.

The study presented herein evaluated the efficacy of LA vs hCG when ultralow-dose hMG stimulation is given to determine if (1) the incidence of LUF following hCG is lower than previously reported when conventional hMG was used, and (2) to see if the superiority of LA over hCG to release oocytes when conventional hMG was used is lost when an ultralow dose regimen is used.

## II. Materials and Methods

One hundred and ten cycles of ultralow dose hMG stimulation were evaluated. All patients had a minimum criteria of a baseline FSH level  $<20$  on day 3 of their cycle. The releasing agent (LA vs hCG) was randomly selected; however, some patients insisted on using the conventional hCG, leading to a slightly uneven grouping of 61 receiving hCG and 49 injected with LA.

The ultralow dose hMG regimen consisted of taking only 75 IU of hMG IM daily. The dosage was increased to 112.5 IU daily only if by 7 days the follicular maturation was not adequately progressing. The objective was to demonstrate at least one follicle by pelvic sonography that had an average diameter of 18–24 mm and a minimum serum  $E_2$  concentration of 200 pg/ml.

hCG and LA were given once the minimal criteria for one mature follicle was attained. If the serum  $E_2$  was only slightly over 200 pg/ml but there were other follicles close to the right size, the hMG was extended for 1 to 2 days because of the possibility that even the proper sized follicles were not quite mature (since the other follicles were likely to contribute to the total serum  $E_2$  level).

hCG was given in a one-time dosage of 10,000 units IM; the LA was given in three doses, 12 hr apart, at 1 mg SC. Because of the possibility of luteal phase defects with LA, 5000 units of hCG was given once there was evidence of oocyte release. Both the hCG and LA groups were also given progesterone (P) support (50 mg oral micronized capsules four times/day) in the luteal phase.

Failure to release an oocyte (LUF) was diagnosed if none of the follicles demonstrated a 5-mm shrinkage in size 3 days following the hCG injection or the first of the three LA injections, and this failure to show follicular collapse was associated with a rise of serum  $P > 2$  ng/ml and a reduction

in the serum  $E_2$  level. All sonograms were performed using an ATL Ultramark 4 unit (Advanced Technology Laboratories, Bothell, WA) using a 5-MHz endovaginal transducer and were interpreted by an experienced sonographer.

### III. Results

There were 44.5% ( $n=49$ ) who received LA for oocyte release instead of hCG, but there were 8 (16.3%) who inadvertently did not receive the 5000 U luteal phase support dosage after oocyte release.

A total of 51 of the 61 patients (83.6%) treated with hCG released oocytes vs 40 of 49 (81.6%) given LA.

There were 11 pregnancies in 61 hMG cycles (18.0% per cycle) given hCG to release vs 28.6% for those taking LA. Subdividing those patients taking LA only vs LA with luteal phase hCG support, 7 of 41 (17.1%) of the former failed to release vs 2 of 8 (25.0%) in the latter. The PR in the former in those releasing was 12 of 34 (35.3%) in the former vs 2 of 6 (33.3%) in the latter. Calculating the PR according to only those releasing with hCG without LA, there were 11 pregnancies in 51 cases (21.5%). There was no difference in PR according LA vs hCG ( $\chi^2 = 2.0, P = .15$ ).

### IV. Discussion

Using conventional hMG doses, the incidence of LUF following hCG was 44.3% (31 of 70); with ultralow dose hMG the LUF rate was 16.3% following hCG. The incidence of LUF with conventional vs ultralow dose hMG following LA was comparable (21.7% in the former vs 18.4% in the latter) (Check *et al.*, 1993). Thus, the reason ultralow dose gonadotropin regimens have produced higher PRs may be related to a lower incidence of LUF when hCG is used for oocyte release. It would be interesting to see if a lower PR still occurs using conventional hMG dosages but with LA as the releasing agent.

The midcycle LH is needed not only to release the oocyte but also to advance the process of meiosis. The fact that the PR following LA was at least as good as the PR following hCG suggests that a GnRHa is effective in oocyte maturation. The use of LA would not be logical in women treated with GnRHa down-regulation followed by hMG.

We did not find an association with blunted LH surges in patients with LUF syndrome not stimulated with gonadotropins (Check *et al.*, 1986). Since the LH surge is suppressed in classical hMG therapy, we did not measure the serum LH prior to hCG. Unfortunately, we did not measure the FSH levels on the day of hCG or after the releasing agent was given.

An interesting future study would be to measure immunoreactive and biologically active FSH levels to see if a lower level correlates with LUF. Until that time one can only speculate that the superiority of LA over hCG to release oocytes following conventional hMG therapy (but not ultralow dose therapy) may be related to inducing a better midcycle FSH surge. Furthermore, it would be of interest to compare sera FSH and  $E_2$  levels in those who still fail to release oocytes despite LA therapy. If indeed FSH does not rise sufficiently in these cases, then additional FSH may be given at the time of LA or hCG. Previous data did suggest some extra benefit of adding hMG to the hCG injection to improve release rates (Check *et al.*, 1992).

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