

# Age-specific FSH levels as a tool for appropriate patient counselling in assisted reproduction

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**BACKGROUND:** The purpose of this study was to assess whether, even within a normal FSH range ( $\leq 10$  mU/ml), age-specific FSH levels are predictive of ovarian reserve. **METHODS:** Between January 1998 and December 2001, 535 women, undergoing controlled ovarian stimulation with 225 IU of recombinant (rec) FSH and 75 IU of recLH, were included in this retrospective cohort study. Criteria for enrolment were: age 25–40 years, basal FSH (b-FSH)  $\leq 10$  mU/ml and basal LH  $\leq 12$  mU/ml. Patients were assigned to three age groups (group I: 25–29 years; group II: 30–35 years; and group III: 36–40 years). Each age group was divided into quartiles according to b-FSH levels, comparing the lowest and highest b-FSH quartiles for basal hormonal patterns and outcome-related parameters. **RESULTS:** At ages 25–35 years, women in the lowest FSH quartiles demonstrated significantly increased numbers of oocytes at retrieval (group I: low b-FSH quartile  $8.4 \pm 3.7$  versus high b-FSH quartile  $6.4 \pm 2.7$ ,  $P < 0.02$ ; group II:  $7.5 \pm 4.0$  versus  $6.3 \pm 3.0$ ,  $P < 0.047$ ), whereas no difference with regard to oocyte yield was observed in patients above age 35 (group III: low b-FSH quartile  $5.5 \pm 3.1$  versus high b-FSH quartile  $5.6 \pm 3.5$ ). No statistical correlation was found between FSH quartiles and clinical pregnancy rates or miscarriage. **CONCLUSIONS:** In young women, age-specific high b-FSH levels, even within normal ranges, are associated with significantly reduced numbers of oocytes retrieved. B-FSH concentrations should, therefore, be interpreted in an age-specific manner to allow for appropriate patient counselling in IVF.

*Key words:* age/FSH/IVF/ovarian reserve/poor responder

## Introduction

The success of IVF is critically dependent on the appropriate evaluation of ovarian function to optimize controlled ovarian stimulation (COS). While follicular depletion and impaired oocyte quality, frequently also called ‘diminished ovarian reserve’ (Kligman and Rosenwaks, 2001; Bancsi *et al.*, 2002; Chuang *et al.*, 2003), are generally acknowledged as the underlying mechanisms for the decline in maternal fecundity, the way to assess the status of ovarian reserve correctly has remained controversial (Fanchin *et al.*, 1994; Lambalk, 2003).

The association between advanced female age and reproductive senescence is well established (Oosterhuis *et al.*, 2002; Jansen, 2003). Nevertheless, in women of the same age, individual variations exist with regard to their ovarian responses (Pellicer *et al.*, 1998; Perez *et al.*, 2000). Chronological female age is universally seen as indicative of qualitative alterations of the remaining follicle pool (Popovic-Todorovic *et al.*, 2003; Toner, 2003; Van Rooij *et al.*, 2003, 2004a), but cannot serve as the sole marker of ovarian status (Kligman and Rosenwaks, 2001).

A variety of tests, such as the antral follicle count, the clomiphene challenge test and measurements of basal

inhibin B (Mukherjee *et al.*, 1996; Creus *et al.*, 2000; Fasouliotis *et al.*, 2000; Meo *et al.*, 2002), have been introduced as predictive of ovarian reserve; however, cycle day 2 or 3 FSH, i.e. basal (b-)FSH, is still the most widely used parameter in the assessment of ovarian function (Tanbo *et al.*, 1992; Letur-Konirsch and Guis, 1996; Bancsi *et al.*, 2003; Smits *et al.*, 2003).

Recently, some controversy has arisen about the clinical utility of b-FSH measurements (Jurema *et al.*, 2003; Scott, 2004; Toner, 2004; Wolff and Taylor, 2004). Abdalla and Thum (2004), as well as Van Rooij *et al.* (2004b), depicted reduced, yet still clinically sound pregnancy and live birth rates in young women with elevated b-FSH levels of up to 20 mU/ml. They, therefore, concluded that the predictive value of b-FSH concentrations should be restricted to the counselling of patients on the probability of achieving pregnancy, but should not be used to exclude them from fertility treatment. Scott (2004) goes even further, denying any predictive value to b-FSH concentrations within normal ranges.

In contrast, Jurema *et al.* (2003) describe substantially reduced cut off-levels for b-FSH values ( $< 6$  IU/l) to predict ovarian response to stimulation accurately, but agree that they do not predict pregnancy potential. They also argue,

however, that b-FSH cut off-values of up to 10 IU/l will include virtually all pregnancies in a cohort with normal prognosis.

Though contradictory opinions exist regarding the appropriate cut-off level for b-FSH values in the evaluation of ovarian reserve, so far there has been unanimity about interpreting b-FSH levels in absolute (i.e. fixed) terms. Since a majority of hormonal test results is subject to age-related alterations (El-Touky et al., 2002) and since ovarian reserve is known to decline in an age-dependent manner (Bancsi et al., 2003), age-specific interpretations of b-FSH values might result in a more accurate assessment of ovarian function.

The study presented here, therefore, was initiated to evaluate the impact of age-specific b-FSH concentrations on ovarian response in young women with normal b-FSH levels ( $\leq 10$  mU/ml).

## Patients and methods

### Study design and patients

Five-hundred and thirty-five regular cycling women, aged 25–40 years, undergoing their first cycle of COS between January 1998 and December 2001, were included in this retrospective cohort study. Only cycles using a combination of clomiphene citrate and gonadotrophins for ovarian stimulation were eligible for enrolment. Patients suspected of having polycystic ovary syndrome were excluded from the analysis.

Cut-off values for b-FSH and LH levels, measured on cycle days 2 or 3, immediately before the commencement of oral contraception, were considered as follows: b-FSH  $\leq 10$  mU/ml and b-LH  $\leq 12$  mU/ml.

Based on age, patients were assigned to the following three groups: group I: age 25–29 years; group II: age 30–35 years; and group III: age 36–40 years. Each age group, in turn, was divided into quartiles according to b-FSH levels. Within each age group, the lowest and highest b-FSH quartiles were compared for the following parameters: female chronological age, treatment indications, b-LH and b-estradiol ( $E_2$ ) levels, smoking status, number of oocytes retrieved, day of embryo transfer, number of embryos transferred, miscarriage and clinical pregnancy rates. A maximum of four oocytes at oocyte retrieval was considered 'poor ovarian response'.

To assess the impact of chronological female age, b-FSH level and smoking on oocyte yield within and between age groups, both a univariate and a multivariate analysis of variance (ANOVA) were

performed, including the following parameters: chronological age (group I, II and III), b-FSH level (low and high b-FSH quartiles) and smoking. Furthermore, the interaction for age–low b-FSH and for age–high b-FSH was calculated.

### Ovarian stimulation and fertilization

After pre-treatment with oral contraceptives (18–28 days), COS was initiated with clomiphene citrate (daily dose of 100 mg per os on cycle days 1–5) and a combination of 225 IU of recombinant (rec) FSH and 75 IU of recLH on alternate days, i.e. on cycle day 1, 3, 5 and 7 (Weigert et al., 2002).

To allow for easy handling and to warrant a fixed ratio of gonadotrophins, no dosage adjustments were performed. In the case of inadequate follicular response, i.e. leading follicle diameter  $< 18$  mm after 7 days of stimulation, an additional dosage of 225 IU of recFSH and 75 IU of recLH was given on cycle day 9.

Cycle monitoring, oocyte retrieval and embryo transfer were performed in a routine fashion, as previously reported (Margreiter et al., 2003). A clinical pregnancy was defined as the presence of fetal cardiac activity beyond 8 weeks of gestation.

### Institutional review board (IRB) approval

Since the present study was based on a retrospective data analysis, no IRB approval was required.

### Statistical analysis

The present data analysis was performed with the Statistics Package for Social Sciences (SPSS, Chicago, IL). Differences in baseline characteristics and outcome measures within and between age groups and b-FSH subsets of patients were investigated by ANOVA. Furthermore, the interaction between b-FSH (two groups: low and high b-FSH quartiles) and age (three groups: groups I–III) was assessed using ANOVA. Descriptive results are presented as means with SD.  $P$ -values  $< 0.05$  were considered statistically significant.

## Results

Indications for fertility treatment and patients' characteristics are presented in Tables I and II. The mean age of the women eligible for enrolment in group I was  $27.5 \pm 1.2$  years in the lowest b-FSH quartile and  $27.8 \pm 1.2$  years in the highest b-FSH quartile. In patients allocated to group II, the mean age was  $32.6 \pm 1.5$  in the lowest b-FSH quartile and  $32.6 \pm 1.6$  years in the highest b-FSH quartile, whereas women in group III were aged on average  $37.5 \pm 1.4$  years

**Table I.** Indications for fertility treatment according to patients' age and basal (b-)FSH levels

	Group I: age 25–29 ( $n = 114$ )		Group II: age 30–35 ( $n = 258$ )		Group III: age 36–40 ( $n = 133$ )	
	Low b-FSH <sup>a</sup> ( $n = 40$ )	High b-FSH <sup>b</sup> ( $n = 30$ )	Low b-FSH <sup>a</sup> ( $n = 68$ )	High b-FSH <sup>b</sup> ( $n = 65$ )	Low b-FSH <sup>a</sup> ( $n = 34$ )	High b-FSH <sup>b</sup> ( $n = 33$ )
Male factor	28 (70.0%)	15 (50.0%)	46 (67.6%)	33 (50.8%)	19 (55.9%)	17 (51.5%)
Tubal factor	3 (7.5%)	8 (26.7%)	14 (20.6%)	21 (32.3%)	8 (23.5%)	10 (30.3%)
Combined factors	2 (5.0%)	1 (3.3%)	3 (4.4%)	2 (3.1%)	0	2 (6.1%)
Endometriosis	4 (10.0%)	3 (10.0%)	1 (1.5%)	2 (3.1%)	1 (2.9%)	2 (6.1%)
Immunological infertility	0	0	0	0	2 (5.9%)	0
Unexplained infertility	3 (7.5%)	3 (10.0%)	4 (5.9%)	7 (10.8%)	4 (11.8%)	2 (6.1%)

<sup>a</sup>Low b-FSH = lowest b-FSH quartile of the age group.

<sup>b</sup>High b-FSH = highest b-FSH quartile of the age group.

**Table II.** Patients' characteristics according to female age and serum b-FSH levels

	Group I: age 25–29 (n = 114)			Group II: age 30–35 (n = 258)			Group III: age 36–40 (n = 133)		
	Low b-FSH (n = 40)	High b-FSH (n = 30)	P-value	Low b-FSH (n = 68)	High b-FSH (n = 65)	P-value	Low b-FSH (n = 34)	High b-FSH (n = 33)	P-value
Age (years)	27.5 ± 1.2	27.8 ± 1.2	NS	32.6 ± 1.5	32.6 ± 1.6	NS	37.5 ± 1.4	37.5 ± 1.5	NS
b-FSH (mU/ml)	5.9 ± 2.5			6.3 ± 2.2			6.2 ± 2.4		
	3.2 ± 1.5	8.8 ± 0.7		3.3 ± 1.4	8.9 ± 0.6		3.0 ± 1.5	9.0 ± 0.6	
b-LH (mU/ml)	2.6 ± 2.4	4.3 ± 2.3	0.04	2.6 ± 2.2	4.6 ± 2.2	0.01	2.6 ± 3.2	4.8 ± 2.1	0.002
Estradiol (pg/ml)	19.5 ± 17.6	21.6 ± 20.7	NS	20.4 ± 24.3	27.7 ± 23.9	NS	20.2 ± 16.7	37.7 ± 23.5	0.002
Smoking status <sup>a</sup>	25.0%	26.7%	NS	26.5%	38.4%	0.01	32.4%	39.4%	NS

<sup>a</sup>Statistical analysis for confounding of smoking did not reveal a significant effect on oocyte yield, either in univariate or in multivariate analysis.

(lowest b-FSH quartile) and 37.5 ± 1.5 years (highest b-FSH quartile), respectively. Age groups and FSH quartiles were similar with regard to cycle length.

Within all age groups, women in the highest b-FSH quartiles showed significantly higher b-LH levels than patients in the lowest b-FSH quartiles. The correlation coefficients between b-FSH and b-LH for low versus high FSH quartiles were as follows: group I: 0.57 versus 0.14; group II: 0.42 versus 0.18; and group III: 0.32 versus 0.13.

At ages 36–40, women in the highest b-FSH quartile also demonstrated statistically elevated b-E<sub>2</sub> levels, whereas younger women showed no differences in E<sub>2</sub> levels between the various FSH quartiles.

The impact of chronological female age and b-FSH level on oocyte yield was assessed further by univariate as well as by multivariate ANOVA. A significant influence on the number of oocytes retrieved was found for female chronological age (univariate,  $P < 0.001$ ; multivariate,  $P = 0.039$ ) and for age-specific high b-FSH levels (univariate,  $P < 0.003$ ; multivariate,  $P = 0.027$ ).

To assess the impact of smoking on oocyte yield, univariate and multivariate ANOVA was performed. Smoking did not, however, have a significant impact on oocyte yield in our patient cohort (univariate analysis,  $P = 0.44$ ; multivariate analysis,  $P = 0.56$ ).

Outcome-related parameters are summarized in Table III. Women aged 25–35 years, in the lowest quartile of b-FSH levels, demonstrated significantly increased numbers of oocytes at retrieval (number of oocytes retrieved in group I, low b-FSH quartile, 8.4 ± 3.7 versus high b-FSH quartile, 6.4 ± 2.7,  $P < 0.02$ ; group II, low b-FSH quartile, 7.5 ± 4.0 versus high b-FSH quartile, 6.3 ± 3.0,  $P < 0.047$ ), whereas no difference with regard to oocyte yield was observed in patients above age 35 (group III, low b-FSH quartile, 5.5 ± 3.1 versus high b-FSH quartile, 5.6 ± 3.5, not significant). To assess further the impact of b-FSH and chronological age on oocyte yield, an interaction with main effects for age (groups I–III) and b-FSH (low and high b-FSH) was performed. However, neither the interaction of low b-FSH levels and age (groups I–III), nor the interaction of high b-FSH levels and age (groups I–III) demonstrated significant results (low b-FSH × age,  $P = 0.2$ ; high b-FSH × age,  $P = 0.6$ ).

No statistical correlation was found between clinical pregnancy rates and miscarriage to b-FSH levels.

## Discussion

A normal b-FSH level (≤10 mU/ml) and young chronological age (≤35 years) are generally acknowledged as the two most promising prognostic factors, reflecting ovarian function, in women initiating fertility treatment (Jurema *et al.*, 2003; Van Rooij *et al.*, 2003). Such patients will, therefore, usually receive age-specific, and as mild as possible, stimulation protocols.

Our study, however, clearly demonstrates that in women, aged 25–35 years, b-FSH levels, even within a normal range, matter with regard to oocyte numbers. Higher age-specific FSH levels lead to fewer eggs (Figure 1). The lack of significance of the interaction between b-FSH and age supports these findings. In contrast, in women of advanced reproductive age (>35 years), the variations of b-FSH levels, as long as they are still <10.1 mU/ml, are not predictive of oocyte yield. The significant increase in b-E<sub>2</sub> levels in patients above age 35 with age-specific high FSH values can, though, be interpreted as reflective of diminishing ovarian reserve (Larsen *et al.*, 2003; Tarlatzis *et al.*, 2003; Gurbuz *et al.*, 2004).

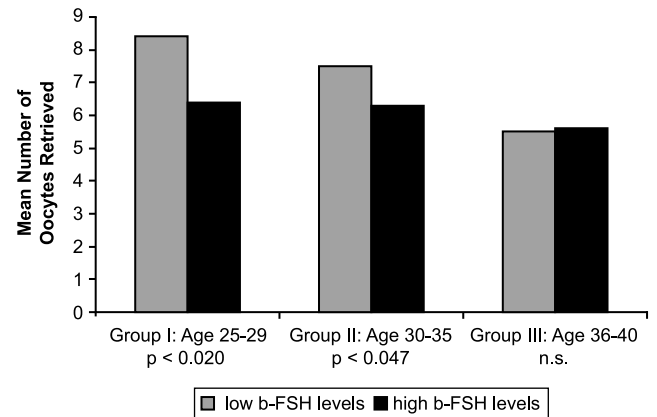
Within our data analysis, a correlation between b-FSH and b-LH was observed in all women; patients in the highest FSH quartiles showed significantly higher LH levels than women with low age-specific FSH values. These findings might be attributable to an increasing sensitivity of the pituitary to GnRH with imminent ovarian failure, as previously reported by de Koning *et al.* (2000).

Variations in b-FSH levels are also not predictive of clinical pregnancy and miscarriage rates. This finding should not be a surprise because, as long as patients are still capable of producing a minimal number of oocytes of acceptable quality, they will also produce adequate numbers of good quality embryos for a single embryo transfer. Consequently, high b-FSH levels, especially in young patients, should not serve as exclusion criteria from fertility treatment, but as a guideline to individual patient counselling.

Large differences in pregnancy (and miscarriage) rates should become statistically visible only if the outcomes of frozen–thawed embryo transfer cycles (FETs) are added in producing cumulative pregnancy rates from single retrievals. This was recently also confirmed by Gleicher *et al.* (personal communication) who in >60 women with proven ovarian resistance, all below age 35, demonstrated ongoing

**Table III.** Cycle outcomes according to female age and serum b-FSH levels

	Group I: age 25–29 (n = 144)			Group II: age 30–35 (n = 258)			Group III: age 36–40 (n = 133)		
	Low b-FSH (n = 40)	High b-FSH (n = 30)	P-value	Low b-FSH (n = 68)	High b-FSH (n = 65)	P-value	Low b-FSH (n = 34)	High b-FSH (n = 33)	P-value
No. of oocytes retrieved	8.4 ± 3.7 (1–17)	6.4 ± 2.7 (1–13)	0.02	7.5 ± 4.0 (1–19)	6.3 ± 3.0 (1–15)	0.047	5.5 ± 3.1 (1–14)	5.6 ± 3.5 (1–13)	NS
No. of oocyte retrievals with > 4 oocytes	33 (82.5%)	24 (80%)	NS	56 (82.4%)	47 (72.3%)	NS	18 (52.9%)	17 (51.5%)	NS
No. of cycles cancelled	1 (2.5%)	2 (6.7%)	NS	2 (2.9%)	1 (1.5%)	NS	2 (5.9%)	3 (9.1%)	NS
No. of embryos transferred	2.0 ± 0.3 (1–3)	2.0 ± 0.5 (1–3)	NS	2.3 ± 0.6 (1–3)	2.2 ± 0.6 (1–3)	NS	2.4 ± 0.7 (1–3)	2.1 ± 0.6 (1–3)	NS
Day of embryo transfer	3.0 ± 0.9 (2–5)	2.7 ± 0.7 (2–4)	NS	3.1 ± 0.9 (2–5)	2.8 ± 0.9 (1–5)	NS	3.0 ± 0.9 (1–5)	2.6 ± 1.0	NS
Miscarriage	3 (7.5%)	6 (20%)	n.s.	6 (8.8%)	3 (4.6%)	NS	3 (8.8%)	4 (12.1%)	NS
Clinical pregnancy rate	6 (15%)	6 (20%)	n.s.	18 (26.5%)	18 (27.7%)	NS	6 (17.6%)	8 (24.2%)	NS



**Figure 1.** Number of oocytes retrieved according to female age and serum FSH levels. Women are allocated to groups according to chronological age; each age group is subdivided into FSH quartiles (grey, lowest FSH quartile of age group; black, highest FSH quartile of age group). Mean basal FSH (b-FSH) levels according to age groups: group I, 3.2 ± 1.5 mU/ml in the lowest FSH quartile versus 8.8 ± 0.7 mU/ml in the highest FSH quartile; group II, 3.3 ± 1.4 versus 8.9 ± 0.6 mU/ml; group III, 3.0 ± 1.5 versus 9.0 ± 0.6 mU/ml.

pregnancy rates identical to those in matched controls with normal ovarian function. However, when cumulative pregnancy rates, indicating potential FET results, were calculated, control patients, indeed, demonstrated significantly higher pregnancy rates due to their larger oocyte numbers at the time of retrieval. Our results also coincide with those of Jurema *et al.* (2003) who also, at normal b-FSH levels, were unable to detect an impact on pregnancy rates in IVF cycles.

Wolff and Taylor (2004) recently suggested that patients with elevated b-FSH levels should not be excluded from IVF treatment. Instead, these authors presented (in intriguing analogy to current prenatal genetic screening) that b-FSH values, among other parameters, such as chronological age and follicular phase inhibin B, should be utilized to establish an age-specific likelihood ratio for ovarian response.

In conclusion, the present study demonstrates that, at young ages, b-FSH, even if within normal ranges, may contribute to the prediction of ovarian reserve, as a reflection of the number of oocytes retrieved. Consequently, b-FSH should not serve as a marker to exclude patients from fertility treatment, but should be interpreted according to patient's age and not in absolute terms, even within the generally considered normal range of ≤ 10 mU/ml. An age-specific definition of ovarian reserve will allow physicians to stimulate patients in a more individualized fashion, which, in turn, will maximize IVF outcomes.

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