Taking a basal follicle-stimulating hormone history is essential before initiating in vitro fertilization

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Objective: To analyze IVF outcomes in patients with a history of one or more elevations in basal FSH who have a normal basal FSH at the start of their IVF cycle, compared with the general IVF population.
Design: Retrospective clinical study.
Setting: University hospital.
Patient(s): General IVF patient population.
Intervention(s): Patients received standard IVF gonadotropin protocols, oocyte retrieval, and embryo transfer.
Main Outcome Measure(s): Oocyte yield, fertilization, implantation, clinical pregnancy, and cancellation rate.
Result(s): Oocyte yields were lower in patients with a history of elevated basal FSH, for all age groups, and showed an age-dependent decline in all patients. Over the age of 40 years, both implantation and clinical pregnancy rates were lower in these patients, with no significant difference observed in patients under the age of 40 years. No pregnancies were observed in patients with a history of three or more elevated FSH levels, regardless of age.
Conclusion(s): A history of elevated basal FSH levels in patients under the age of 40 years predicts a lower oocyte yield in IVF cycles with normal basal FSH levels but does not translate to either lower pregnancy or implantation rates. Patients aged >40 years with prior elevations in basal FSH levels have both compromised ovarian response and compromised embryo quality relative to those with normal FSH levels, as illustrated by lower oocyte yield, higher cancellation rates, and lower implantation and pregnancy rates. (Fertil Steril® 2005;83:37–41. ©2005 by American Society for Reproductive Medicine.)

Key Words: Follicle stimulating hormone, FSH, in vitro fertilization, IVF, ovarian reserve testing, age

As the average age of patients increases, age-related decline in fecundity is becoming the most foreseeable cause of subfertility. Observations of Hutterite populations have demonstrated the effects of advancing age on reproductive performance, and the world experience with donor oocytes has clearly identified the oocyte as the principal source of this effect (1). Loss of fecundity with age appears to be a consequence of both reduced oocyte numbers (primordial follicle population) and reduced oocyte quality. A patient's functional ovarian reserve is predictive, independently of age, of both natural conception rates and success with artificial reproductive technologies (2).

Ovarian biopsy with segmental follicle counts is the only direct method of estimating follicle population. Several indirect measures of ovarian reserve can be used to screen out poor-prognosis patients before initiating potentially ineffective treatments, with their associated risks and expense. Many groups have advocated the routine use of provocative ovarian reserve testing, such as the clomiphene challenge test, but basal FSH levels remain for "prognosticating" IVF patients (3–6). Although the clomiphene challenge test may be more predictive of a patient's response to gonadotropins, it is limited to use during clomiphene cycles and is logistically too cumbersome for most busy IVF clinics.

Our patients are screened with a basal FSH level at the start of each IVF cycle, and if it is elevated, are discouraged from proceeding in light of their low chances of success (7). In the months leading up to their first IVF attempt, patients often have multiple FSH level measures and present to IVF referral centers with results in hand. Several authors have demonstrated the poor prognosis of cycles initiated with elevated basal FSH levels. We proposed to determine the impact of a patient's FSH history on IVF outcome and how to best counsel these couples at their initial visit, before time and money has been spent in preparation for treatment. Such patients should be channeled to either adoption or oocyte donation and spared the time and expense on low-yield treatments. Stratifying for age, we retrospectively analyzed IVF outcomes in patients with a history of one or more elevated basal FSH levels and a normal basal FSH during the IVF cycle.

MATERIALS AND METHODS

Patients

We retrospectively analyzed 1,928 consecutive IVF cycles at the Center for Reproductive Medicine and Infertility at Weill-Cornell Medical Center, between July 2001 and De-

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cember 2003. Because of the retrospective nature of the article and the fact that blood samples were drawn as part of the patients' routine medical care, institutional review board approval was not obtained. In vitro fertilization outcomes in patients with a history of at least one FSH level ≥20 IU/mL (n = 180) were compared with the remaining cohort of IVF patients (n = 1,748). Within these groups, patients were stratified by age: <35 years, 35 to 40 years, and >40 years. All patients had a normal basal FSH (<20 IU/mL) and E_2 (<75 pg/mL) level at the start of their IVF cycle and had at least one basal FSH level measured at our center within the previous year. All serum FSH and E_2 levels were measured on site with a commercially available RIA kit (Leeco Diagnostics, Southfield, MI). The interassay and intra-assay coefficients of variation were 7.4% and 7.1%, respectively.

In Vitro Fertilization

In vitro fertilization treatments included a variety of standard protocols, including luteal GnRH-agonist, GnRH-agonist flare, and GnRH-antagonist. Gonadotropins (FSH with and without hMG) were initiated on either day 2 or 3 after menstruation and continued in a step-down fashion until the lead follicle size reached approximately 17 mm, at which time hCG was administered. Treatment monitoring consisted of serial serum E_2 levels and transvaginal ultrasound. Oocytes were retrieved 34–36 hours after hCG administration and fertilization achieved with either IVF or ICSI. Embryos were transferred on either day 3 or 5 after the retrieval depending on the number and quality of embryos.

Outcome measures included oocyte yield and fertilization, implantation, clinical pregnancy, and cancellation rates. Patients canceled for reasons other than poor response were not included in the analysis. Poor response was defined as fewer than three intermediate or large follicles or as an E_2 level of <500 pg/mL, after a reasonable period of gonadotropin administration. Clinical pregnancy was defined as the presence of a gestational sac on ultrasound examination.

Statistical Analysis

Pregnancy and cancellation rates were analyzed by using a χ^2 test. All other comparisons between basal FSH groups were made by using a two-sample *t*-test, whereas comparisons between age groups were made by ANOVA.

RESULTS

The primary etiologies of the patients' infertility are summarized in Table 1. By definition, our patient population had a higher incidence of diminished ovarian reserve, as defined by a history of basal FSH levels. In vitro fertilization outcomes based on age at retrieval and basal FSH history are summarized in Table 2.

In all three age groups, oocyte yield was lower in patients with prior elevations in their basal FSH levels. Independent of a patient's basal FSH history, an age-dependent decline in oocyte yield was observed. Fertilization rates were not significantly different between groups and did not change with age. After the age of 40 years, both implantation and clinical pregnancy rates were lower in patients with prior elevations in FSH, and before the age of 40 years, the rates were not significantly different from those of the general IVF population. Over the age of 35 years, cancellation rates were higher in patients with a history of elevated FSH. No pregnancies were observed in patients with a history of three or more elevations in basal FSH, regardless of age (0 vs. 40.6%, $P<.01$). Pregnancy rates for patients with one, two, and three prior elevations in basal FSH are summarized in Table 3.

TABLE 1

Primary etiologies of infertility in patients with prior elevation in basal FSH vs. the general IVF population with history of normal FSH levels.

Variable	Elevated FSH (n = 180)	Normal FSH (n = 1,748)
FSH level (IU/L ± mean)	7.5 ± 6.1	8.3 ± 5.7
Male factor	31	39
Tubal factor	20	26
Diminished ovarian reserve	59	0
Endometriosis	16	16
Idiopathic	6	4
DES exposure	1	1
Polycystic ovarian disease	1	5

Note: All data are percentages unless otherwise noted. DES = diethylstilbestrol.

Roberts. Basal FSH history and IVF. Fertil Steril 2005.

DISCUSSION

In our general IVF population, we demonstrated that a history of elevated basal FSH and a normal basal FSH at the start of IVF, in patients aged younger than 40 years, predicts a lower oocyte yield but does not translate to either lower pregnancy or implantation rates. This would suggest that despite a diminished ovarian response, embryo quality is not significantly compromised. Patients aged >40 years with prior elevations in basal FSH have both compromised ovarian response and embryo quality relative to those with normal FSH levels, as illustrated by lower oocyte yields, higher cancellation rates, and lower implantation and pregnancy rates. As expected, age is an excellent predictor of IVF success; however, the combination of age >40 years and prior elevations in basal FSH predicts a particularly poor outcome.

TABLE 2

In vitro fertilization outcomes in patients with prior elevations in basal FSH vs. in the general IVF population (normal FSH).

	All ages			<35 y			35–40 y			>40 y		
Variable	Elevated FSH	Normal FSH	*P* value	Elevated FSH	Normal FSH	*P* value	Elevated FSH	Normal FSH	*P* value	Elevated FSH	Normal FSH	*P* value
n	180	1,748	—	30	550	—	56	651	—	94	547	—
FSH level (IU/L ± mean)	7.5 ± 6.1	8.3 ± 5.7	NS	—	—	—	—	—	—	—	—	—
Age (y)	—	—	—	31 ± 2.3	31.4 ± 2.5	NS	37.4 ± 1.4	37.0 ± 1.4	NS	41.9 ± 1.5	41.8 ± 1.5	NS
Oocyte yield	—	—	—	8.4 ± 5.63[a]	11.6 ± 6.5[b]	<.01	7.0 ± 5.4	9.7 ± 6.3	<.005	5.2 ± 4.5	7.7 ± 6.0	<.001
Embryos transferred	—	—	—	2.3 ± 1.3	2.4 ± 1.2	NS	2.6 ± 1.6	2.7 ± 1.6	NS	2.4 ± 2.0	2.9 ± 2.2	NS
Fertilization rate (%)	—	—	—	66.2 ± 8.1	70.3 ± 8.4	NS	74.4 ± 8.6	71.0 ± 8.4	NS	69.8 ± 8.4	73.6 ± 8.6	NS
Implantation rate (%)	—	—	—	25.4 ± 5.0	32.7 ± 5.7	NS	26.2 ± 5.1	23.2 ± 4.8	NS	2.3 ± 1.5	9.0 ± 3.0	<.005
Clinical pregnancy rate (%)	—	—	—	33.3 (10/30)	51.5 (283/550)	NS	35.7 (20/56)	43.3 (282/651)	NS	9.6 (9/94)	26.2 (143/546)	<.01
Cancellation rate (%)	—	—	—	16.7 (5/30)	8.0 (44/550)	NS	26.8 (15/56)	12.1 (79/651)	<.005	36.2 (34/94)	21.1 (115/546)	<.005

Note: Values expressed as mean ± SD, except clinical pregnancy and cancellation rates. NS = not significant; — = not available.

[a] $P<.01$, between age groups in patients with a history of elevated basal FSH levels.

[b] $P<.001$, between age groups in patients with a history of normal basal FSH levels.

Roberts. Basal FSH history and IVF. Fertil Steril 2005.

TABLE 3

Clinical pregnancy rates with IVF among all patients with a history of one, two, and three elevated basal FSH levels vs. the general IVF population (normal FSH).

Parameter	Normal FSH	One prior elevation of FSH	Two prior elevations of FSH	Three prior elevations of FSH
Clinical pregnancy rate, n (%)	709/1,748 (40.6)	35/154 (22.7)	4/18 (22.2)	0/8 (0)
P value		<.0005	NS	<.01

Note: NS = not significant.

Roberts. Basal FSH history and IVF. Fertil Steril 2005.

Age is an important independent marker of fecundity in the general population, as well as of pregnancy with IVF; but compared with basal FSH, age has a weaker association with ovarian response to gonadotropin stimulation. Indeed, several groups have found that basal FSH levels are more predictive of ovarian response to gonadotropin stimulation, than of pregnancy (8–10). Aging clearly has an effect on oocyte quality and on the subsequent ability of the embryo to implant and develop, whereas basal FSH better serves as an indicator of the available pool of primordial follicles (functional ovarian reserve). Van Rooij et al. (11) found a similar relationship between FSH levels, age, and IVF outcome. In their prospective observational study (11), they compared IVF outcomes in patients aged >41 years with normal range FSH levels with those of younger patients with elevated FSH levels. The high FSH group had more cycles canceled for poor response (31% vs. 8%) and a lower peak E_2 level (1,488 vs. 2,904 pmol/L), whereas patients >41 years of age had lower implantation rates (11% vs. 34%) and lower pregnancy rates (10% vs. 25%). Other groups have also noted a weak association between basal FSH and pregnancy outcome after IVF in younger patients (9, 12). Spandorfer et al. (13) supports these observations with a retrospective analysis of the impact of age on implantation rates after day 3 transfer. In 1,621 consecutive IVF cycles, they found that implantation rates remained constant until the age of 35 years and then declined linearly by 2.8% per year, from 36.8% at 33 years of age to 2.3% at 44 years of age. All of these studies support the premise that basal FSH measurements estimate ovarian reserve, whereas age predicts egg quality.

The triad of subfertility, regular menses, and elevated basal FSH has been categorized by some as occult ovarian failure (14). Aside from poor response to ovarian hyperstimulation, the condition has been associated with polyglandular autoimmunity (14). Determining which of these patients will fail to respond to controlled ovarian hyperstimulation is the principal goal of ovarian reserve testing. As demonstrated by van Montfrans et al. (15), basal FSH is probably not an appropriate screening test for subfertility in the general population but can be used effectively as a screening tool for IVF and, to a lesser extent, ovulation induction. In unstimulated IVF cycles, elevated cycle day 3 FSH levels (≥20 IU/mL) do not appear to foretell abnormal follicle growth, fertilization, or embryo development but are not compatible with pregnancy. Since the original work on early follicular phase FSH and IVF (7, 16), several groups have shown its predictive value for individual IVF outcomes (12, 17, 18). Similar to our findings, Martin et al. (19) found that patients with a history of basal FSH elevations (≥20 mIU/mL) had a poor outcome with IVF. In a cohort of 1,868 consecutive IVF cycles, the pregnancy rate in all patients with a history of one elevated FSH was 5.6%, whereas no pregnancies occurred with a history of two elevations. Unfortunately, a recent meta-analysis of the use of basal FSH for the prediction of poor outcome from IVF failed to find a single study of sufficient quality to include in the analysis (8). They concluded that basal FSH levels are moderately predictive of poor response and poorly predictive of nonpregnancy. Despite limitations in the studies, basal FSH screening is time tested, inexpensive and simplistic, with sufficient predictive value for use in IVF.

As a general rule, IVF cycles at our clinic are not started with cycle day 2 or 3 levels in excess of 20 IU/mL on RIA. Patients are advised of the high risk of a poor outcome and are advised to attempt IVF during a future cycle, when basal levels are within the normal range. Fluctuations of basal FSH levels within the normal range commonly occur between cycles, particularly at levels exceeding 15 IU/mL, but cannot be used reliably to predict response during a given cycle (20, 21). Our study is limited by the fact that it is a crude summary of our experience over an 18-month period and therefore does not control for several parameters, including etiology of infertility, patient demographics, or treatment protocol; however, we clearly have shown that elevations in basal FSH levels above 20 IU/mL over the preceding year are predictive of a poor IVF outcome in women aged >40 years.

Several excellent screening tests of ovarian reserve have been described, with widely variable predictive values (5). Our institution has adopted a combination of basal FSH, basal E_2, and antral follicle count as the baseline workup for each IVF cycle. Elevated basal E_2 levels are attributed to the rapid premature follicle recruitment that is observed in pa-

tients with poor ovarian reserve and the consequent loss of pituitary inhibition during the luteal phase. Original observations by Licciardi et al. (22) demonstrated a graded decline in IVF pregnancy rates with increasing basal E_2 levels. No pregnancies were seen when levels exceeded 75 pg/mL. Antral follicle count during the early follicular phase is predictive of both ovarian response to gonadotropins and pregnancy (23–25). A recent prospective analysis used logistic models of screening tests for poor ovarian response in IVF and found that a combination of antral follicle count and basal endocrine markers (FSH and inhibin B) was better than either alone (26). Among the three tests, antral follicle count was the best single predictor of poor response, with an area under the receiver-operating curve of 0.87, whereas a combination of all three tests yielded most highly, at 0.92. Combining baseline screening tests is common practice and appears to optimize their predictive power (3, 22).

On the basis of our retrospective analysis of a large cohort of IVF patients, a history of one of more elevated basal FSH levels is associated with poor response to gonadotropins, irrespective of age; as well as with poor embryo quality in women aged >40 years, as exemplified by a reduction in implantation and pregnancy rates. These results outline the difference between the chronological and biological age of the ovary (functional ovarian reserve), in terms of response to controlled ovarian stimulation and competency of the oocyte and embryo. We have shown that a woman's FSH history should be paramount in pretreatment counseling. Certainly women aged >40 years with a history of elevated basal FSH levels should be counseled on their poor prognosis with IVF and directed toward more appropriate options such as oocyte donation or adoption. Prospective studies need to be done to more precisely define predictive values of basal FSH levels. Even so, basal FSH is probably the most commonly performed laboratory test in subfertile couples and should remain an important prognostic tool before starting IVF.

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