High FSH:LH Ratio and Low LH Levels in Basal Cycle Day 3: Impact on Follicular Development and IVF Outcome

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Purpose: To examine the impact of low basal cycle day 3 serum LH levels or a high FSH:LH ratio on IVF results.

Methods: A homogeneous group of patients was analyzed as identified by normal basal cycle of follicle stimulating hormone (FSH), Luteinizing hormone (LH), and estradiol (E_2) levels. High responders (high LH:FSH ratio) and low responders (high FSH or E_2 levels, and women ≥ 42 years of age) were excluded from analysis. Only cycles stimulated with a combination of a GnRH α (luteal suppression) and pure FSH were studied.

Results: Patients with low basal LH levels (< 3 mIU/mL) did not differ significantly from controls in terms of response to controlled ovarian hyperstimulation but there was a clear trend toward poorer implantation and clinical pregnancy rates. On the other hand, patients with a high FSH:LH ratio (> 3) had significantly fewer mature oocytes aspirated, and lower implantation and clinical pregnancy rates than patients with gonadotropin ratio ≤ 3 . These negative effects were evident in the presence of normal basal FSH levels and after adequate matching of female's age and number of embryos transferred.

Conclusions: These studies highlight a negative impact of a basal cycle high FSH:LH ratio (and possibly low LH levels) on follicular development and oocyte quality in these patients subjected to pituitary down-regulation followed by pure FSH administration. A high FSH:LH ratio may be therefore used as an early biomarker of poor ovarian response.

KEY WORDS: basal serum LH/FSH:LH ratio; fertilization; implantation; pregnancy; preovulatory oocytes.

INTRODUCTION

The outcome of in vitro fertilization (IVF) is strongly dependent upon ovarian responsiveness to gonadotropin stimulation. Unfortunately, some patients respond poorly to this treatment, commonly referred to as "low or poor responders" (1,2). Female's age and basal cycle day 3 serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E_2) (ovarian reserve) are the main predictors of ovarian response to controlled ovarian hyperstimulation (3–5).

Typically, patients with normal LH and FSH levels and those with a high LH:FSH ratio respond as "normal" and "high" responders, respectively, often yielding an adequate number of mature oocytes available for fertilization (4–6). On the other hand, patients with high FSH (or elevated E_2 levels) respond poorly both in terms of oocyte numbers and quality (3,7). There is a clear relationship between female's chronological age and ovarian reserve, and both indices are used to counsel patients at the time of IVF. However, a group of young patients with normal FSH levels sometimes respond poorly to standard ovarian stimulation protocols. In this group of patients, several hypotheses have been proposed to explain the low ovarian response, but none has been proved (8,9). The identification of such patients to perform ovarian stimulation regimens using more adequate, tailored protocols represents a constant effort for physicians in order to avoid frustrating and disappointing outcome of infertility treatments.

The two-cell theory suggests that both FSH and LH are needed for normal follicular growth and maturation, but until now the main role had been attributed to FSH (10). We were interested in examining whether the presence of low basal LH levels in patients with

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normal basal FSH values would have a significant impact on ovarian responsiveness and overall outcome during IVF therapy, as recently has been suggested (11–13).

To answer this question we performed a retrospective analysis of patients with low basal cycle day 3 serum LH levels and compared their stimulation response and IVF results with those of a control group of patients with normal LH levels and who were treated within the same time frame. Additionally, we analyzed results segregating patients according to their FSH:LH ratio. In order to assess a homogenous group of patients, those cases with a high LH:FSH ratio (polycystic ovarian syndrome PCO- or PCO-like, typically high responders) and those with high basal FSH or high E_2 levels (poor ovarian reserve or low responders) were excluded. All patients were stimulated with a combination of a gonadotropin releasing hormone agonist (GnRHa) and pure FSH.

MATERIALS AND METHODS

The study population included patients undergoing IVF at the Jones Institute for Reproductive Medicine between January 1993 and December 1997. Study and control groups were identified from our computer database according to basal cycle day 3 serum FSH, LH, and E_2 levels. Two groups of patients were initially established: the study group, with patients having LH values <3 mIU/mL and a control group with patients having LH values ≥ 3 mIU/mL. The basal serum LH level of 3 mIU/mL used as a cutoff was determined as the mean minus a standard deviation of the LH levels of the total population of patients undergoing IVF during the study period. Importantly, those patients with FSH ≥ 11 mIU/mL by MEIA-IMX (equivalent to ≥ 15 mIU/mL as determined by radioimmunoassay (RIA)), and/or more than 42 years of age (predictive of a poor ovarian response) were excluded from the analysis. In addition, patients with a LH:FSH ratio of 0.85:1 or higher (PCO or PCO-like subjects) and those with hypothalamic hypogonadism were also excluded.

We therefore selected a homogeneous patient population with the exclusion of “poor” and “high” responders as identified by the basal endocrine profile. Only patients stimulated with a GnRHa, using a luteal phase down-regulation protocol in combination with pure FSH, were studied. Therefore, we excluded all other cycles where ovarian stimulation was performed without a GnRHa, with GnRHa used in a

flare-up fashion, and those where human menopausal gonadotropin (hMG) was used (alone or in combination with FSH). Groups were also assembled and compared according to the FSH:LH ratio. Receiver operating characteristics (ROC) curve analysis was used to establish an optimal cutoff for the FSH:LH ratio. Results of this analysis revealed that a FSH:LH ratio of 3 demonstrated highest specificity and sensitivity to distinguish groups with different ovarian response and IVF outcome.

All patients had previously been tested for basal cycle day 3 serum FSH, LH, and E_2 levels within 6 months of the IVF treatment cycle. Serum hormone levels were measured with a microparticle enzyme immunoassay (MEIA-IMX: Abbott Laboratories, Abbott Park, IL). The intraassay coefficients of variation were 4.3, 4.1, and 6.1% for FSH, LH, and E_2 , respectively. The interassay coefficients of variation were 4.9, 5.8, and 8.2% for FSH, LH, and E_2 , respectively. The lower limits of sensitivity were as follows: LH = 1.0 mIU/mL, FSH = 1.0 mIU/mL, and E_2 = 25 pg/mL, respectively. The regression equations to convert RIA to IMX are as follows: IMX FSH = $0.46 \times \text{RIA} - 2.2$; IMX LH = $0.3 \times \text{RIA} - 1.1$; IMX E_2 = $1.26 \times \text{RIA} - 1.5$.

All patients were suppressed with GnRHa leuprolide acetate (Lupron: TAP Pharmaceuticals, Abbott Park, IL) using a luteal protocol. The GnRHa was commenced in the midluteal phase of the preceding cycle at the dose of 0.5 mg/day and reduced to 0.25 mg/day at the first day of menses and continued until human chorionic gonadotropin (hCG) administration (long GnRHa protocol). Pure FSH (urinary FSH (Metrodin) or highly purified urinary FSH-Fertinex: Serono Laboratories, Randolph, MA) was initiated on Day 3 of the menstrual cycle with three ampoules (75 IU/ampoule) and then the dose was adjusted in an individualized fashion using a step-down protocol. For both protocols, when at least three follicles ≥ 16 mm were seen on ultrasound, 10,000 IU IM of hCG was administered. Cycles were canceled if fewer than three mature follicles were recruited by cycle day 9 or if peak serum levels rose inappropriately (14).

Follicular aspiration was performed 34–36 h after hCG administration; only results of mature, preovulatory oocytes (Metaphase I and II at the time of aspiration) were analyzed. Laboratory procedures for oocyte insemination (standard or through assisted fertilization by intracytoplasmic sperm injection or ICSI) and embryo culture have been reported previously (3,6). Three to five embryos were transferred to the uterine cavity with additional embryos being

cryopreserved. All patients received supplementation of the luteal phase with progesterone in oil (50 mg IM daily). The implantation rate was calculated by the total number of gestational sacs identified by first trimester ultrasound divided by total number of embryos transferred. Only the results of the "fresh" transfer cycles (in terms of implantation and pregnancy outcome) were considered in this study.

Statistical Analysis

Study (low LH levels or high FSH:LH ratio) and respective control groups were compared using unpaired *t* test and chi-square test as appropriate. Results are expressed as mean $\pm$ standard deviation. *P* levels $<.05$ were considered significant.

RESULTS

The present study included a total of 186 IVF cycles. According to the analysis of basal serum day 3 LH levels alone, two groups were compared: the study group (composed of 38 IVF cycles with basal serum LH values <3 mIU/mL) and a control group (composed of 148 cycles with basal serum LH values ≥ 3 mIU/mL). There were no differences in the etiologic categories of infertility, the proportion of initial or repeat attempts, or the proportion of patients having received one or the other type of urinary FSH preparation between the two groups (data not shown).

Ovarian stimulation results and IVF outcome are shown in Table I. By study design, LH levels differed significantly between groups ($P = .0001$). There were no differences in basal FSH levels between groups.

The groups were adequately matched in terms of female's age and number of embryos transferred per cycle. There were no significant differences in the cancellation rate (cases not reaching embryo transfer stage), peak serum E_2 levels, number of gonadotropin ampoules used, number of mature preovulatory oocytes recovered, fertilization, delivery, implantation and miscarriage rates, and number of embryos cryopreserved between the groups. The proportion of cycles with ICSI was similar among groups (33 and 33%, respectively) for study and control groups. The difference in the number of oocytes aspirated (10.7 ± 4.9 in the low LH group vs. 13 ± 6.8 in the control group) was of borderline significance ($P = .05$). In addition, there was a clear trend toward a lower implantation rate (6 vs. 12%) and a lower clinical pregnancy rate (20 vs. 36%) when comparing study and control groups.

Table II shows ovarian stimulation response and IVF outcome after segregating groups according to the FSH:LH ratio. Two groups were analyzed accordingly: patients with an FSH:LH ratio >3 (study group, $n = 28$) and patients with an FSH:LH ratio ≤ 3 (control group, $n = 158$). By study design, LH levels were significantly different between groups ($P = .0001$). Importantly, groups were adequately matched in terms of female's age, basal serum FSH levels, and number of embryos transferred per cycle. Additionally, the proportion of attempts where ICSI was performed (35 and 33%, respectively) was not significantly different between the study and control groups. The number of preovulatory oocytes aspirated was significantly lower in the study group ($P = .001$). The cancellation rate was not different in both groups. There were no differences in the number of gonadotropin ampoules used or in the day of hCG

Table I. Ovarian Stimulation Response and IVF Outcome According to Basal Serum LH Levels

	Study group (LH < 3 mIU/mL)	Control group (LH ≥ 3 mIU/mL)	<i>P</i> value
<i>n</i> (cycles)	38	148	
Age (years)	33.2 ± 3.4	33.6 ± 3.5	NS
Basal FSH (mIU/mL)	6.2 ± 1.4	6.6 ± 1.3	NS
Basal LH (mIU/mL)	1.7 ± 0.4	4.3 ± 1.3	.0001
Peak estradiol (pg/mL)	1850 ± 1160	2042 ± 1205	NS
Day of hCG	10.7 ± 0.9	11.0 ± 1.1	NS
No. of FSH ampoules	27.4 ± 9.8	29.2 ± 9.6	NS
No. of preovulatory oocytes aspirated	10.7 ± 4.9	13.0 ± 6.8	.05
Fertilization rate (%)	83 (276/332)	76 (1305/1702)	NS
No. of embryos transferred	3.9 ± 1.1	3.7 ± 1.4	NS
Implantation rate (%)	6 (8/128)	12 (63/512)	NS
Clinical pregnancy rate (%)	20 (6/30)	36 (45/125)	NS
Delivery rate/transfer (%)	20 (6/30)	28 (35/125)	NS
Miscarriage rate (%)	0 (0/6)	22 (10/45)	NS
No. of embryos cryopreserved	2.6 ± 3.4	3.5 ± 4.6	NS

Table II. Ovarian Stimulation Response and IVF Outcome According to FSH:LH Ratio

	Study group (FSH:LH > 3 mIU/mL)	Control group (FSH:LH < 3 mIU/mL)	P value
n (cycles)	28	158	
Age (years)	33.3 ± 3.3	33.5 ± 3.5	NS
Basal FSH (mIU/mL)	6.7 ± 1.2	6.5 ± 1.3	NS
Basal LH (mIU/mL)	1.7 ± 0.5	4.2 ± 1.4	.0001
Peak estradiol (pg/mL)	1617 ± 1079	2071 ± 1206	NS
Day of hCG	10.6 ± 0.9	11.0 ± 1.1	NS
No. of FSH ampoules	28.0 ± 10.1	28.9 ± 9.6	NS
No. of preovulatory oocytes aspirated	9.3 ± 4.4	13.0 ± 6.6	.001
Fertilization rate (%)	86 (166/193)	77 (1415/1841)	.01
No. of embryos transferred	3.9 ± 1.2	3.7 ± 1.4	NS
Implantation rate (%)	4 (4/90)	12 (67/550)	NS
Clinical pregnancy rate (%)	15 (3/20)	35.5 (48/135)	NS
Delivery rate/transfer (%)	15 (3/20)	28 (38/135)	NS
Miscarriage rate (%)	0 (0/3)	21 (10/48)	NS
No. of embryos cryopreserved	1.8 ± 2.9	3.5 ± 4.6	NS

administration between groups. However, significant differences in fertilization rate were observed (86 and 77%, respectively, for study and control groups). There were large differences in implantation rate (4 vs. 12%) and in clinical pregnancy rate (15 vs. 35%), with low rates observed in the low LH group; however, these differences did not attain significance.

The statistical power for the evaluation of the impact of FSH:LH ratios on ovarian response (judged as the number of mature oocytes recovered) was adequate at levels of $\alpha = 0.05$ and $\beta = 0.80$. The number of oocytes marking the 50 percentile of the distribution for all patients was 11. This number or fewer oocytes was used to define a "low" response. The FSH:LH ratio of 3 provided the best estimate for prediction of a low response with a positive predictive value of 80% and a specificity of 96%. However, the negative predictive value (51%) and the sensitivity (13%) were low. The area under the ROC curve was only 60%. On the other hand, the study did not have enough statistical power to establish significant differences in implantation or pregnancy rates.

DISCUSSION

In spite of the introduction of a number of diagnostic tests, including basal serum concentrations of gonadotropins (3) and/or E₂ (15), clomiphene challenge test (16), measurement of ovarian volume (17), and intraovarian blood flow (18), at present there is no test which is absolutely reliable in predicting a patient's response to gonadotropins during ovarian stimulation. However, measurement of basal serum concentrations of FSH, LH, and E₂ remains currently the most commonly employed method (3).

Here, we studied a homogeneous group of IVF patients based upon their basal endocrine profile. All patients had basal cycle day 3 serum FSH levels <11 mIU/mL (corresponding to 15 mIU/mL as measured by RIA) and were <42 years of age. High responders (PCO and PCO-like) and low responders (high basal FSH or E₂ levels) were excluded from the analysis.

The results of this study demonstrated that among a select population of "normal" responders, those patients having a high basal cycle serum FSH:LH ratio (>3) has a significantly lower ovarian stimulation response and also a poorer IVF outcome. This was true even in the presence of similar (and normal) basal serum FSH levels (Table II). Patients with a high FSH:LH ratio (>3) had significantly fewer mature oocytes recovered while receiving the same total dose of FSH throughout the stimulation when compared to the group with a lower basal gonadotropin ratio. In addition, and for the same number of embryos transferred per cycle, patients with a high FSH:LH ratio demonstrated an evident trend toward poorer implantation and pregnancy rates.

A larger sample size needs to be tested in order to confirm those trends. Since these rates reflect the implantation potential of each embryo, it may be speculated that a higher FSH:LH ratio impacts oocyte quality negatively leading to poor embryonic development. An endometrial effect seems to be highly unlikely because of the high supraphysiologic steroid levels typically observed in the luteal phase during IVF. Therefore, an FSH:LH ratio >3 is indicative of a compromised follicular development and probably also of poor oocyte quality in this group of patients subjected to controlled ovarian hyperstimulation with a combination of GnRHa and pure FSH.

We have previously shown that in the overall IVF population (unselected) an improved oocyte quality is obtained with FSH alone when compared to FSH/hMG combinations (19). Here, all patients were stimulated with pure FSH. Cases using hMG were excluded from the analysis to be able to obtain a homogeneous group of subjects in terms of protocols used and probably also to assess outcome without the bias that would result from the utilization of preparations containing variable amounts of LH.

The presence of low basal cycle day 3 LH alone was not associated with a negative (statistically significant) impact on ovarian response to FSH stimulation or overall IVF outcome. However, there was also a clear trend toward lower implantation and pregnancy rates in this group of women. Table II also depicts the unexpected finding of higher fertilization rates in the study group. This difference could not be attributed to the incidence of male factor infertility but the finding may be of doubtful clinical significance.

The result of the present study therefore suggested that a subpopulation of responder patients; i.e., those having a high FSH:LH ratio or a low LH concentration on basal cycle day 3 (but with a normal FSH value), may represent a distinct group of women that may be identified prospectively as poor responders. Some questions immediately arise: Is this a group of women with a compromised ovarian reserve (not identified by the assessment of basal FSH and E_2 levels)? If so, can they be individualized by their response to a dynamic test such as the clomiphene citrate challenge test or GnRH or GnRHa stimulation test (3,7,16,20)? Are inhibin-B levels lower (21)? Is it possible that this group of women may require exogenous LH supplementation because of a "chronic" lower pituitary LH output (therefore behaving as poor responders due to a chronic low LH exposure and not to an inherently reduced follicular pool)?

Murkherjee *et al.* (11) reported in a short communication that low day 3 LH levels in the presence of normal baseline FSH (with patients having an elevated FSH:LH ratio of 3:1) predicted a poor response to controlled ovarian hyperstimulation. However, the same authors subsequently analyzed a limited sample of IVF patients treated with GnRHa and gonadotropins and concluded that a high FSH:LH ratio of ≥ 3.6 predicted a poor response to controlled ovarian hyperstimulation and could be used as an early marker of decreased ovarian reserve (12). These authors reported that the group of patients with a higher FSH:LH ratio had lower E_2 peak levels, fewer follicles, and a higher cancellation rate. No information

was provided in relation to implantation or pregnancy rates. Such study was confounded by the facts that (a) hMG or combination of FSH and hMG were used; (b) high responders were not excluded from analysis; and (c) the group of patients with high FSH:LH ratio could be used as a marker of poor ovarian reserve (before a dramatic increase in FSH levels occur), but still the poor response to ovarian stimulation could be due to the low day 3 LH concentrations.

Nocci *et al.* (13) communicated that low day 3 LH values (i.e., an arbitrary selected threshold of <3 mIU/mL measured with an immunoradiometric assay) are predictive of a reduced response to ovarian stimulation as judged by decreased peak E_2 and a lower number of preovulatory follicles. Their study was based on a population subjected to ovulation stimulation (not for the purpose of IVF) with patients receiving pure FSH treatment without GnRHa and, therefore, information on oocyte numbers and quality was not obtained. Although the relatively small sample size did not allow a definite conclusion on the predictive value of the two criteria, they concluded that the significance of day 3 LH < 3 mIU/mL is independent of the day 3 FSH:LH ratio and that a sustained secretion of LH from the pituitary is necessary for the correct development of selected follicles to preovulatory follicles (13). It was speculated that when early follicular LH levels are low there may be reduced activity of one or more of the known ovarian regulators (i.e., steroids or proteins such as inhibin, activin, follistatin, or insulin-like growth factors), which can influence follicular growth through actions by autocrine or paracrine routes. Alternatively, the low LH levels could simply be a marker of an impaired balance between the gonad and the pituitary gland (13).

Our studies extended these observations by the demonstration of a negative impact of a high FSH:LH ratio (>3) on follicular development and a possible effect on embryo implantation potential in a more homogenous group of responders subjected to controlled ovarian hyperstimulation with pure FSH. In addition to an impaired capacity to respond with an adequate multifollicular growth, there is a possibility that the quality of oocyte may be suboptimal under the high FSH:LH ratio (or low LH) conditions may be due to an altered follicular microenvironment. Unfortunately, our study cannot determine whether this impaired response is due to a primary alteration of the ovarian milieu (oocyte-follicle units, regulatory factors) or to a primary or secondary hypothalamic-pituitary dysfunction.

The negative findings observed in the patients with a high FSH:LH ratio are evident even in the presence of pituitary down-regulation using a GnRHa. Although the LH that remains in circulation after pituitary desensitization following the use of GnRHa is of low biological activity (22), it may still provide enough drive for adequate steroidogenesis in the developing follicles. Loumaye *et al.* (23) demonstrated that in GnRHa-treated down-regulated IVF patients, the response to FSH is independent of serum LH levels at the time of starting FSH administration or on the day of hCG administration. Thus, measuring residual serum LH levels is of no practical use for predicting the patient's response to FSH, nor is it of use for defining a subpopulation that might benefit from exogenous LH administration during FSH stimulation. Analyzing IVF outcome after stimulation with a combination of GnRHa (luteal suppression) and highly purified FSH, Develioglou *et al.* (24) presented data that are in line with the notion of facilitatory role for LH in ovarian steroidogenesis but that down-regulated LH levels are not further predictive of outcome of stimulation. Our results demonstrate that the negative impact of a chronic state of low levels associated with a high FSH:LH ratio is still manifested in GnRH-down regulated cycles subjected to pure FSH stimulation.

In conclusion, IVF patients previously identified as "normal" responders but with a high FSH:LH ratio and low basal LH levels (and in the presence of a normal basal FSH) had a significantly lower ovarian response in terms of follicular development and a trend toward poorer implantation and pregnancy rates (suggestive of a compromised oocyte quality) when stimulated with a combination of GnRHa and pure FSH. In this group of patients a high FSH:LH ratio >3 may be used as an early biomarker of poor response to controlled ovarian hyperstimulation. Whether the exogenous addition of LH (possibly using a new recombinant LH preparation to allow for a more accurate determination of dose and timing of administration) may be of benefit in this subgroup of patients in order to enhance oocyte quality needs to be further investigated.

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