Article

# Relevance of basal serum FSH to IVF outcome varies with patient age

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## Abstract

Live birth rate (LBR), age and basal serum FSH values were analysed in 1589 women undergoing their first cycle of IVF. Four age groups (<30, 30–34, 35–38, 39–45 years) and three FSH groups (<5, 5–9.9, ≥10 IU/l) were established. Logistic regression analysis was used to determine the effect of age and FSH on live birth. A model to predict the probability of a live birth suggests that an additional 10 years of age reduces the odds for live birth (OR = 0.66, 95% CI 0.48–0.91); an increase of FSH by 5 IU/l reduces the probability of live birth (OR = 0.75, 95% CI 0.61–0.92); women ≥39 years have an additional reduction in probability of live birth (OR = 0.58, 95% CI 0.61–0.92). Analysis by age and FSH categories showed that pregnancy rate (PR) did not change significantly with rising FSH for women <35 years old. In cycles started with serum FSH <5 IU/l, increasing age did not effect PR and LBR. Cycles started with serum FSH ≥10 IU/l had a PR and LBR of 23.6 and 16.9% respectively. The clinical relevance of elevated FSH varies according to age; younger women with elevated FSH and older women with low FSH still have an acceptable LBR.

**Keywords:** *age, FSH, IVF, live birth*

## Introduction

Evaluating the fertility potential of women is a challenging task for clinicians dealing with infertile couples. Ageing of the ovaries is known to be the main cause of declining fecundity (Menken *et al*., 1986), but a woman's age is only partially accurate in predicting her reproductive potential (Schwartz and Mayaux, 1982; van Noord-Zaadstra *et al*., 1991; Akande *et al*., 2002; te Velde and Pearson, 2002). Early follicular phase serum FSH concentration (basal FSH) has been advocated as a further indicator of ovarian reserve (Navot *et al*., 1987; Lenton *et al*., 1988; Muasher *et al*., 1988), and it has been used to develop prognostic models for assisted reproductive technology (Scott *et al*., 1989; Toner *et al*., 1991, Sharif *et al*., 1998; Shrim *et al*., 2006). Age and basal FSH are the most widely studied and used parameters for the prediction of outcome in assisted reproduction, as they are inexpensive to determine and cause minimal inconvenience to the patients.

The term 'ovarian reserve' is frequently used in relation to female fecundity in assisted reproduction. It has been used in describing both ovarian responsiveness to stimulation (e.g. number of developing follicles, number of oocytes retrieved, cancellation rate) and the reproductive potential, such as implantation and delivery rates (Scott, 2004). The indiscriminate association of a raised basal FSH concentration with 'reduced ovarian reserve' has resulted in a group of women finding difficulty in accessing fertility treatment, as they are regarded as having a very low chance of success (Nasseri *et al*., 1999; Levi *et al*., 2001; El-Toukhy *et al*., 2002; Scott, 2004).

This controversial issue has been reviewed by several authors, who have described the basal FSH concentration to be of limited value in predicting fecundity in subfertile women undergoing assisted reproduction (Bancsi *et al.,* 2003; Sharif and Afnan, 2003; Toner, 2004). Although basal FSH concentration is inversely related to ovarian responsiveness, the take home baby (live birth) rate seems to be less dependent on this parameter, particularly if the patient is young (Esposito *et al.,* 2002; Abdalla and Thum, 2004; van Rooij *et al.,* 2004; Roberts *et al.,* 2005) and younger women with significantly elevated basal FSH can have a very successful ovarian stimulation and live birth following IVF (Tozer *et al.*, 2003).

On the basis of these reports, specialists have started to question the ethical and clinical value of excluding women with elevated baseline FSH concentration, irrespective of other factors (Bukman and Heineman, 2001; Wolff and Taylor, 2004; van der Steeg *et al.,* 2006). The debate will continue until more sensitive and cost-effective indicators are introduced to enable clinicians to be more accurate in defining a woman's ovarian reserve (Broekmans *et al.*, 2006; Johnson *et al.,* 2006; Meheshwari *et al.*, 2006).

In this study, the outcomes for 1589 women were reviewed following their first cycle of IVF treatment. The results were analysed with respect to age and basal FSH, in order to establish their impact on assisted reproduction outcome and birth rate. By using a logistic regression model, a normogram has been developed to predict the likelihood of achieving a live birth based on age and basal serum FSH concentration.

# Materials and methods

All first IVF cycles of 1589 consecutive patients initiating treatment at Barts and the London Centre for Reproductive Medicine from January 1998 to February 2004 were analysed. Data were extracted from a computer database that collates patient information prospectively during fertility treatment in the centre.

The upper age limit for undergoing a cycle of IVF treatment with the patient's own oocytes was 45 years. There was no upper limit to the concentration of basal serum FSH, providing there had been regular menstruation in the previous 6 months.

Serum basal FSH and oestradiol concentrations were measured on day 3 (range 1–4) of a menstrual cycle, within 6 months from the start of ovarian stimulation. Since an elevated basal oestradiol concentration might suppress an elevated FSH concentration (Smotrich *et al.*, 1995), a re-evaluation of serum basal FSH concentrations was carried out during the following cycle (day 1–2) if the serum basal oestradiol was higher than 200 pmol/l. Typically, repeat testing on days 1 or 2 of the cycle results in oestradiol concentrations <200 pmol/l and hence a more accurate FSH value. Serum FSH values with serum oestradiol <200 pmol/l were considered as a basal FSH analysis.

## Hormone analysis

Oestradiol and FSH measurements were performed using a Bayer immuno-1 automated analyser (Bayer, Newbury, Bucks, UK) with a 5% coefficient of variation in the range 75–13,200 pmol/l for oestradiol and 1% coefficient of variation for FSH.

The serum FSH concentration was measured by calibrating to the Second International Reference Preparation of the World Health Organization (WHO) (2nd IRP 78/549). The upper level of 'normality' in the study centre is 9.9 IU/l.

## IVF treatment protocol

The stimulation protocol was determined by patient age, body mass index (BMI) and basal FSH concentration (Al-Shawaf *et al.*, 2001). In brief, the exogenous FSH starting dosage to facilitate ovarian stimulation was age dependent: 110 IU/day if <30 years of age, 150 IU/day if 30–34 years, 225 IU/day if 35–38 years and 300 IU/day if >38 years. If the basal FSH concentration was >9.9 IU/l, the dose was increased by 50% and a BMI of >30 increased the dose by 50%. The dosage of gonadotrophin was further adjusted based on ultrasound ± serum oestradiol after 7–9 days of stimulation. A long luteal phase downregulation with a gonadotrophin releasing hormone analogue (GnRHa) was used in 96% of cycles. Embryo transfer was performed on day 2 or 3 following oocyte retrieval. A maximum of three embryos were transferred for women ≥40 years old and a maximum of two embryos were transferred for those <40 years old.

## Definitions

A clinical pregnancy was defined as ultrasonographic confirmation of a gestation sac with fetal heartbeat movement seen 4–5 weeks following embryo transfer. A miscarriage was defined as a clinical pregnancy ending spontaneously before the age of viability (24 weeks). Live birth (LB) was defined as a delivery of one or more live babies. Twins and triplets were counted as one live birth in this analysis.

An abandoned cycle was defined as the commencement of ovarian stimulation, but no oocyte retrieval was performed. A cycle was abandoned if there were fewer than three follicles ≥14 mm of diameter seen on ultrasound after 10–12 days of ovarian stimulation. The fertilization rate was calculated as the number of two pronucleate (2PN) zygotes per number of oocytes retrieved per 100 for each IVF cycle. The implantation rate was defined as the number of gestational sacs seen at the first ultrasound divided by the number of embryos transferred.

## Statistical analysis

Patients were categorized by age and FSH concentration. There were four age groups: <30 years (group 1), 30–34 (group 2), 35–38 (group 3) and 39–45 years (group 4), and also three basal serum FSH concentration groups: 0.5–4.9, 5–9.9, ≥10 IU/l.

A Kolmogorov–Smirnov test was used to assess all variables for normality. As the data were not normally distributed, they are presented as median and range. The differences between categories for numerical data were analysed by Kruskal–Wallis test with Dunnett's multiple comparison test, while categorical data (proportions) were analysed by chi-squared for trend and chi-squared analysis. This tested for differences between the groups and not for an effect of increasing age or FSH. Differences between the groups after adjustment for multiple comparisons identified some effects of age or of FSH. This