

## Low-Dose Gonadotrophin Stimulation for Luteal Phase Defects — Does Absence of LH Help Pregnancy Rates?

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### Brief Summary

Based on data suggesting that higher serum LH levels during the follicular phase may decrease subsequent pregnancy rates and increase spontaneous abortion rates, the study presented herein was designed to compare the pregnancy and abortion rates in patients treated with gonadotrophin preparations with and without LH content. Infertile patients with luteal phase defects related to releasing eggs prior to complete follicular maturation were randomized into two treatment arcs: ultra-low-dose (75IU) human menopausal gonadotrophin (hMG) versus pure FSH. However, they were given the right to refuse the recommended treatment and use the other one if they preferred. Pregnancy and spontaneous abortion rates were determined for first cycle of therapy. The pregnancy rates for hMG versus pure FSH was 22.7 percent and 20.3 percent, respectively. The spontaneous abortion rates were also similar (8 percent and 9.1 percent). There were no multiple births resulting from these 36 pregnancies. Ovarian hyperstimulation syndrome was not observed in any of the 164 stimulation cycles. These data demonstrate that the use of an ultra-low-dose gonadotrophin stimulation regimen is an

effective method of correcting infertility related to luteal phase defects related to follicular maturation defects since the overall pregnancy rate per first cycle of treatment was 22 percent despite a minimum of 10 months of infertility duration. Furthermore, an ultra-low-dose gonadotrophin regimen is safe for treating luteal phase defects in that there was no ovarian hyperstimulation or multiple births demonstrated. These results also show no advantage of choosing a preparation devoid of LH, thus giving the patient the opportunity to purchase the least expensive medication that is available.

### Introduction

A previous study found that treatment with the combination of follicle-maturing drugs (either clomiphene citrate [CC] or gonadotrophins) and progesterone (P) support in the luteal phase resulted in a higher viable pregnancy rate (PR) than did either of these two therapies alone in patients with luteal phase defects who did not attain a mature follicle.<sup>1</sup> The gonadotrophin preparation used in that study was human menopausal gonadotrophins (hMG) exclusively and the dosage used was conventional (mostly 150 IU hMG daily).<sup>1</sup>

The use of an ultra-low-dose gonadotrophin regimen was found to be safer and more effective than conventional use of hMG in patients with polycystic ovarian syndrome.<sup>2</sup> The gonadotrophin preparation used for that

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study was purified follicle stimulating hormone (pFSH).<sup>2</sup> The study presented herein compares the efficacy of low-dose hMG vs. pFSH for infertile women with luteal phase defects whose oocyte released prior to attaining a serum estradiol (E<sub>2</sub>) of 200 pg/mL.

**Materials and Methods**

All patients diagnosed with luteal phase defects (by demonstrating a late luteal phase endometrial biopsy more than two days out-of-phase in two consecutive cycles) from October 1991 to December 1992 who did not attain a serum E<sub>2</sub> ≥ 200 pg/mL prior to oocyte release (demonstrated by pelvic sonography) were given ultra-low dose hMG or pFSH. The initial option of hMG or pFSH was on a randomized basis; however, they were advised that we believed that at least with conventional dosages of pFSH there may be an increased risk of ovarian hyperstimulation syndrome.<sup>3</sup> If the patient refused pFSH, she was given ultra-low-dose hMG and still included in the study. The study would be concluded when there were at least 50 patients in each group. Patients were required to have a minimum of 10 months of infertility duration (unless they were being seen for recurrent spontaneous abortion [SAB]), at least one patent fallopian tube by hysterosalpingography or laparoscopy, and a male partner with at least an 8x10<sup>6</sup>/mL motile density, to be included in the study. Furthermore, a mid-luteal phase serum P was required to be > 5 ng/mL.

The hMG and pFSH were started with one ampule (75 IU FSH and luteinizing hormone [LH]; 75 IU pFSH) daily from day five, and continued at this dosage for at least seven days.

If the E<sub>2</sub> levels were progressively rising, the one ampule dosage was maintained; however, an inadequate response would prompt an increase in dosage to 1.5 ampules/day. When at least one follicle attained an average diameter of 18-24 mm with a serum E<sub>2</sub> of a minimum of 200pg/mL for one follicle or 150 IU per each follicle attaining an 18 mm diameter, 10,000 U human chorionic gonadotrophin (hCG) was given intramuscularly (IM). Following oocyte release, the luteal phase was supplemented by oral micronized P capsules 50 mg 4x/day.

Patients were monitored by sera E<sub>2</sub> and sonography at mid-cycle. Only those patients demonstrating a gestational sac on ultrasound were considered pregnant. Only first cycles of gonadotrophin therapy were included.

**Results**

Ninety percent of the patients had been treated with one to four cycles previously with CC and had failed to conceive. One hundred and ten patients received ultra-low-dose hMG vs. 54 taking ultra-low dose pFSH.

Pregnancies were achieved by 25 patients (22.7 percent) treated with hMG vs. 11 (20.3 percent) with pFSH (p=NS, chi-square analysis). Spontaneous abortion occurred in two of 25 (8 percent) pregnant patients treated with hMG and in one of 11 (9.1 percent) pregnant patients treated with pFSH.

The risk for multiple births with gonadotrophin therapy has been estimated at approximately 11 to 42 percent per treatment cycle. All 36 pregnancies in this study were singletons. There were no cycles with clinical ovarian hyperstimulation syndrome with either gonadotrophin preparation.

	hMG group (n=110)	FSH group (n=54)
<b>Race</b>		
White	62 (56.4%)	31 (57.4%)
Black	1 (.9%)	1 (1.8%)
Other	2 (1.8%)	0 (0.0%)
Not available	45 (40.9%)	22 (40.7%)
<b>Age (years)</b>		
Mean (SD)	33.1 (4.6)	31.3 (3.7)
<b>Insurance type</b>		
HMO	25 (22.7%)	15 (27.8%)
Private	79 (71.8%)	37 (68.5%)
Unknown	6 (5.5%)	2 (3.7%)

p > .05, all comparisons (no significant differences)

Table 1. Demographic profile

	hMG (n=110)	FSH (n=54)
<b>Length of infertility (years)</b>		
Mean (SD)	1.8 (1.2)	1.9 (1.2)
<b>Type</b>		
Primary	42 (38.2%)	26 (48.1%)
Secondary	66 (60.0%)	27 (50.0%)
Recurrent abortions	2 (1.8%)	1 (1.8%)

Table 2. Infertility history

Hormone levels on initial consultation	hMG	Normal range	FSH
<b>Androgens</b>			
Androstenedione	164.5 ± 64.8	10-299ng/dL	162.0 ± 61.9
Dehydroepiandrosterone sulfate (ug/dL)	206 ± 98.7	25-10ug/dL	206 ± 101.8
Testosterone (ng/dL)	34.4 ± 23.6	20-80ng/dL	33.0 ± 17.0
Free testosterone (pg/mL)	2.5 ± 2.5	0.7-3.6pg/mL	2.7 ± 2.3
Prolactin (ng/mL)	9.4 ± 7.2	5.1-22.6ng/mL	8.8 ± 3.6
<b>Day 2 or 3 hormonal levels</b>			
FSH (initial consult) (mIU/mL)	12.7 ± 7.4	1.3-15.0mIU/mL	15.1 ± 13.5
LH (mIU/mL)	16.1 ± 13.9	1-31mIU/mL	17.7 ± 13.7
FSH	12.0 ± 2.9		13.8 ± 5.4
LH	12.1 ± 4.8		9.7 ± 5.3

\* Data presented as mean ± SD (n); p > .05 for all sera levels measured (no significant differences)

Table 3. Baseline endocrine profile\*

The demographic profile of the hMG vs. pFSH group is seen in Table 1. There were no differences seen in race, age or insurance type. The infertility history of the two groups is presented in Table 2; no statistical differences were noted.

The sera hormone levels obtained on initial consultation are seen in Table 3; no differences in androgen levels or prolactin were noted. Furthermore, no differences were seen in day two or three sera LH and FSH levels.

Furthermore, no differences were noted between the groups in number of mature follicles >15 mm or >17 mm, incidence of luteinized unruptured follicle syndrome, or sera E<sub>2</sub>, P or LH at the time of hCG injection as seen in Table 4.

Finally, no differences were noted in the amount of medication needed to induce follicular maturation (Table 5).

**Discussion**

There have been several manuscripts demonstrating the safety and efficacy of ultra-low-dose pFSH therapy for anovulatory patients with polycystic ovarian syndrome.<sup>2,4</sup> The study presented herein is unique because it evaluated ultra-low-dose gonadotrophin therapy in patients with luteal phase defects not attaining mature follicles. In contrast to a previous study where pFSH was found more risky than hMG for developing ovarian hyperstimulation syndrome following conventional dosages,<sup>3</sup> no

	hMG	FSH
<b>Mature follicles</b>		
> 15 mm (mean)	1.8 ± 1.1	1.9 ± 1.3
> 17 mm (mean)	1.4 ± 1.0	1.5 ± 1.3
<b>Sonographic confirmation of release</b>		
Yes	91 (82.7%)	39 (72.2%)
No	9 (8.2%)	8 (14.8%)
Inconclusive	10 (9.1%)	5 (9.2%)
Luteinized unruptured follicle	0 (0.0%)	2 (3.7%)
<b>Sera hormone levels at peak follicular development</b>		
E <sub>2</sub> (pg/mL)	364.5 ± 183.1	409.8 ± 253.4
P (ng/mL)	.6 ± .4	.6 ± .5
LH (mIU/mL)	27.8 ± 32.2	31.4 ± 25.1

\* Data presented as mean ± standard deviation (sample size); p > .05 comparing groups on each parameter

Table 4. Mid-cycle follicular dynamics and sera hormone levels

ovarian hyperstimulation syndrome was found with either ultra-low-dose gonadotrophin regimen.

The PRs with both ultra-low-dose regimens were certainly comparable to higher dose conventional regimens, with greater safety to the patient. Multiple births would normally be expected with conventional hMG therapy in 20 percent of the cases and even a low-dose (but not ultra-low-dose) regimen was found to be associated with a frequency of 15 percent.<sup>5</sup> There were no multiple births in 36 pregnancies in this study as compared to the expected five to seven with higher dose gonadotrophin regimens.

There has been another manuscript randomly comparing ultra-low-dose pFSH vs. hMG with similar conclusions, i.e., that both drugs are equally safe and effective.<sup>4</sup>

	hMG	FSH
<b>Total ampules administered</b>		
Mean ± SD	9.3 ± 4.2	10.8 ± 5.0
<b>Total days on medication</b>		
Mean ± SD	8.5 ± 2.9	9.6 ± 3.4
<b>Number of patients requiring</b>		
1 amp dosage only	74 (67.3%)	32 (58.2%)
1 amp and 1.5 amps	22 (20.0%)	16 (29.6%)
1, 1.5, and 2	4 (3.6%)	3 (5.6%)
1 and 2 amps	9 (8.2%)	2 (3.7%)
Not available	1 (.9%)	1 (1.8%)

\* p > .05 all on tests (no significant differences)

Table 5. Comparison of ovulation induction therapy

However, the patients used in Sagle et al.'s study all had polycystic ovarian syndrome.<sup>4</sup> The study presented herein, to our knowledge, is unique in the world's literature in randomly comparing these two gonadotrophin preparations in patients with luteal phase defects associated with immature follicles.

There have been some studies suggesting that higher levels of serum LH in the follicular phase reduce PRs and increase SAB rates.<sup>6,7</sup> Based on these studies, some clinicians have hypothesized that the LH content of gonadotrophin preparation, e.g., hMG, may have negative effects on pregnancy outcome.

Daya et al. evaluated fertilization rates and PRs with in vitro fertilization using a short flare-up controlled ovarian hyperstimulation regimen and found a significantly higher fertilization rate and a trend to higher PRs when the gonadotrophin regimen used was pFSH compared to hMG.<sup>12</sup> They attributed the decreased fertilization and PRs with hMG to the possible adverse effects of high LH during the follicular phase.

However, we published data involving the longer use of luteal phase leuprolide acetate followed by gonadotrophin therapy (pFSH vs. hMG) and found no differences in fertilization or PRs though there was a trend toward higher cancellation rates with pFSH.<sup>9</sup> Furthermore, we have found that women with luteal phase defects do not have a lower PR or higher SAB rate in women with high serum LH levels during the follicular phase;<sup>10</sup> this study suggested that the adverse effects of high serum LH may be overcome by the use of supplemental P in the luteal phase. In fact, there have been studies demonstrating a reduction in SABs with the use of supplemental P in the luteal phase when women have been stimulated with either CC or hMG.<sup>15,16</sup> Though the spontaneous abortion rates were <10 percent with either hMG or pFSH in the study presented herein, both groups did receive P in the luteal phase. Thus, the possibility does exist that the use of gonadotrophin preparations containing LH could be associated with lower PRs or higher spontaneous abortion rates when P is not

supplemented in the luteal phase when stimulating with pFSH.

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