

# Similar pregnancy and spontaneous abortion rates after treatment with low-dose human menopausal gonadotropin versus pure follicle stimulating hormone in women with luteal phase defects

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## Summary

The study presented herewith was designed to compare the pregnancy and abortion rates in patients treated with gonadotropin preparations with and without LH content based on data suggesting that higher serum LH levels during the follicular phase may reduce subsequent pregnancy rates and increase spontaneous abortion rates. Infertile patients with luteal phase defects related to releasing eggs prior to complete follicular maturation were treated with either ultra-low dose (75 IU) hMG or pure FSH. The pregnancy rates for first treatment cycles for hMG versus pure FSH was 22.7% and 20.3%, respectively. The spontaneous abortion rates were also similar (8.0% and 9.1%). There were no multiple births resulting from these 36 pregnancies. Ovarian hyperstimulation syndrome was not observed in any of the 164 stimulation cycles. Thus these results show no advantage in choosing a preparation devoid of LH therefore giving the patient the opportunity to purchase the least expensive medication that is available.

**Key words:** Luteinizing hormone; Pregnancies; Multiple births; Gonadotropins; Abortions.

## Introduction

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

The use of an ultra-low dose gonadotropin regimen was found to be safer and more effective than conventional use of hMG in patients with polycystic ovarian syndrome [2]. The gonadotropin preparation used for that study was purified follicle stimulating hormone (FSH) [2]. The study presented herewith compared the efficacy of low dose hMG vs pure FSH for infertile women with luteal phase defects whose oocyte released prior to attaining a serum estradiol of 200 pg/mL. Furthermore, the incidence of ovarian hyperstimulation syndrome and multiple births while on low-dose gonadotropin therapy were evaluated.

## 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) who, between October 1991 and December 1992, did not attain a serum estradiol  $E_2 \geq 200$  pg/mL prior to oocyte release (demonstrated by pelvic sonography) were given ultra-low dose hMG or pure FSH. Patients were required to have a minimum of 10 months of infertility duration (unless they were being seen for recurrent

spontaneous abortion), at least one patent fallopian tube by hysterosalpingography or laparoscopy, and a male partner with at least an  $8 \times 10^6$ /mL motile sperm density, were to be included in the study. Furthermore, a mid-luteal phase serum progesterone was required to be  $> 5$  ng/mL.

The hMG and pure FSH were started with one ampule (75 IU FSH and LH; 75 IU pure-FSH) daily from day five and continued at this dosage for at least seven days. If the estradiol levels were progressively rising the one ampule dosage was maintained; however, an inadequate response (i.e., failure to generate a progressive rise in serum  $E_2$ ) would prompt an increase in dosage to 1 1/2 ampules/day. Follicular maturation was monitored by transvaginal ultrasound using an ATL Ultramark 4 Unit (Advanced Technologies Laboratories, Bothell, WA) and serum  $E_2$  levels using a radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA). A follicle was considered mature if it attained an average diameter of 18-24 mm with a serum  $E_2$  of at least 200 pg/mL (conversion factor to SI, 3.67). When at least one follicle attained maturity, 10,000 U human chorionic gonadotropin (hCG) was given intramuscularly. In the cases of multiple follicles, hCG was administered if the  $E_2$  levels were at least 150 pg/mL (conversion factor to SI, 3.67) per each follicle attaining a diameter of 18 mm. Following oocyte release the luteal phase was supplemented by oral micronized progesterone 50 mg 4x/day. Pregnancy was defined as sonographic evidence of a gestational sac.

Statistical analysis included chi-square test or student's t-test for independent groups as appropriate. A p value of .05 was used to assess significance.

## Results

Ninety percent of the patients had previously been treated with one to four cycles with clomiphene citrate and had failed to conceive. One hundred and ten patients

Table 1. — Demographic profile

	hMG group (n = 110)	FSH group (n = 54)
<b>Race*</b>		
White	62 (56.4%)	31 (57.4%)
Black	1 (0.9%)	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%)

\*  $p > .05$ , chi-square, comparing proportions by treatment\*\*  $p > .05$ , t-test, comparing mean by treatment

Table 2. — Infertility history

	hMG group (n = 110)	FSH group (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%)

\*  $p > .05$ , t-test, comparing mean by treatment\*\*  $p > .05$ , chi-square, proportions by treatment

Table 3. — Baseline endocrine profile\*

Hormone levels on initial consultation	Normal range	hMG group (n = 110)	FSH group (n = 54)
<b>Androgens</b>			
Androstenedione*	10-299ng/dL	164.5±64.8	162.0±61.9
Dehydroepiandrosterone sulfate (ug/dL)*	25-410ug/dL	206±98.7	206±101.8
Testosterone (ng/dL)*	20-80ng/dL	34.4±23.6	33.0±17.0
Free testosterone (pg/mL)	0.7-3.6pg/mL	2.5±2.5	2.7±2.3
Prolactin (ng/mL)*	5.1-22.6ng/mL	9.4±7.2	8.8±3.6
FSH (initial consult) (mIU/mL)*	1.3-15.0mIU/mL	12.7±7.4	15.1±13.5
LH (mIU/mL)*	1-31mIU/mL	16.1±13.9	17.7±13.7
<b>Day 2 or 3 hormonal levels</b>			
FSH*		12.0±2.9	13.8±5.4
LH*		12.1±4.8	9.7±5.3

\*  $p > .05$ , t-test, comparing mean sera levels by treatment

received ultra-low dose hMG vs 54 taking ultra-low dose pure FSH.

The demographic profile of the hMG vs pure FSH 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. Moreover, no differences were seen in day 2 or 3 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  $E_2$ , progesterone or LH at the time of hCG injection as seen in Table 4. Finally, no differences were

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

	hMG group (n = 110)	FSH group (n = 54)
<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>		
$E_2$ (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);  $p > .05$ , t-test, comparing means by treatment\*\*  $p > .05$ , chi-square, comparing proportion by treatment

Table 5. — Comparison of ovulation induction therapy

	hMG group (n = 110)	FSH group (n = 54)
<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%)

\*  $p > .05$ , t-test, comparing means by treatment\*\*  $p > .05$ , chi-square, comparing proportions by treatment

noted in the amount of medication needed to induce follicular maturation (Table 5).

All 36 pregnancies were singletons. There were no cycles with clinical ovarian hyperstimulation syndrome with either gonadotropin preparation.

Pregnancies were achieved by 25 patients (22.7%) treated with hMG vs 11 (20.3%) with pure FSH ( $p = NS$ , chi-square analysis). Spontaneous abortion occurred in 2 of 25 (8.0%) pregnant patients treated with hMG and in 1 of 11 (9.1%) pregnant patients treated with pure FSH ( $p = NS$ , chi-square analysis).

## Discussion

There have been several manuscripts demonstrating the safety and efficacy of ultra-low dose pure FSH therapy for anovulatory patients with polycystic ovarian syndrome [2, 3]. The study presented herewith is unique because it evaluated ultra-low dose gonadotropin therapy in patients with luteal phase defects related to not attaining mature follicles. In contrast to a previous study where pure-FSH was found more risky than hMG for developing ovarian hyperstimulation syndrome following conventional dosages, no ovarian hyperstimulation syndrome was found with either ultra-low dose gonadotropin regimen [4].

The pregnancy rates 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% of the cases [5-9] and even a low dose (but not ultra-low dose) regimen was found to be associated with a frequency of 15% [10]. There were no multiple births in 36 pregnancies in this study as compared to the 5-7 that would be expected with higher dose gonadotropin regimens.

There have been some studies suggesting that higher levels of serum luteinizing hormone in the follicular phase reduce pregnancy rates and increase spontaneous abortion rates [11-14]. Based on these studies some clinicians have hypothesized that the LH content of gonadotropin preparation, e.g., hMG may have negative effects on pregnancy outcome.

Daya *et al.*, evaluated fertilization rates and pregnancy rates 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 pregnancy rates when the gonadotropin regimen used was pFSH compared to hMG [15]. They attributed the reduced fertilization and pregnancy rates with hMG to the possible adverse effects of high LH during the follicular phase.

However, we published data involving the longer use of leuprolide acetate during the luteal phase followed by gonadotropin therapy (pFSH vs hMG) and found no differences in fertilization or pregnancy rates, though there was a trend toward higher cancellation rates with pFSH [16]. Furthermore, we have found that women with high serum LH levels during the follicular phase and who have luteal phase defects do not have a lower pregnancy rate or higher spontaneous abortion rate than women with normal serum follicular phase LH levels [17]; this study suggested that the adverse effects of high serum LH may be overcome by the use of supplemental progesterone in the luteal phase [17].

In fact, there have been studies demonstrating a reduction in spontaneous abortions with the use of supplemental progesterone in the luteal phase when women have been stimulated with either clomiphene citrate or hMG [18, 19]. Though the spontaneous abortion rates were <10% with either hMG or pFSH in the study presented herein, both groups did receive progesterone in the luteal phase. Thus, the possibility does exist that the use of gonadotropin preparations containing LH could be associated with lower pregnancy rates or higher spontaneous abortion rates if progesterone supplementation in the luteal phase is not given. We are not aware of any studies evaluating the benefit of progesterone in the luteal phase when stimulating with pFSH.

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