

MIDCYCLE STEROIDAL LEVELS AFTER ULTRA-LOW-DOSE PURE FOLLICLE-STIMULATING HORMONE STIMULATION VERSUS HUMAN MENOPAUSAL GONADOTROPIN STIMULATION IN EUESTROGENIC WOMEN WITH FOLLICULAR MATURATION DEFECTS

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ABSTRACT

Objective: To compare the midcycle endocrine steroidal variables in 32 infertile women with follicular maturation defects treated with ultra-low-dose pure follicle-stimulating hormone (FSH) or human menopausal gonadotropins (hMG).

Methods: A crossover design was used in which women were randomly assigned to a treatment modality (pure FSH or hMG) in the first cycle, and the alternative treatment was used in the second cycle. In the ultra-low-dose regimen, the dosage began at 1 ampule/day (75 IU) and could increase to a maximum of 1.5 ampules/day. The mean midcycle serum levels determined at the time of peak follicular maturation and before the administration of human chorionic gonadotropin or gonadotropin-releasing hormone for release of oocytes were compared.

Results: In the pure FSH cycle, the mean estradiol (E_2), progesterone, and luteinizing hormone (LH) levels were 316 ± 119 pg/mL, 0.6 ± 0.4 ng/mL, and 23 ± 22 IU/L, respectively; in the hMG cycle, the mean E_2 , progesterone, and LH levels were 361 ± 193 pg/mL, 0.5 ± 0.4 ng/mL, and 21 ± 18 IU/L, respectively.

Conclusion: Ultra-low-dose gonadotropin therapy produces similar midcycle steroidal levels (E_2 , progesterone, and LH) whether or not LH is present in addition to FSH in the medications used for follicle stimulation. (*Endocr Pract.* 1996; 2:173-175)

INTRODUCTION

Human menopausal gonadotropins (hMG), an equal mixture of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH), followed by human chorionic gonadotropins (hCG) are a commonly used treatment to correct follicular maturation in women with ovulatory defects. Conventional therapy, however, is occasionally complicated by increased estrogen production from multi-follicular development, which could result in ovarian hyperstimulation syndrome (1). Ovarian hyperstimulation syndrome consists of a series of iatrogenically induced

complications that have life-threatening potential. On the basis of clinical, laboratory, and ultrasonographic findings, ovarian hyperstimulation syndrome has been classified into mild, moderate, and severe cases (2). The characteristic symptoms of this syndrome are massive ovarian enlargement and increased capillary permeability, which causes a loss of protein-rich fluid from the intravascular compartment. Patients with severe ovarian hyperstimulation syndrome have ovarian enlargement, ascites, hemoconcentration, electrolyte disturbances, and various degrees of renal failure and generally require hospitalization. Multiple pregnancies could also jeopardize the outcome of the treatment (3,4).

The LH present in hMG preparations could influence the estrogen production by granulosa cells by stimulating more androgen precursors from the theca cells and therefore could be incriminated as an important factor in more than desired estrogen production. Furthermore, the increased preovulatory circulating levels of LH may cause the formation of luteinized unruptured follicles (5-7) and be detrimental to oocyte quality, and postfertilization events may result in failure of implantation and increased gestational loss (8,9). Finally, some reports suggest that higher LH levels in the follicular phase reduce pregnancy rates, increase spontaneous abortion rates, and may even decrease pregnancy success after in vitro fertilization-embryo transfer (8,10,11).

The objective of this study was to compare the midcycle serum hormonal levels after ultra-low-dose gonadotropin stimulation to determine whether the absence of exogenous LH in the stimulating medication (pure FSH) causes a different hormonal profile than a preparation containing exogenous LH (hMG). Midcycle levels were measured at the time of peak follicular maturation before the administration of hCG or gonadotropin-releasing hormone (GnRH) for oocyte release.

PATIENTS AND METHODS

Experimental Design

A crossover design was used in which patients were randomly assigned to one of two treatment modalities on their first cycle of treatment and then received the alternative treatment modality on their second cycle. Thus, each patient in the study underwent two cycles of follicular stimulation—one with ultra-low-dose pure FSH and one with ultra-low-dose hMG—and the order of administration was chosen randomly for each patient. We assumed that the medication had no carryover effect from one cycle to the next.

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Study Subjects

The study group consisted of 32 women with follicular maturation defects detected in a university-associated private reproductive endocrinology practice. The women ranged in age from 24 to 43 years (mean age \pm standard deviation, 31.5 ± 4.2). On the basis of vaginal ultrasound studies and serum hormone studies, a follicular maturation defect was diagnosed as a failure to produce a follicle that attained a diameter of more than 17 mm with an estradiol (E_2) level of more than 200 pg/mL.

Although a follicular maturation defect was the primary indication for treatment, some of the women (12 of the 32) had secondary problems: 11 had stage I endometriosis or pelvic adhesions (or both), and 1 had male factor. Because each patient received both treatments in the crossover design of the study, differences in secondary conditions did not influence the results.

Treatment Protocols

Baseline early follicular phase E_2 , FSH, LH, and prolactin levels were determined during a cycle before treatment began. Patients were treated with either hMG (Pergonal—each ampule, 75 IU of FSH and 75 IU of LH) or pure FSH (Metrodin—each ampule, 75 IU of FSH and <1.0 IU of LH). The low-dose protocol used necessitated onset of therapy on day 3 to 5 of the menstrual cycle. The initial dosage was 1 ampule daily. If after 7 days of therapy ultrasound findings and circulating E_2 levels revealed inadequate follicular maturation (for example, follicles <10 mm and E_2 <100 pg/mL), the dosage was increased to 1.5 ampules daily. Serum hormone levels were determined and ultrasound studies of follicular size were performed every other day for the first week of therapy and then daily until a mature follicle was observed (maturity was defined as a follicle with a diameter that exceeded 17 mm and an E_2 level of more than 200 pg/mL). When a mature follicle was observed, hCG (10,000 U intramuscularly) or GnRH (1 mg every 12 hours for three doses) was given at the physician's discretion for release of oocytes; these hormones have been found to be equally effective (12). The serum levels measured at time of peak follicular maturation and before administration of a releasing agent were recorded as midcycle values.

This protocol was reviewed and approved by an internal advisory committee that consisted of members of the clinical practice staff. Patients were informed of the objectives and methods of the study and consented to participate.

Hormonal Studies

Serum LH, FSH, and progesterone levels were assayed by a semiautomated enhanced luminescence method (Amersham, Arlington Heights, IL). The progesterone assay had an intra-assay coefficient of variation (CV) of 11.78% at a concentration of 0.9 ng/mL and an interassay CV of 12.25%. The intra-assay and interassay CVs for LH and FSH were all less than 7% at concentrations of 11.5 IU/L and 18.5 IU/L, respectively.

Estradiol was assayed by a solid-phase radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA). A control serum sample with a mean value of 95 pg/mL yielded an intra-assay CV of 4.4% and an interassay CV of 6.9%.

Prolactin level was also determined by radioimmunoassay (Becton Dickinson, Orangeburg, NY). The intra-assay CV for this kit was 4.4% (at 12 ng/mL), and the interassay CV was 6.9%.

All serum levels were determined in the morning before the follicle-stimulating drug was injected.

Statistical Analysis

Paired *t* tests were used to compare the mean midcycle hormone levels by treatment used. *P* values of 0.05 or less were considered significant.

RESULTS

All 32 study participants completed two cycles of treatment, one with pure FSH and one with hMG. The baseline early follicular phase serum levels for these women were as follows: LH, 12.8 ± 3.2 IU/L; FSH, 12.8 ± 3.3 IU/L; E_2 , 32.0 ± 21.1 pg/mL; and prolactin, 8.0 ± 4.0 ng/mL.

During the treatment cycle with pure FSH, patients received the FSH for a mean duration of 9.1 ± 2.8 days. The mean total dosage administered was 8.6 ± 3.1 ampules. During the treatment cycles with hMG, patients received hMG for a mean duration of 8.9 ± 2.7 days; the mean total dosage administered was 9.0 ± 3.4 ampules. In the pure FSH treatment cycle, 20 patients received hCG for oocyte release, and 12 received GnRH for release. Similarly, in the hMG treatment cycle, 20 patients received hCG for oocyte release, and 12 received GnRH for release. Ultrasound studies confirmed oocyte release in all cycles, with no evidence of premature luteinization. No incidences of ovarian hyperstimulation syndrome were noted.

The mean midcycle serum hormone levels for each treatment modality are summarized in Table 1. The mean midcycle levels of LH did not differ significantly (paired *t* test) by treatment used: 20.7 ± 18.3 IU/L for hMG versus 22.6 ± 21.6 IU/L for pure FSH. Furthermore, no differences were found in the mean E_2 levels or progesterone levels by treatment group (Table 1).

DISCUSSION

Beginning with the lowest recommended dose of gonadotropins, we found no significant difference in steroidogenesis of the ovaries, as reflected in midcycle circulating progesterone and E_2 levels. The levels of pre-hCG (or pre-GnRH) concentrations of LH also were the same in both groups. Of practical value are that the average amount of gonadotropins used in our patients was considerably lower than that reported in other studies and that no differences were noted in the two groups.

We conclude from our comparative study of ultra-low-dose gonadotropin regimens that (1) no differences existed in circulating E_2 , progesterone, and LH concentrations at midcycle between hMG- and FSH-treated cycles in euestrogenic women and (2) the amount of medication needed to achieve follicular maturation did not differ whether hMG or pure FSH was used.

This study, however, does not rule out the possible advantage of use of pure FSH in certain clinical conditions, such as increased basal serum LH concentrations.

Table 1
Comparison of Midcycle Steroidal Levels by Treatment Used for Follicular Stimulation*

Hormone level	Pure follicle-stimulating hormone (N = 32)	Human menopausal gonadotropin stimulation (N = 32)
Progesterone (ng/mL)	0.6 ± 0.4	0.5 ± 0.4
Estradiol (pg/mL)	316.0 ± 118.9	360.8 ± 193.1
Luteinizing hormone (IU/L)	22.6 ± 21.6	20.7 ± 18.3

*Data are shown as mean ± standard deviation. No significant differences were noted between treatment groups.

Further studies are needed with larger numbers of patients with polycystic ovarian syndrome to evaluate this special situation.

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