The Relationship of Early Follicular Phase Serum LH and Pregnancy Rates in Women With Regular Menses

JEROME H. CHECK, MD, MARK PEYMER, BA, DEBORAH LURIE, PhD, AND CHITOOR SURYANARAYAN, MA

Objective: **To investigate the relationship of early follicular phase serum LH levels and pregnancy rates in ovulatory women with regular menstrual cycles.**

Methods: **One hundred consecutive couples seeking help for infertility who had bilateral tubal patency, a minimum motile sperm density of 2.5 million/mL, and regular menstrual cycles were enrolled in the study. Baseline serum measurements of LH, FSH, and testosterone were obtained before treatment. Patients were treated with clomiphene citrate, human menopausal gonadotropin, or progesterone supplementation, as needed. Treatment continued for 6 months or until conception occurred. The 6-month pregnancy rates were correlated with baseline early follicular phase serum levels and age.**

Results: **The 6-month viable pregnancy rates did not decrease with an increase in baseline LH serum levels; they were 50% if LH was 10 mIU/L or less, 15.3% if LH was 11–20 mIU/mL, and 71.4% if LH was more than 20 mIU/mL. The 16.7% pregnancy rate in women whose baseline FSH exceeded 25 mIU/mL was significantly lower than the 56.3% rate in women whose FSH was 25 mIU/mL or lower. The pregnancy rates also declined significantly with age. When we controlled for age, FSH did not have an independent effect on conception rates.**

Conclusion: **Early follicular phase serum levels of LH were not associated with pregnancy rates in infertile ovulatory women who were treated with progesterone in the luteal phase when needed. However, early follicular levels of FSH and age at treatment were found to be related to pregnancy rates.** *(Obstet Gynecol 1996;87:291–6)*

Several studies[1–3] have demonstrated the adverse affect of elevated concentrations of follicular phase serum LH on subsequent conception rates and outcomes in women with polycystic ovarian syndrome. Luteinizing hormone concentrations in the follicular phase were found to be significantly lower in women who conceived and also in women whose pregnancy progressed beyond 4 weeks. Because the prevalence of polycystic ovarian syndrome is over 20% in the general and infertile population,[2,3] the authors suggested that many cases of spontaneous abortion may be related to high serum LH concentrations.[2,3]

Regan et al[4] found a lower pregnancy rate and a higher spontaneous abortion rate in women with regular menses whose early follicular phase serum LH exceeded 10 mIU/mL. They concluded that the hypersecretion of LH, rather than the presence of polycystic ovaries, was the immediate cause of the poor prognosis in these women. Most of the subjects in the study by Regan et al[4] had a history of spontaneous abortions.

The objective of this study was to investigate the relationship of early follicular phase LH concentrations to pregnancy rates in ovulatory women who had regular menses and were seeking treatment for infertility. The relationship of age and early follicular phase FSH was also considered, and in contrast to previous studies, progesterone supplementation was given in the luteal phase to the following women: 1) those diagnosed with luteal phase defects based on an endometrial biopsy that was more than 2 days out-of-phase, 2) those who had previous spontaneous abortions, and 3) those requiring follicle-maturing drugs.

Materials and Methods

For inclusion in the study, all female subjects had to demonstrate bilateral tubal patency and regular menstrual cycles (and attain a serum progesterone level of at least 6 ng/mL within 10 days of menstruation), and the

From the Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Camden, New Jersey.

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male partner was required to have a hypo-osmotic swelling test score of 50% or higher[5] and a minimum sperm motile density of 2.5×10^6/mL (because previous studies by our group found a significant reduction in pregnancy rates only below this level).[6] Similar cutoff values for motile sperm per milliliter were proposed by Enginsu et al[7] and Glazener et al.[8] The first 100 women who presented for infertility treatment in an outpatient university-associated facility between March and November 1993 and who met the criteria of eligibility were enrolled in the study. None of the women received GnRH-modifying pharmacologic substances or underwent treatment with assisted reproduction techniques. They were followed-up for 6 months or until conception.

Follicle-maturing drugs, such as human menopausal gonadotropins and clomiphene citrate, were used if the dominant follicle did not attain an average diameter of at least 18 mm and secrete sufficient estradiol (E2) to allow the serum to attain a 200 pg/mL level. Progesterone supplementation in the luteal phase was given to patients with any of the following: luteal phase defects as diagnosed by endometrial biopsies more than 2 days out-of-phase, a history of previous spontaneous abortion, or use of a follicle-maturing drug. Patients not treated with follicle-maturing drugs were treated with a variety of other therapies, including therapeutic donor insemination or intrauterine insemination for cervical or male factor.

Baseline early follicular phase serum levels of LH, FSH, testosterone, and free testosterone were drawn on day 2 or 3 of the menstrual cycle before the initiation of treatment. Baseline levels were not repeated during the course of treatment. Hormonal assays for LH and FSH used radioimmunoassay (RIA) kits from Diagnostic Products Corporation (Los Angeles, CA). The manufacturer's normal ranges, excluding the midcycle peak, were 0–38 mIU/mL for LH and 0–20 mIU/mL for FSH. The coefficient of variation for each assay was less than 8.0% for both inter- and intra-assay. All assays were run in duplicate.

Serum total testosterone was measured at the same time as gonadotropin levels by an RIA coated tube kit (ICN Biomedicals, Costa Mesa, CA). The manufacturer's normal range for females was given as 20–80 ng/dL; the intra-assay coefficient of variation was 4.0%, and the inter-assay coefficient of variation was 3.7%. Serum free testosterone was measured using an RIA coated tube kit (Diagnostic Products Corporation). The manufacturer-suggested normal range for this assay was 0.7–3.6 pg/mL, with coefficient of variation 9.57% for intra-assay and 11.63% for inter-assay. Serum β-hCG levels were used to detect and monitor pregnancy on a weekly basis. Fetal sonograms were performed at 7, 9, and 12 weeks. Pregnancy outcomes were reported as spontaneous abortion if nonviability, as determined by sonography, occurred within the first 12 weeks of pregnancy and ongoing in pregnancy if fetal viability was found at week 12.

Because the Kolgomorov-Smirnov test found that the distributions of LH and FSH levels were not normal, nonparametric statistical methods were used. Results were presented as median levels and ranges. Spearman rank-order correlations were used to measure the correlation between LH, FSH, and age. Mann-Whitney *U* test was used to compare the median serum levels by pregnancy outcome. Chi-square analysis was used to compare pregnancy rates. Logistic regression was used to evaluate the independent effect of LH and FSH to predict the probability of conception after we accounted for the patient's age. A *P* value of .05 was considered statistically significant. Power analysis showed that with a sample size of 100, this study had 80% power to detect a correlation of at least 0.3 at the .05 level of significance.

Results

Fourteen women withdrew from the study voluntarily. There was no difference in the mean LH, FSH, or indication for treatment between the women who withdrew and those who completed the study. The analysis presented was based on the 86 women who completed the study.

Forty-five women were treated for ovulatory dysfunction (failure to produce a mature follicle at least 18 mm in diameter with an E2 level of 200 pg/mL): three for endometriosis, 12 for male factor (ie, a sperm count less than 20×10^6/mL or less than 50% progressive motility according to World Health Organization criteria), nine for donor insemination, three for uterine abnormalities, three for recurrent spontaneous abortion, two for multiple factors, and nine for unexplained infertility. None of the patients demonstrated sonographic evidence of polycystic ovaries.

Ovulation-inducing drugs were administered to 64 (74.4%) of the women; 22 received no ovulation induction therapy. Table 1 presents a comparison of the baseline serum levels and outcomes by use of ovulation-inducing drugs. There were no differences between the median baseline LH, FSH, and testosterone levels by ovulation-inducing drug use ($P > .05$, Mann-Whitney *U* test). Furthermore, there were no differences in the 6-month pregnancy rate or abortion rate by use of ovulation-inducing drugs, so the two groups were combined for further analysis ($P > .05$, χ^2). There were

Table 1. Comparison of Baseline Characteristics and Outcomes by Use of Ovulation-Inducing Drugs

	Ovulation-inducing drugs (n = 64)	No ovulation-inducing drugs (n = 22)
Baseline LH (mIU/mL)	8 (3–40)	7.5 (3–49)
Baseline FSH (mIU/mL)	12 (2–34)	13 (7–67)
Age (y)	34 (22–45)	34 (28–44)
Total testosterone (ng/mL)	35.5 (19.9–108)	24 (19.9–100)
Free testosterone (pg/mL)	2.1 (0.3–6.1)	1.4 (0.3–3.5)
Pregnancy rate*	53.1% (34)	54.5% (12)
Abortion rate*	11.8% (4)	16.7% (2)

Data are presented as median (range), except as noted.
* Data are presented as % (number of pregnancies or abortions).

two patients whose serum testosterone exceeded the upper limits of normal for the assay and six patients whose serum free testosterone were elevated.

The early follicular phase serum LH concentrations ranged from 3–49 mIU/mL (median 8.0). Two patients had LH levels above the normal range for the assay (38 mIU/mL). Table 2 presents a comparison of pregnancy rate by baseline LH. No reduction in pregnancy rate or increase in abortion rate by 12 weeks was found for higher ranges of LH levels ($P > .05$, χ^2). The highest LH level in a woman who conceived was 40 mIU/mL. This woman was 30 years old, had a corresponding FSH level of 67 mIU/mL, and had a viable pregnancy at the end of week 12.

The FSH levels ranged from 2–67 mIU/mL (median 12.5). Thirteen women had early follicular phase FSH levels exceeding 20 mIU/mL, the upper limit of the normal range for the assay. Table 3 presents a comparison of pregnancy rates by baseline FSH levels. As the FSH levels increased, we found a decrease in pregnancy rate ($P < .05$, χ^2) from 59.0% in women with FSH levels up to 10 mIU/mL to 16.7% in women whose FSH levels exceeded 25 mIU/mL. The pregnancy rate for all women with FSH levels at or below 25 mIU/mL was 56.3%.

Table 2. Comparison of Pregnancy Rates by Baseline LH Levels

LH levels (mIU/mL)	Median age (range)	N	Pregnancy rate*	Abortion rate	Ongoing rate*†
3–10	34 (22–45)	66	59.1% (39)	6 (9.1%)	50.0% (33)
11–20	38 (26–43)	13	15.3% (2)	0 (0.0%)	15.3% (2)
21–44	30 (29–44)	7	71.4% (5)	0 (0.0%)	71.4% (5)

* Not significant, χ^2 test.
† Viable pregnancy at 12 weeks.

Table 3. Comparison of Pregnancy Rates by Baseline FSH Levels

FSH levels (mIU/mL)	Median age (range)	N	Pregnancy rate*	Abortion rate	Ongoing rate*†
0–10	30 (22–43)	29	72.4% (21)	4 (13.8%)	58.6% (17)
11–20	34 (26–44)	44	47.7% (21)	3 (6.8%)	40.9% (18)
21–25	36 (31–44)	7	42.9% (3)	0 (0.0%)	42.9% (3)
26–67	42 (30–45)	6	16.7% (1)	0 (0.0%)	16.7% (1)

* $P < .05$, χ^2.
† Viable pregnancy at 12 weeks.

The women were 22–45 years old (median 34); 31.4% were under 30, 32.5% were 31–35, 19.8% were 36–40, and 16.3% were over 40. The pregnancy rate decreased as age increased ($P < .05$, χ^2) (Table 4). Women younger than 30 had a 6-month pregnancy rate of 65.3%, those 31–35 had a rate of 46.4%, those 36–40 had a 47% rate, and those over 40 had a 7.1% pregnancy rate.

Forty-six (53.5%) of the women conceived; six aborted spontaneously, for a 6-month ongoing pregnancy rate of 47.0%. A comparison of baseline early follicular serum levels between conceivers and nonconceivers is presented in Table 5. Mann-Whitney U test showed that the median LH, LH to FSH ratio, testosterone levels, and free testosterone levels did not differ by conception outcome. The median LH level was 8.0 mIU/mL for conceivers and 7.0 mIU/mL for nonconceivers. The LH levels for the six women who aborted were 4–9 mIU/mL (median 5.5). As illustrated in Figure 1, we did not find an association between baseline LH levels and conception outcome.

However, there was a significant difference in the baseline FSH levels by conception outcome groups, a median of 11.0 mIU/mL for conceivers and 15.0 mIU/mL for nonconceivers ($P < .05$, Mann-Whitney U test). The FSH levels for the six women who aborted spontaneously in the first trimester ranged from 9–16 mIU/mL (median 9.5) (Figure 1). The conceivers were also significantly younger than the nonconceivers (median age 31.5 versus 37.5 years, respectively). For those who did conceive, the median baseline LH level, FSH level, and age by cycle conception is presented in

Table 4. Comparison of Pregnancy Rates by Age

Age (y)	LH (mIU/mL)	FSH (mIU/mL)	N	Pregnancy rate*	Abortion rate	Ongoing rate*†
<30	7 (4–42)	10 (4–67)	27	74.1% (20)	2 (10.0%)	66.7% (18)
31–35	6 (3–21)	13 (2–24)	28	57.1% (16)	3 (18.7%)	40.9% (13)
36–40	9 (3–15)	14 (9–29)	17	47.9% (8)	0 (0.0%)	42.9% (13)
41–44	8.5 (4–28)	19.5 (7–34)	14	14.2% (2)	1 (50.0%)	7.1% (1)

* $P < .05$, χ^2.
† Viable pregnancy at 12 weeks.

Table 5. Comparison of Serum Characteristics by Outcome

	Viable pregnancy*	First-trimester spontaneous abortion	All conceivers	Nonconceivers
LH (mIU/mL)	8 (3–42)	5.5 (4–9)	8 (3–42)	7 (4–22)
FSH (mIU/mL)	11 (4–67)	9.5 (9–16)	11 (4–67)*	15 (2–34)
Age (y)	31 (26–44)	34 (29–43)	31.5 (26–44)*	37.5 (22–45)
Testosterone (ng/dL)	35 (19.9–72)	19.9 (19.9–49)	34.8 (19–72)	32 (19–108)
Free testosterone (pg/mL)	2.4 (0.3–5.7)	1.4 (0.4–1.4)	2.3 (0.3–5.7)	1.2 (0.3–6.5)
LH-FSH	0.6 (0.2–5.7)	0.5 (0.4–0.8)	0.6 (0.2–5.7)	0.5 (0.2–2.4)

Data are presented as median (range).
* Viable pregnancy at 12 weeks.
† $P < .05$, Mann-Whitney U test comparing conceivers with nonconceivers.

Table 6. Because the number of patients in each group was small, the groups were combined for statistical analysis. Those conceiving in the first two cycles were compared with those requiring three or more cycles. We found no significant differences by time required to conceive ($P > .05$, Mann-Whitney U test). The median levels of LH, FSH, and age for those conceiving in the first two cycles were 7.5 mIU/mL, 10.0 mIU/mL, and 32.5 years, respectively. For those requiring 3 months or longer to conceive, the median levels of LH, FSH, and age were 8.5 mIU/mL, 11.5 mIU/mL, and 30.5 years, respectively.

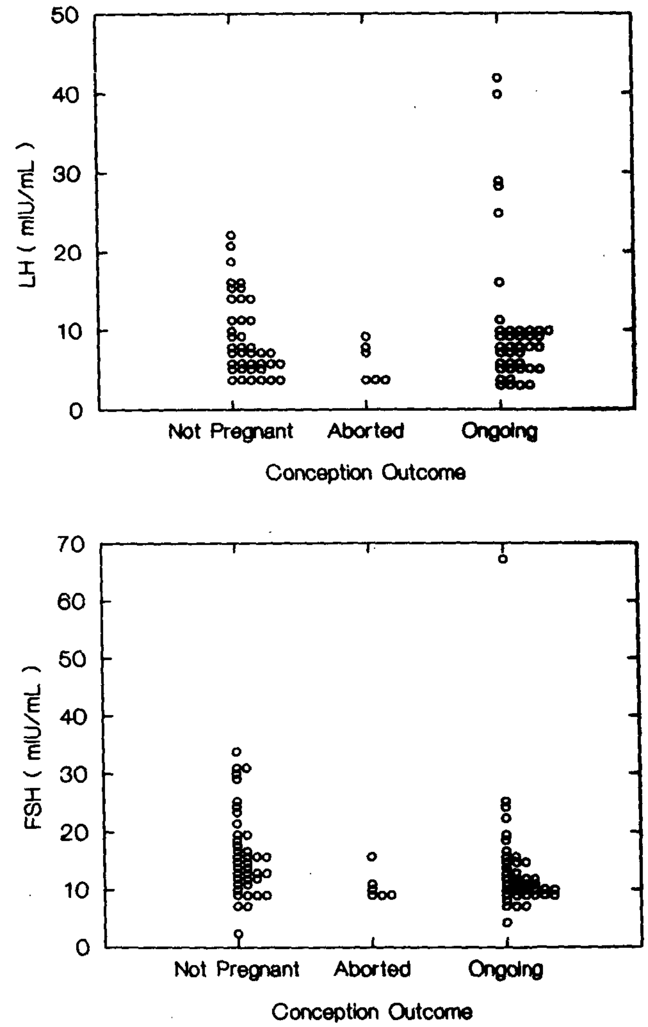

Figure 1. Distribution of early follicular phase FSH (*bottom*) and LH (*top*) levels by conception outcome (ongoing = viable pregnancy at 12 weeks).

The correlation between FSH and LH was statistically significant (Spearman $r = 0.434$, $P < .05$), as was the correlation between FSH and age (Spearman $r = 0.422$, $P < .05$). However, age and LH were not correlated significantly (Spearman $r = 0.006$, $P > .05$). To assess whether age and FSH had independent effects on the probability of conception, a multivariate logistic regression analysis was performed. The prognostic variables of age in years and FSH classified as 25 mIU/mL or less or greater than 25 mIU/mL were entered into a model to predict conception. Age was the only variable to attain statistical significance. The equation that quantifies this relationship is $P = 1\ (1 + e^{-\text{logit score}})$, where P = probability of conception and logit score = $5.52 - 0.16 \times$ age.

Discussion

Regan et al[4] hypothesized that the poor pregnancy rate when follicular phase serum LH was high might reflect the fact that the condition for producing a normal

Table 6. Comparison of Baseline Hormone Levels by Cycle Conception Was Achieved

Mo until conception	LH (mIU/mL)	FSH (mIU/mL)	Age (y)
1 (n = 16)	8 (4–29)	11 (7–25)	33.5 (26–44)
2 (n = 12)	6 (3–25)	9 (7–15)	31.5 (26–36)
3 (n = 4)	7 (6–10)	11 (4–16)	34.0 (26–35)
4 (n = 9)	10 (4–49)	11 (4–67)	31.0 (26–39)
5 or 6 (n = 5)	7 (6–16)	13 (9–15)	29.0 (26–35)

Data are presented as median (range).

embryo requires a specific interval between completion of the first meiotic division of oocytes and their fertilization. They considered that if the interval is extended, either by premature exposure to the ovulatory stimulus[9] or a delay in fertilization,[10] subsequent pregnancy rates are low and spontaneous abortion rates are high. The results of our study do not support the theory that early follicular LH levels affect subsequent pregnancy rates in treated cycles when ovulation-inducing drugs and/or progesterone is administered as needed. In our study, luteal phase progesterone supplementation was administered to 72% of the patients. The possibility exists that the use of progesterone negated defects in the corpus luteum that may have been caused by the subtle rise of LH. Hormone supplementation was not given in the studies of Homburg et al[1] and Regan et al.[4]

Another study supporting the concept that higher LH levels may adversely affect pregnancy rates was provided by Stanger and Yovich,[11] who found a significant reduction in the fertilization rate of mature oocytes in those patients whose basal serum LH values exceeded one standard deviation above the mean. We considered that, because no GnRH agonists were used by Stanger and Yovich,[11] perhaps premature luteinization accounted for the different results. Premature luteinization may be present but is uncommon in natural cycles[12]; however, it becomes more frequent after the use of follicle-maturing drugs, especially with a goal of controlled ovarian hyperstimulation.[13–15] Although there was not a statistically significant difference in serum progesterone levels in Stanger and Yovich's series before hCG injection, there was a trend for higher levels of progesterone in women with LH levels exceeding 20.6 mIU/L (mean serum progesterone 1.6 nmol/L) compared with those having lower LH levels (mean serum progesterone 0.85 nmol/L). The fertilization rate was 83.5% when serum progesterone was at or below 1.84 nmol/L but was reduced to 63.1% when the serum progesterone exceeded 1.84 nmol/L. A possible explanation of lower fertilization rates, other than premature luteinization, is that the hyperstimulation regimen in the presence of high LH may lead to a greater number of follicles recruited with higher serum E2 levels, leading to premature administration of hCG to avoid potential ovarian hyperstimulation syndrome.

There was no adverse effect of elevated early follicular phase LH levels on pregnancy outcome in our patients presenting for treatment of infertility. This is the first study to evaluate the detrimental effect of high follicular phase LH levels in treated women with regular menses. However, in our younger population, we did not find an independent effect of age and FSH, whereas Pearlstone et al[16] found that women 44 years of age or older have a low chance of pregnancy independent of serum FSH levels. We had only three women at least 44 years old.

Based on previous findings of an association of high serum LH, poor pregnancy rates, and higher spontaneous abortion rates, some clinicians have suggested that LH be suppressed in these instances by several months of GnRH agonist treatment. This medication is expensive and has side effects. There are no controlled studies showing any improvement in fecundity by suppression of LH. In fact, high LH may be associated with luteal phase defects and the use of supplemental progesterone in the luteal phase is needed to improve fecundity. A randomized study comparing progesterone to placebo in the luteal phase in patients with high early follicular phase serum LH levels is needed. This study would be easier to perform than a randomized comparison of GnRH agonist suppression against no suppression for higher LH levels because it would be difficult to convince half of the patients to delay their fertility and take an expensive GnRH agonist preparation first.

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Address reprint requests to:
Jerome H. Check, MD
7447 Old York Road
Melrose Park, PA 19027

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