The Practical Implications of a Raised Serum FSH and Age on the Risk of IVF Treatment Cancellation Due to a Poor Ovarian Response

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Purpose: Chronological age, or biological age as indicated by elevated FSH levels, are related to ovarian reserve. This study addresses the likelihood of cancellation of IVF treatment due to a poor ovarian response utilising both basal serum FSH and woman's age.

Methods: A prospective cohort of 536 infertile but ovulating women were studied in their first cycle of IVF treatment. Standardised methods of pituitary desensitisation and ovarian stimulation prior to IVF treatment were employed. Treatment cycles cancelled due to a poor ovarian response to gonadotrophins were studied. A series of logistic regression models were used to explore the probabilities of cancellation in relation to age and FSH.

Results: Both age and basal serum FSH levels were independently associated with the risk of treatment cancellation. A low risk of treatment cancellation was observed in women under the age of 35 irrespective of serum FSH, however in older women the risk of treatment cancellation was most likely in women with a high FSH.

Conclusions: In combination both age and FSH may serve as a valuable indicator of poor ovarian response leading to treatment cancellation. However, among older women FSH has particular importance, while less so in younger women with regular menstrual cycles.

KEY WORDS: Age; FSH; infertility; IVF; poor ovarian response.

INTRODUCTION

The success of in vitro fertilisation and embryo transfer (IVF-ET) is dependent in part on the response of the ovaries to exogenous gonadotrophin stimulation (1). Treatment cancellation because of poor ovarian response is a significant problem and is mainly

due to underresponse. In general about 12–30% of stimulated cycles show a poor response as evidenced by low peak oestradiol concentrations and decreased number of preovulatory follicles (2,3), many of which result in treatment being discontinued (cancelled). A diminishing ovarian response to stimulation is observed as a consequence of advancing chronological age (4). Basal serum FSH levels, an indication of biological age, are also predictive of ovarian response to stimulation independent of age (1,5,6).

A poor ovarian response is a reflection of reduced total ovarian follicular capacity (reserve). Identification of women with a markedly reduced ovarian reserve, likely to lead to cycle cancellation, is paramount prior to embarking on expensive and invasive treatment such as IVF. Numerous methods of assessing

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ovarian reserve exist such as serum inhibin B levels (7), ovarian volume (8,9), early menstrual phase oestradiol levels (10,11), antral follicle count (12,13), and the clomiphene challenge test (14). However, basal serum FSH levels are currently the most commonly used validated test to assess ovarian reserve (15,16). Ovarian reserve, as indicated by basal serum FSH, may not correlate with chronological age (1). We therefore explored utilising the combination of a woman's age and basal serum FSH as predictors of the risk of treatment cancellation in women undergoing IVF treatment.

MATERIALS AND METHODS

We studied all couples attending the University of Bristol IVF service and undergoing their first cycle of IVF treatment during the 4 years 1993–1996 meeting the following criteria: the women had a normal uterus and normal ovulatory cycles (mid-luteal $P \geq 30$ nmol/mL); the men had favorable sperm function as indicated by normal penetration of normal cervical mucus in vitro compared with normal control semen and/or normal motility after swim-up into culture medium in the absence of seminal antisperm antibodies by specific testing.

Serum FSH concentration was measured in one cycle during the early follicular phase (days 2–5) within 6 months of treatment [FSH concentrations have been shown to be constant between at least days 2 and 5, although oestradiol rises] (17). Patients were offered treatment irrespective of age and FSH level if ovulating regularly but were advised about their declining chance of success because of increased age and raised FSH level and about the increased risk of a poor ovarian response (18).

Standard clinical and laboratory methods of IVF treatment were employed as previously described from our center (19). To avoid other potential selective bias we also limited study to the first cycle of treatment only. In brief, pituitary desensitization was started in the midluteal phase of the cycle before IVF treatment, using intranasal buserelin acetate spray (Suprefact; Hoechst, Hounslow, United Kingdom) 600 μ g daily in five divided doses, 100 μ g at 4-h intervals during the day and 200 μ g at bedtime. After 10–14 days, to fit in with the most convenient day to start ovarian stimulation but always after menstruation had occurred, FSH treatment (Metrodin or Metrodin HP;

Serono Laboratories Limited) using 150 IU daily (d) was routinely administered by SC or IM injection. Older women ≥ 35 years of age had 225 IU/d, or if their basal FSH was elevated then ≥ 9 IU/L (6). Monitoring by vaginal ultrasound scanning of the ovarian follicles and measurement of the serum oestradiol (E_2) concentration was started on day 8 of stimulation with a view to increasing the dose to 225 IU/d or 300 IU/d if there was no significant appearance of follicles and $E_2 < 82$ pg/mL (300 pmol/L) as appropriate. Monitoring was repeated every 2–4 days stopping up to 2 days before HCG administration. The aim was to achieve three follicles ≥ 18 mm diameter (mean of three measurements at right angles) and appropriate E_2 (≥ 136 pg/mL [500 pmol/L] per follicle ≥ 15 mm diameter). Treatment with buserelin acetate and FSH was continued up to and including the day of administration of HCG (Profasi; Serono Laboratories Limited) in patients who achieved the above criteria. No uniform definition of a very poor response is available (3,20,21). The practice in our center however, was to cancel cycles in which three or less follicles developed with a correspondingly low serum E_2 levels following appropriate stimulation (22,23). Treatment cycles that were cancelled due to overresponse to gonadotrophin stimulation were excluded from the study.

Serum FSH concentration was measured using a two-site immunofluorimetric method employing two monoclonal antibodies directed first against the β subunit and then the α subunit (DELFI; Wallac Oy, Turku, Finland). Interassay variation over the useful range was 4–6% and intraassay variation $< 5\%$. The normal range during the early follicular phase was 0.8–8.9 IU/L (95% confidence limits). These values and the assay performance were consistent with most laboratories participating in the UK Quality Assurance Scheme for Peptide Hormones.

Two-tailed Mann–Whitney U tests were used to compare the ages and serum FSH concentrations for women with cancelled/noncancelled cycles. A series of logistic regressions were used to model the relationship between the cancellation rate and both age and FSH together. Our approach was first to explain the relationship between cancellation probability and age, using a log transformation of age since this best fitted the data; we added FSH to this to assess the additional contribution. “Fractional polynomials” (24) were used to determine the best transformations for the predictors. All modelling used the software package Stata 6.0 (25).

Table I. Number and Proportion of Women Studied According to Whether They Underwent Treatment or Were Cancelled in Relation to the Age and Basal Serum FSH

	Number (%; 95% CI)	Median age [years] (range)	Median FSH [IU/L] (range)
All women	536 (100)	35 (22–49)	6.0 (0.5–22.0)
Women treated	504 (94.0; 91.7–95.9)	34 (22–49)*	6.0 (0.5–21.4) [†]
Cancelled cycles	32 (6.0; 4.1–8.3)	40 (29–45)*	11.4 (3.8–22.0) [†]

* $p < 0.001$; [†] $p < 0.001$ using the Mann–Whitney U test.

RESULTS

There were 536 patients undergoing their first attempt at IVF treatment who were eligible for this study. Thirty-two (6%) treatment cycles were cancelled due to a poor ovarian response. The ages and serum FSH of the women studied are shown in Table I.

Women with cancelled cycles were older and had significantly higher serum FSH concentrations than the remainder ($P < 0.001$ for both, Table I). Since age and FSH were positively correlated with each other (Pearson's $r = 0.219$, $P < 0.001$), Table II gives cancellation rates for subgroups of women defined both by age and FSH. Treatment cancellation rates were very low for younger women, increasing sharply after late 30's, but within the older group of women there seemed to be a relationship also with FSH.

We used logistic regression firstly to model the relationship between the cancellation rate and age, and then to see if FSH had an additional contribution. Both age and FSH were highly significant individually; the coefficient for $\log(\text{age})$ was 10.3 (SE = 1.9), which was slightly reduced to 8.1 (SE = 1.9) when FSH was added and the coefficient for FSH alone was 0.36 (SE = 0.05) which reduced to 0.31 (SE = 0.05) when taken together with age. Separate models fitted to age strata <34, 35–40, and >40, each yielded coefficients of FSH of approximately 0.3 (SE = 0.1).

There was a significant relationship with age ($P < 0.001$); the best transformation for age being its nat-

ural logarithm. FSH was significant when added to this model ($P < 0.001$), suggesting that FSH had an additional contribution. The fitted model was:

$$\log_e(P/(1 - P)) = 8.10 \log_e(\text{age}/10) + 0.31 \text{FSH} - 15.84$$

Age in integral years, FSH in IU/L, and P is the expected probability of cancellation.

The fit of the model can be assessed from Table III which compares observed numbers of cancellations with expected numbers derived from the model. Figure 1 shows a graph of the expected cancellation probabilities across all ages for four specified FSH concentrations: 3, 6, 9, and 12 IU/L. This emphasises the importance of FSH in the older women, as already observed in Table II. Because, the analysis showed that significant problems with cancellation arose from age 35 onwards, Fig. 2 shows model-derived contours corresponding to 10, 30, and 50% probability of cancellation for women over 35 years. Raw data are also shown for completeness.

DISCUSSION

The decision to cancel or abandon a treatment cycle of IVF (or any assisted conception) treatment is an intractable one. The rationale for cancellations in the light of a very poor ovarian response is based on the likelihood of a very low number of oocytes,

Table II. Proportions of Cancelled Cycles for Subgroups of Women Defined by Age and Basal FSH Concentration Percentages Given in Parenthesis if Subgroup Size >10

Age (years)	FSH (IU/L)					Total
	0–2.9	3–5.9	6–8.9	9–11.9	≥12	
20–24	0/0	0/3	0/1	0/0	0/0	0/4
25–29	0/5	0/30 (0%)	0/21 (0%)	0/6	1/3	1/65 (2%)
30–34	0/10	1/91 (1%)	1/78 (1%)	1/15 (7%)	1/3	4/197 (2%)
35–39	0/16 (0%)	2/75 (3%)	2/72 (3%)	2/15 (13%)	1/12 (8%)	7/190 (4%)
40–44	0/2	1/20 (5%)	5/23 (22%)	1/10	12/17 (71%)	19/72 (26%)
45–49	0/0	0/2	1/2	0/3	0/1	1/8
Total	0/33 (0%)	4/221 (2%)	9/197 (5%)	4/49 (8%)	15/36 (42%)	32/536 (6%)

Table III. Model Validation: Observed/Expected Numbers of Cancellations for Subgroups of Women Defined by Age and FSH; Subgroup Sizes Given in Square Brackets

Age (years)	FSH (IU/L)				
	0–2.9	3–5.9	6–8.9	9–11.9	≥12
<30	0/0.0 [5]	0/0.1 [33]	0/0.1 [22]	0/0.1 [6]	1/0.4 [3]
30–34	0/0.0 [10]	1/0.7 [91]	1/1.2 [78]	1/0.6 [15]	1/0.7 [3]
35–39	0/0.1 [16]	2/1.8 [75]	2/3.4 [72]	2/1.8 [15]	1/3.0 [12]
≥40	0/0.1 [2]	1/1.1 [22]	6/3.3 [25]	1/3.8 [13]	12/9.7 [18]

Note. Expected numbers were calculated using the fitted logistic model with predictors age and FSH.

embryos, implantation and pregnancy rates in such cycles. These reasons are not in dispute. Attempts at prospectively predicting which women will have a poor response prior to the initiation of a treatment cycle are equally difficult. The findings of this study confirm its frequent occurrence particularly in older women. Generally younger women do not pose a significant clinical challenge in this respect (26).

An irreversible, accelerated depletion of ovarian follicle numbers occurs from the age of 38 years (27). This leads to a diminished ovarian reserve, the onset of which can be variable (15,28), and thus often occurs at a younger age in some women. The accelerated diminution of ovarian reserve is reflected by a rise in serum FSH levels (29). The women we studied all experienced normal menstrual cycles in spite of many having raised serum FSH levels and is common in women despite some being perimenopausal (30). The higher levels of FSH which follow advancing age as noted in our study are a reflection of the requirements of the ovary to elicit a response, with recent evidence substantiating the notion that women with a poor

Fig. 1. Model derived probability (%) of cancellation for basal serum FSH (IU/L) concentrations 3, 6, 9, and 12 in relation to age. [shaded area relates to data on eight patients only].

Fig. 2. Model derived contours of 10, 30, and 50% probability of cancellation for women aged 35 years or more in relation to basal serum FSH (IU/L) concentration. [Raw data is shown with solid circles denoting cancelled cycles; crosses the remainder.]

ovarian response are likely to attain the menopause sooner (31). As such, advancing biological age, indicated by elevated serum FSH levels is associated with poor ovarian response (5,32–34) and a reduction in implanting ability of embryos (1,18,35).

In our study, women with cancelled cycles were older and had higher serum FSH concentrations than women who reached oocyte retrieval ($P < 0.001$, Table I), consistent with the findings of others (34). The present study observed few cancellations in women aged under 35 years, irrespective of their serum FSH level. In older, regularly menstruating women, the implications of a raised serum FSH were more pronounced; cancellation rates increased rapidly with an increase in either age or FSH (Fig. 2). However, the use of model such as the fractional polynomial method may lead to underestimation of the likelihood of cancellation, especially at the age range over 45 years where there were little data. As such the data in the shaded area of Fig. 1 should be interpreted with caution in the women over 45 years of age.

Differences of opinion exist in thresholds for defining a poor response and acceptable criteria for offering or cancelling treatment. Many centers offering IVF treatment therefore apply age restrictions. Some studies however, show that FSH may be a better predictor of ovarian response than age (5,6,33,34,36). The present study questions this assertion in view of the adverse independent effect of advancing chronological age observed, but reinforces the impression that among older women FSH has particular importance while less so in younger ones. In further contrast, others (5) found age alone to be of no significant value in predicting ovarian response. However,

the proposition that a normal FSH in older patients has different implications than for younger patients is evident in our findings. Another study (37), found similar outcomes in patients that responded well to stimulation irrespective of age. Hence the authors (37) recommended that age limits for such treatment should not be restricted. However, information on ovarian responsiveness is only available in retrospect after a patient has commenced ovarian stimulation and therefore would not be applicable to women undergoing their first cycles.

Nonetheless, prediction of a treatment cancellation remains difficult because of wide human variation in ovarian response to exogenous FSH stimulation (38). Heterogeneity of FSH receptors and hormones have been implicated (39,40) but these are unlikely to be common causes. Because current research evidence does not support improved response rates with increasing stimulation doses of FSH (above 300 IU of FSH) (3,22,41–43), this practice was not undertaken in our center, however, we recognize that other center do it favorably.

The results of this study were based on a single FSH measurement taken within 6 months of treatment. Variation in cycle to cycle basal FSH levels is recognised (44) and any raised serum FSH recorded in one cycle may be associated with a poor response irrespective of subsequent normal values (32). It is thus possible that in our analysis the prognosis for patients with a normal FSH is overstated. Despite these considerations, the results clearly demonstrate the marked impact of an elevated serum FSH concentration particularly in older women. Thus, normally menstruating patients of younger age are reassured of a good response while older patients, with a raised FSH, should be counselled appropriately of their risk of cycle cancellation before they commence their IVF cycle.

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