

Moderately elevated levels of basal follicle-stimulating hormone in young patients predict low ovarian response, but should not be used to disqualify patients from attempting in vitro fertilization

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Objective: To evaluate and compare IVF outcomes of patients within different age categories who had a normal basal FSH level with outcomes of patients with an elevated day 3 FSH level.

Design: Retrospective analysis.

Setting: Large, private IVF center.

Patient(s): We analyzed 2,708 patients. Of these, 2,477 had normal basal FSH levels, and 231 had elevated basal FSH levels (≥ 13.03 IU/L). Patients were segregated into various age groups.

Intervention: Follow-up.

Main Outcome Measure(s): Outcomes of IVF overall, including cancellation rates, oocyte yield, and fertilization, implantation, and clinical pregnancy rates (PRs).

Result(s): Cancellation rates were significantly higher in patients with elevated day 3 FSH levels compared with patients with normal FSH levels in all age groups. A significantly lower oocyte yield was observed in patients with elevated basal FSH. Fertilization rates were not affected by FSH levels. A significant decrease in the number of embryos available for transfer in patients ≥ 38 with an elevated day 3 FSH level was found. Implantation and clinical PRs were lower in patients >40 years of age who had an elevated day 3 FSH level when compared to same age patients with a normal day 3 FSH level. Loss rates were not significantly different.

Conclusion(s): Young women with an elevated basal FSH level should be counseled differently than older women, and should be given adequate counseling and granted the opportunity to undergo an IVF cycle. (Fertil Steril® 2007;xx:xxx. ©2007 by American Society for Reproductive Medicine.)

Key Words: Elevated basal FSH, IVF, age, pregnancy, cancellation

Early follicular phase (basal) FSH is a widely used endocrine marker to predict ovarian reserve in women presenting for fertility evaluation and treatment (1). Elevation in basal FSH levels is thought to reflect ovarian aging, and the low pregnancy rates (PRs) in these patients are related to the natural age-dependent decline in oocyte quality (2). Substantial data show that basal FSH can be an independent predictor of IVF outcome (1, 3). It was demonstrated that elevations in this parameter are strongly associated with poor ovarian response, low E₂ levels, and low PRs in patients undergoing assisted reproductive technologies (ARTs), independent of age (4). Low rates of conception and high rates of fetal loss were also shown in a group of infertile patients with elevated FSH levels (5).

Early studies of the significance of FSH were performed at a time when IVF was less efficient and resulted in lower success rates than are currently expected. Furthermore, controversy exists as to whether basal FSH is superior to age in

evaluating reproductive potential. In fact, other studies showed comparable PRs between patients with normal and elevated basal FSH levels (6). Others showed FSH to be of less value than age in predicting PRs (7). Therefore, the question arises as to whether an elevated basal FSH level should be used as an entrance criterion to discourage patients' access to treatment with ARTs. The purpose of this study was to evaluate and compare IVF outcomes in patients within several age categories who had a normal basal FSH level with outcomes of patients with an elevated day 3 FSH level.

MATERIALS AND METHODS

Design

This study is a retrospective data analysis of patients with infertility undergoing IVF treatment between July 2001–August 2005 at the Reproductive Medicine Associates of New York, New York, New York. Institutional review board approval was not required, because of the retrospective nature of the study. Data were collected by means of our electronic medical records database (Morristown, NJ). Patients who had one or more basal FSH measurements, and

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who underwent only fresh IVF cycles with the use of their own oocytes, were included. Cycle patients were segregated according to age: group A, <35 years of age; group B, ≥ 35 and <38 years of age; group C, ≥ 38 and <40 years of age; and group D, ≥ 40 years of age. Patients were subdivided into two groups (normal FSH and elevated FSH) according to their day 3 FSH level. The cutoff level for FSH used in this study was provided by calculating the 95% confidence interval (CI) of the study population that did not undergo cancellation. The 95% CI was 1.65–13.03 IU/L. Thus, 13.03 IU/L was selected as the threshold between normal and elevated FSH levels. The FSH levels were analyzed in our own endocrinology laboratory with the use of the DPC chemiluminescent Immulite 2000 assay (Diagnostic Products Corp., Los Angeles, California). Patients were classified as having an elevated day 3 FSH when their level was ≥ 13.03 IU/L in the same stimulated cycle or in a previous cycle. In vitro fertilization outcome variables included patient age, baseline FSH, number of oocytes retrieved, fertilization rates, implantation rates, clinical PRs, cancellation rates, and loss rates. Patients with an elevated FSH were then segregated according to their level (group A, FSH ≥ 13.03 to <15 IU/L; group B, FSH ≥ 15 IU/L), and the same variables were analyzed.

Stimulation

Standardized controlled ovarian hyperstimulation was performed with the down-regulation protocol, antagonist protocol, or microflare protocol, using either recombinant FSH (follitropin alfa, Gonal F; Serono, Inc., Rockland, MA; or follitropin beta, Follistim; Organon, Inc., West Orange, NJ), hMG (Repronex or Menopur; Ferring Pharmaceuticals, Suffern, NY), or a combination of the two. In the down-regulation protocol, patients were given a GnRH agonist (leuprolide acetate, Lupron; TAP Pharmaceuticals, North Chicago, IL) in the midluteal phase, followed by gonadotropins after the onset of withdrawal bleeding. In the antagonist protocol, oral contraceptives were given for 21 days, and initiation of gonadotropins occurred on cycle day 3 (after withdrawal bleeding). When the leading follicle reached 14 mm in diameter, a GnRH antagonist (cetrotirelix acetate, Cetrotide; Serono, Inc.; or ganirelix acetate, Antagon; Organon, Inc.) was administered daily. Ovarian suppression with oral contraceptives was also utilized prior to initiating the microflare protocol. A GnRH agonist (leuprolide acetate, Lupron; TAP Pharmaceuticals) was administered on cycle day 3 (after withdrawal bleeding) during morning and evening hours (flare effect) (50 μ g twice a day). On cycle day 4, gonadotropins were added to the stimulation. Ovarian stimulation was monitored by the measurement of serum E₂ concentration and by ultrasonographic assessment of the follicle diameter every day or every other day. Final oocyte maturation was achieved by the administration of hCG (Novarel, Ferring Pharmaceuticals; or choriogonadotropin alfa, Ovidrel; Serono, Inc.) when at least two of the leading follicles reached 18 mm in diameter. Oocyte retrieval was

performed 36 hours after hCG administration by means of transvaginal guidance. Fertilization was performed through conventional insemination or intracytoplasmic sperm injection, depending on the patient's history. Embryo morphology was assessed daily, and embryos were transferred on day 3 or day 5 after retrieval, using a Wallace catheter (Smiths Medical, Portex Ltd., Kent, UK) with transabdominal ultrasound guidance. All patients received daily IM P (50 mg) as a supplement during the luteal phase. A pregnancy test was performed 16 days after the hCG injection. A clinical pregnancy was defined as the presence of an intrauterine gestational sac. A loss was defined by the lack of embryonic growth or development after the visualization of a gestational sac by transvaginal ultrasound. Cycle cancellation was determined on the basis of low ovarian response, when <4 mature follicles were visualized ultrasonographically, or when no viable embryos were available for transfer.

Statistical Analysis

Statistical analysis was performed with one-way analysis of variance and nonparametric tests (Kruskal-Wallis) to compare age, FSH level, number of eggs retrieved, fertilization rates, implantation rates, and number of transferred embryos. The chi-square test was used to analyze the significance in the difference related to clinical pregnancy rates, loss rates and cancellation rates. Receiver-operating-characteristic (ROC) curves were obtained to determine the performance of basal FSH in predicting cancellation at different cutoff levels of 10, 13, 15, and 17 IU/L for the different age categories. Overall cancelled cycles were analyzed with the use of age and FSH as continuous variables for the determination of an ROC curve. Statistical analysis was performed with the use of Analyse-it Software, Ltd. (Leeds, England, UK) from Microsoft Excel[®] 2000. Statistical significance was set at $P < .05$.

RESULTS

In total, 2,708 fresh IVF cycles were performed during a 3-year period. The overall number of patients with normal basal FSH was 2,477. Two hundred and thirty-one patients were found to have an elevated basal FSH level. The distribution of patients according to age and FSH level is shown in Table 1.

Cancellation rates were significantly higher in patients with an elevated day 3 FSH compared with patients with normal FSH levels in all age groups: group A, 35.1% versus 11.4% ($P < .0001$); group B, 44.2% versus 19.8% ($P < .0002$); group C, 56.8% versus 23.9% ($P < .0001$); and group D, 60% versus 25.9% ($P < .0001$). Eighty-three percent of cancelled patients with a normal day 3 FSH, and 89% of cancelled patients with elevated day 3 FSH, underwent cycle cancellation prior to retrieval, because of low ovarian response. The remaining 17% of patients with a normal day 3 FSH, and 11% of patients with elevated day 3 FSH, were cancelled after retrieval, and thus did not undergo an ET procedure (Table 2).

TABLE 1

Distribution of patients according to age category and FSH level.

Age group	No. of patients with normal FSH (<13.03 IU/L)	Mean (\pm SD) FSH (IU/L)	No. of patients with high FSH (\geq 13.03)	Mean (\pm SD) FSH (IU/L)	Total no. of patients
A	915	6.5 \pm 2.3	37	14.9 \pm 2.1	952
B	531	7.4 \pm 2.4	43	15.4 \pm 3.2	574
C	556	7.8 \pm 2.5	81	16.4 \pm 3.9	637
D	475	8.2 \pm 2.4	70	16.1 \pm 6.8	545

Luna. FSH as a predictor of poor ovarian response. *Fertil Steril* 2007.

An analysis of the outcome of patients who underwent oocyte retrieval was performed. A correlation was identified between low counts of retrieved oocytes and elevated basal FSH levels. Patients in group A, with a normal day 3 FSH, had a mean number (\pm SD) of 16.5 \pm 8.4 oocytes retrieved, compared to patients in the same age group with an elevated day 3 FSH (9 \pm 4.8 oocytes) ($P < .0001$). A similar difference was encountered in group B (14.1 \pm 7.5 retrieved oocytes for patients with normal FSH, compared to 11 \pm 6.4 oocytes for the elevated FSH group) ($P = .02$). When analyzing group C, the number of eggs retrieved overall was 13.3 \pm 7.5 oocytes in the normal FSH group, compared with 7.9 \pm 3.5 oocytes in the elevated FSH group ($P < .0001$). Group D also demonstrated a decrease in oocyte yield based on FSH levels, with 12 \pm 6.2 oocytes in the normal FSH group, compared with 7.3 \pm 3.8 oocytes in the elevated FSH group ($P < .0001$).

Fertilization rates were not significantly different when comparing normal day 3 FSH patients with elevated day 3 FSH patients in all age groups. The mean number of embryos transferred was no different in groups A and B. However, in groups C and D, we found a significant decrease in the number of embryos available for transfer in patients with elevated day 3 FSH. Although a decrease was found in the implantation rates of patients with elevated day 3 FSH levels compared with patients with normal basal FSH levels, statistical significance was found only in the oldest age category (0). Clinical PRs of patients who underwent an ET were not significantly different between patients with a normal day 3 FSH and patients with an elevated day 3 FSH, when analyzing groups A, B, and C. However, a significant decrease in clinical PRs was encountered in patients >40 years of age who had an elevated day 3 FSH, when compared with patients of the same age with a normal day 3 FSH (Table 3).

The ROC curves used to evaluate the performance of basal FSH to predict cancellation at different cutoff levels are shown in Figure 1. The diagnostic screening tests, as well as the predictive values obtained at the different cutoff levels, were poor to predict cancellation throughout the different age groups, considering that when sensitivity increased, specificity decreased and vice-versa. However, in

age group A, the most efficient cutoff level in predicting cancellation rates is 17 IU/L, while in other age groups this is determined at lower cutoff levels (data not shown). The ROC curve for the analysis of cancelled cycles according to age and FSH is demonstrated in Figure 1. The curve demonstrates that the level of FSH is more predictive of cancellation than age.

Because the FSH cutoff level of 13.03 IU/L may be arbitrary, we further analyzed the elevated FSH group at two different cutoff levels: borderline FSH (>13.03 to <15 IU/L), and elevated FSH (≥ 15 IU/L). The outcome of these patients was analyzed according to their age and FSH level.

Patients in group A were found to have a similar overall outcome, independent of FSH level. Patients in group B were found to have a significantly lower oocyte yield when basal FSH levels were ≥ 15 IU/L. Implantation rates, clinical PRs, cancellation rates, and loss rates were not significantly different in this age group. Patients in group C presented similar outcomes, independent of their elevated FSH level. Patients in group D were found to have overall similar implantation rates and clinical PRs. However, cancellation rates were statistically higher in patients with an FSH ≥ 15 IU/L (Table 4).

DISCUSSION

Although there are multiple scenarios in which FSH elevation might result, including assay drifts, immunological response, FSH receptor polymorphisms, ovarian surgeries, and others (8, 9), the overall pregnancy outcome in these patients was found to be poor (10). Recent studies resulted in seemingly contradictory data. Many authors found that age has a stronger impact than day 3 FSH levels in IVF cycles (7, 11, 12). Others demonstrated that an elevated level of basal FSH affects both ovarian quality and quantity (4), and that this marker is superior to age in predicting outcome (4,13–15). We retrospectively analyzed our IVF patients who had normal day 3 FSH, and compared their outcomes to those of IVF patients with an elevated day 3 FSH. In our analysis, we found that patients with an elevated basal FSH had overall poor ovarian responsiveness, independent of age, when com-

TABLE 2**Cancellation rates according to age and FSH levels.**

Cancellations	Age group A		Age group B		Age group C		Age group D	
	Normal FSH	High FSH	Normal FSH	High FSH	Normal FSH	High FSH	Normal FSH	High FSH
Total cancelled cycles (%)	104/915 (11.4) ^a	13/37 (35.1) ^a	105/531 (19.8) ^a	19/43 (44.2) ^a	133/556 (23.9) ^a	46/81 (56.8) ^a	123/475 (25.9) ^a	42/70 (60) ^a
Cancelled prior to oocyte retrieval (%)	74/104 (71.2)	10/13 (76.9)	85/105 (81)	18/19 (94.8)	107/133 (80.5)	42/46 (91.3)	108/123 (87.8)	39/42 (92.9)
Cancelled after oocyte retrieval (%)	30/104 (28.8)	3/13 (23.1)	20/105 (19)	1/19 (5.2)	26/133 (19.5)	4/46 (8.7)	15/123 (12.2)	3/42 (7.1)

Note: Cancellation rates were significantly higher in patients with high FSH, in all age groups. Normal FSH, <13.03IU/L; high FSH, ≥13.03IU/L.
^a P<.05.

Luna. FSH as a predictor of poor ovarian response. *Fertil Steril* 2007.

TABLE 3**Outcomes of IVF patients who underwent an ET procedure, according to age and FSH.**

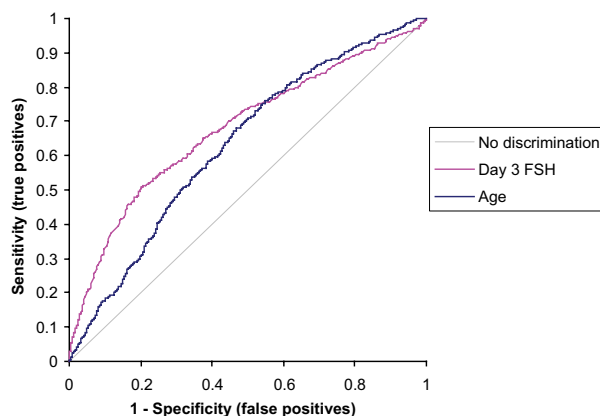
Group	Fertilization per M2 OR (%)		Mean no. of ETs (SD)		Implantation per TTE (%)		Clinical pregnancies (%)		Loss (%)	
	Normal FSH	High FSH	Normal FSH	High FSH	Normal FSH	High FSH	Normal FSH	High FSH	Normal FSH	High FSH
A	8,076/12,195 (66.2)	136/218 (62.4)	2.4 (0.7)	2.6 (0.8)	877/1,950 (45)	27/63 (42.9)	543/811 (67)	15/24 (62.5)	70/543 (12.9)	1/15 (13.3)
B	3,613/5,521 (65.4)	150/251 (59.8)	2.6 (0.9)	2.7 (1.1)	428/1,109 (38.6)	19/64 (29.7)	259/426 (60.8)	14/24 (58.3)	36/259 (13.9)	4/14 (28.6)
C	3,125/5,082 (61.5)	141/237 (59.5)	3.1 (1) ^a	2.6 (1.2) ^a	340/1,308 (26)	25/92 (27.2)	226/423 (53.4)	15/35 (42.9)	56/226 (24.8)	4/15 (26.6)
D	2,481/3,979 (62.4)	130/196 (66.3)	3.7 (1.4) ^a	2.8 (1.3) ^a	185/1,296 (14.3) ^a	5/79 (6.3) ^a	141/352 (40.1) ^a	4/28 (14.3) ^a	64/141 (45.4)	2/4 (50)

Note: Patients in groups C and D, with high FSH, demonstrated a significantly lower number of embryos transferred per cycle. Implantation rates and clinical PRs were significantly lower in group D. Normal FSH, <13.3 IU/L; high FSH, ≥13.03 IU/L. M2 OR = metaphase II oocytes retrieved. TTE = total number of transferred embryos.
^a P<.05.

Luna. FSH as a predictor of poor ovarian response. *Fertil Steril* 2007.

FIGURE 1

The ROC curve that describes the impact of age and FSH in predicting cancellation rates. Basal FSH is a better marker than age in predicting cancelled cycles.



Luna. FSH as a predictor of poor ovarian response. *Fertil Steril* 2007.

This finding was attributed to the lack of responsiveness and lack of adequate embryo development within this subgroup. However, we found that the proportion of patients who were cancelled after oocyte retrieval because of poor embryo development was no different from the proportion of patients with normal FSH levels who were cancelled for the same reason (Table 2). We decided to perform diagnostic screening tests at different cutoff levels for each of our age groups, to determine the thresholds at which patients will have a greater likelihood of cancellation. However, this analysis did not yield useful data. The ROC curve demonstrated that the level of FSH was more predictive of cancellation than age itself (Fig. 1).

Our population with high FSH was limited in number, and power analysis cannot be performed at 1–2-IU/L increments to determine the best threshold for this age group. We decided only to analyze the outcome of patients with a basal FSH >13.03 IU/L, and determine whether a difference would result when evaluating the same variables for patients with basal levels >13.03 to <15 IU/L and those with basal levels ≥ 15 IU/L. We found that for young patients, the prognosis was not different.

Qualitative changes in oocytes are principally responsible for the low reproductive potential in older women, as demonstrated by enormous differences in fecundity with advancing age in natural cycles in fertile couples (16). Several theories were proposed to explain the decline in oocyte quality that occurs with advancing maternal age. In the so-called “production line hypothesis,” oocyte quality is established during fetal life, and oocytes that are less sus-

pared with those with normal parameters. That being said, those patients who progressed to ovum retrieval and ET had acceptable reproductive outcomes, suggesting that withholding ART in patients with borderline measures of ovarian reserve may not be indicated.

The cancellation rate within the high FSH group was the only variable that was significantly higher across all ages.

TABLE 4

Outcomes of IVF according to age and elevated FSH levels.

Age group	N	Mean no. of OR (SD)	Fertilization per M2 OR (%)	Implantation per TTE (%)	Cancellations (%)	Clinical PR (%)	Loss (%)
A							
FSH-a	25	9.2 (5.2)	88/148 (59.5)	16/42 (38.1)	9/25 (56.3)	9/16 (56.3)	2/9 (22.2)
FSH-b	12	8.7 (4.3)	48/70 (68.6)	11/21 (52.4)	4/12 (33)	6/8 (75)	0/6 (0)
B							
FSH-a	27	12.84 (6.5) ^a	125/218 (57.3)	16/50 (32)	9/27 (33)	11/18 (61)	3/11 (27.3)
FSH-b	16	6 (2.6) ^a	25/33 (75.8)	3/14 (21.4)	10/16 (63)	3/6 (50)	1/3 (33.3)
C							
FSH-a	36	8.2 (3.2)	57/87 (65.5)	7/32 (21.9)	23/36 (63.9)	4/13 (30.8)	1/4 (25)
FSH-b	45	7.8 (3.5)	84/150 (56)	18/60 (30)	23/45 (53.5)	11/22 (50)	3/11 (27.3)
D							
FSH-a	43	7 (3.3)	98/149 (65.8)	4/64 (6.3)	21/43 (48.8) ^a	3/22 (13.6)	1/3 (33.3)
FSH-b	27	8.2 (5.3)	32/47 (68.1)	1/15 (6.7)	21/27 (77.7) ^a	1/6 (16.6)	1/1 (100)

Note: FSH-a, ≥ 13.03 to <15 IU/L; FSH-b, ≥ 15 IU/L. OR = oocytes retrieved. M2 OR = metaphase II oocytes retrieved. TTE = total number of transferred embryos.

^a $P < .05$.

Luna. FSH as a predictor of poor ovarian response. *Fertil Steril* 2007.

ceptible to nondisjunction are ovulated first, leaving poor-quality oocytes to be ovulated later in life. Another theory assumes an age-dependent accumulation of damage due to several proposed mechanisms, e.g., a gradual increase in intracellular oxidative stress (17). Because quality seems to be less impaired in younger patients with elevated FSH levels, the latter theory seems to match our results more closely than the former. Regardless, the question remains as to whether the decline in ovarian reserve observed with advancing age may not be merely the result of follicular attrition, but may also reflect the lower quality of the follicles that remain. In other words, as the functional capacity of the granulosa cells diminish, so might the quality of the oocyte.

It is our recommendation that young women (aged <35 years) with a moderately elevated basal FSH level be counseled differently than older women, and should be given adequate counseling and then granted the opportunity to undergo an IVF cycle. These young patients should be informed that women with elevated FSH have a high risk of cycle cancellation due to low oocyte production. In fact, should these women conceive, scattered reports in the literature suggest that there may even be an increased risk of fetal aneuploidy in these patients (18).

According to our results, if young patients do undergo the ET procedure, they have a possibility of conceiving comparable to that of patients with normal FSH. In fact, in our study, women aged <35 years with an elevated day 3 FSH had higher clinical PRs than the older patient category with a normal day 3 FSH. Patients between the ages of 35–40 years with elevated FSH should be counseled similarly because of the acceptable clinical PRs shown, but emphasizing the likelihood of low ovarian response and cancellation. Finally, older women (aged >40 years) with an elevated day 3 FSH may not be candidates for undergoing ART, as we found a significantly lower implantation rate and clinical PR in these patients, compared with women with a normal day 3 FSH in the same age category. Assisted reproductive technologies can be attempted in young women with a high FSH level, since those who do not experience cycle cancellation often become pregnant, despite low oocyte production.

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