Repeated testing of basal FSH levels has no predictive value for IVF outcome in women with elevated basal FSH

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BACKGROUND: It is a common practice to repeatedly test the level of basal FSH early in the cycle and to start IVF treatment only when the FSH level is below a certain threshold value. This is based on the idea that these women will respond better to ovarian stimulation when the basal FSH level is lower at the start of the cycle. The aim of this study is to assess the value of this practice. METHODS: Between January 1995 and January 2003, 39 women were identified. These women underwent two IVF treatment cycles within a 12 month period. The basal FSH level prior to each of these cycles was known to have changed. The treatment cycles were divided into cycles with a high basal FSH (≥10 IU/l) and cycles with a low basal FSH (<10 IU/l). RESULTS: The 39 women underwent a total of 78 treatment cycles (in the first cycle 20 had elevated level of FSH and 19 had low FSH and vice versa in the second cycle). Therefore, there were 39 cycles with high FSH and 39 cycles with low FSH. There was obviously no live birth in the first treatment cycle, hence the reason for the patient undergoing another treatment cycle within 12 months of the first one. In the high FSH group, six became pregnant [pregnancy rate (PR) = 15.4%] and five delivered [live birth rate (LBR) = 12.8%]. In the low FSH group, three became pregnant (PR = 7.7%) and two delivered (LBR = 5.1%). The difference in PR and LBR, however, was not significant. Neither were there significant differences between the two groups with regard to the number of oocytes collected, oocytes fertilized, embryos transferred or miscarriage rate. CONCLUSION: The results of this study reveal that women who are poor responders or with reduced ovarian reserve have a poor outcome and repeatedly testing them will add no value. Cycling women with a history of elevated FSH should be offered treatment without further delay. Delaying treatment for these women could be counterproductive, as they may have to wait for many months, during which time they are getting older and closer to their menopause.

Key words: basal stimulating hormone/FSH/IVF outcome/pregnancy rate

Introduction

The basal level of serum FSH is used as a screening test for patients undergoing IVF. It is well documented that a high day 3 basal level of FSH is associated with a lower pregnancy rate (Sharif et al., 1998; El-Toukhy et al., 2002; Abdalla and Thum, 2004). Indeed, some Units have been using this test to screen patients with a lower chance of a pregnancy in view of maintaining high clinic success rates (Sharif and Afnan, 2003).

It has also been a common practice to try to continue to monitor the patient until such time that the FSH and estradiol levels fall below a certain point, indicating perhaps that the ovary will be more responsive to stimulation. In these patients they are subjected to repeated tests for day 3 basal FSH and the treatment cycle will be started only if the basal FSH and estradiol are below certain cut-off levels.

Lass et al. (2000) suggested that, in patients with high basal FSH, if the level returns to normal then the patient may have a reasonable pregnancy rate. However, this has not been compared with the chances of achieving a pregnancy when the level of basal FSH remains high.

On the other hand, a high basal FSH level is perhaps reflective of reduced ovarian reserve (Scott et al., 1989). It has also been suggested that if the FSH level is high on one or two occasions then this may reflect the situation inside the ovary, in which case waiting or not for that level to change will make no substantial difference for the outcome (Scott et al., 1990).

In our department we treat any normally cycling woman regardless of the level of her basal FSH and for those women with elevated FSH we will counsel patients appropriately regarding the realistic chance of conception (Abdalla and Thum, 2004). Therefore we have patients being treated with high basal FSH and on occasions their FSH may have been low as well. The question remains as to whether patients with reduced ovarian reserve would have the same response to medication if the treatment was affected in a cycle with lower basal FSH. We have searched through the literature and there is no published work that looks at the same patient to see whether the outcomes of two different treatment cycles when the FSH was high or low were any different. We have therefore decided to search our database for all patients who underwent treatment cycles at least twice where on one occasion the basal FSH was high and on the other the basal FSH was low.
The purpose of this study is to examine the hypothesis that the outcome of IVF treatment in cycling women with reduced ovarian reserve will not change whether the basal level of FSH was above or below a certain threshold level.

Materials and methods
Data of patients undergoing IVF/ICSI treatment in our Unit are prospectively routinely collected and stored (MedicalSys, London, UK).

Study population
We screened our database for women who underwent treatment cycles for IVF/ICSI who had the following criteria: two consecutive cycles within 12 months; one cycle with FSH ≥10 IU/l and other cycle with FSH <10 IU/l and estradiol <200 pmol/l.

Between January 1995 and January 2003, 39 women who underwent 78 treatment cycles were identified. In these women the basal FSH prior to each of these cycles was known to have changed. The treatment cycles were divided into cycles with a high basal FSH (≥10 IU/l) and cycles with a low basal FSH (<10 IU/l). Each patient therefore acted as her own control. The level of 10 IU/l was found to be the level above which there was a significant change in the pregnancy rate from our previous study (Abdalla and Thum, 2004).

Treatment protocol
Ovarian stimulation was carried out with either recombinant FSH, HMG or urinary FSH. A transvaginal scan was performed prior to ovarian stimulation to ensure that the ovaries were quiescent. For the long protocol, patients were down-regulated with either nafarelin or buserelin at mid-luteal phase. For Cetrotide protocol, GnRH antagonist was commenced when the leading follicle reached 12 mm. When follicles reached pre-ovulatory size (18–22 mm), 10 000 IU (for patients taking HMG) or 15 000 IU (for patients taking FSH) of HCG was administrated. Oocytes were aspirated using transvaginal ultrasound guidance 34–36 h after HCG administration. Embryo transfer was performed on day 2 or day 3 using a soft catheter with transabdominal ultrasound guidance. All patients received progesterone 400 mg pessaries as supplement throughout the luteal phase. A pregnancy test was performed 2 weeks after embryo transfer.

Data analysis
Data were collected in Medical System for IVF (MedicalSys, London, UK) and analysed with Statistics Package for Social Sciences (SPSS, Surrey, UK). Analysis of variance (ANOVA) was used to compare means and $\chi^2$-test was used to analyse the significance of the difference between pregnancy rate and live birth rate. Associations between FSH values with pregnancy rates, miscarriage rates and live birth rates were examined with $\chi^2$ cross-tabulation test. ANOVA was then conducted to assess the relations between FSH levels with duration and amount of gonadotrophin required to achieve follicular maturity, number of mature follicles, number of available embryos for transfer, number of oocytes collected and fertilization rate. Statistical significance was set at $P < 0.05$.

Results
In total, 39 women underwent 78 treatment cycles (in the first cycle 20 had elevated level of FSH and 19 had low FSH and vice versa in the second cycle). Therefore, there were 39 cycles with high FSH and 39 cycles with low FSH. There was obviously no live birth in the first treatment cycle, hence the reason for the patient undergoing another treatment cycle within 12 months of the first. Patients were then grouped between cycles in which the treatment cycle was performed when the FSH was low, compared to those cycles in which the FSH was elevated. The mean time lapsed between the two IVF cycles in the high FSH group was 6.5 months (SD 4.3), whereas in the low FSH group it was 6.5 months (SD 3.7) (not significant).

As can be seen in Table I, the only significant difference was in relation to the level of FSH. There was no significant difference between both groups in relation to age, duration of infertility, the total dose of gonadotrophins used, level of estradiol at the time of HCG or the level of estradiol per follicle. The numbers of oocytes collected, oocytes fertilized and embryos transferred were also not significantly different between the groups. Although the pregnancy and the live birth rate (LBR) were lower in the normal FSH group, the difference was not significant. A subgroup analysis was performed for good responders (collected ≥4 oocytes) and poor responders (collected <4 oocytes). The results showed that, within the poor responder, there was no significant difference in terms of LBR between the low FSH group (0%, n = 0/24) and high FSH group (8%, n = 2/25). Likewise within the good responder, the

Table I. Treatment outcome in cycle with high or low basal FSH

<table>
<thead>
<tr>
<th></th>
<th>High basal FSH</th>
<th>Low basal FSH</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cycles$^a$</td>
<td>39</td>
<td>39</td>
<td>NA</td>
</tr>
<tr>
<td>Basal FSH levels (prior to treatment cycle) (IU/l) [mean ± SD (range)]</td>
<td>13.9 ± 3.9 (0.5–10.0)</td>
<td>7.3 ± 2.3 (10.2–30.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Basal estradiol levels (prior to treatment cycle) (pmol/l) [mean ± SD (95% CI)]</td>
<td>135.9 ± 48.1 (120.3–151.5)</td>
<td>96.5 ± 76.9 (71.6–121.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years) [mean ± SD (range)]</td>
<td>39.1 ± 3.4 (31–45)</td>
<td>39.2 ± 3.3 (32–45)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean duration of infertility in years [mean (95% CI)]</td>
<td>1.28 (0.44–2.13)</td>
<td>1.26 (0.43–2.07)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of previous failed IVF attempts [mean (95% CI)]</td>
<td>2.9 (2.32–3.58)</td>
<td>3.0 (2.33–3.67)</td>
<td>NS</td>
</tr>
<tr>
<td>Gonadotrophin$^b$ (IU) [mean ± SD]</td>
<td>6718.4 ± 725.76</td>
<td>5911.7 ± 437.8</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol (pmol/l) on HCG day (mean ± SD)</td>
<td>3603.9 ± 2198.0</td>
<td>3228.1 ± 2901.0</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol (pmol/l) per follicle &gt;13 mm (mean ± SD)</td>
<td>780 ± 467.0</td>
<td>823 ± 451.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean no. of stimulation days (95% CI)</td>
<td>16.08 (14.7–17.5)</td>
<td>15.49 (14.04–16.94)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean no. of oocytes collected (95% CI)</td>
<td>4.5 (3.76–5.32)</td>
<td>4.2 (3.23–5.24)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean no. of embryos transferred (95% CI)</td>
<td>1.74 (1.41–2.08)</td>
<td>1.56 (1.18–1.95)</td>
<td>NS</td>
</tr>
<tr>
<td>Pregnant [no. (%)]</td>
<td>6 (15.4)</td>
<td>3 (7.7)</td>
<td>0.294</td>
</tr>
<tr>
<td>Live birth [no. (%)]</td>
<td>5 (12.8)</td>
<td>2 (5.1)</td>
<td>0.240</td>
</tr>
</tbody>
</table>

$^a$Each patient underwent two treatment cycles and acted as their own control.

$^b$Mean amount of gonadotrophin used for stimulation in IU (recombinant FSH, HMG or urinary FSH).

NA = not applicable; NS = not significant.
LBR was not significantly different between the low FSH group (13.3%, \( n = 2/15 \)) and high FSH group (21.4%, \( n = 3/14 \)). Further subgroup analysis was conducted with regard to women’s age. There were only eight women with aged <35 years; none of them had a successful live birth regardless of the FSH levels. For women aged >35 years, the LBR for the high FSH group was 15.6% (\( n = 5/32 \)) and for the low FSH group was 6.5% (\( 2/31 \)) (not significant).

Discussion
This is, to our knowledge, the first study ever to evaluate the difference in the outcome of assisted conception treatment cycles in the same patient, with a diagnosis of reduced ovarian reserve, when treatment cycles were initiated with differing levels of basal FSH. Scott and Hofmann (1995) in a review article suggested that serial screening of FSH levels to select the optimal cycle for stimulation would be of limited value; this suggestion is in accord with the findings of our study. This study, in our view, provides a specific answer to the question as to whether repeated testing of FSH for patients to bring their basal FSH levels down to what is presumed to be an acceptably low level will be beneficial for the patient’s treatment. In this study we not only examined the level of basal FSH, but we insisted that if the basal FSH level was low, we wanted the level of estrodiol also to be low to exclude the possibility that the FSH was brought down because of a high circulating level of estradiol. Although different types of gonadotrophins and agonist or antagonist protocols were used for stimulation, this should have had no effect on the outcome of ovulation induction as there is strong evidence in the literature suggesting that different gonadotrophins and agonist or antagonist protocols ultimately have the same effect on follicular development (Agrawal et al., 2000; Borm and Mannaerts, 2000; Van Wely et al., 2003; Mohamed et al., 2005). Whether the long protocol or Cetrotide protocol was used, the FSH which was measured was the nearest to the cycle. There was no attempt to insist that the FSH measurement be performed in the same cycle in which treatment was performed but the nearest value to that cycle was used. Nevertheless we believe that the value of FSH, though not in the actual cycle in which treatment was performed, reflects the state of the ovary at the time the ovulation induction regime was started. We have also limited our study to a 12 month period to negate the effect of ageing and also to exclude any patients who had had a live birth in their first cycle. Although not all FSH levels were checked within the same cycle, they were checked in the cycle before the treatment, which is the common practice in the UK when the patient was having IVF treatment with the long protocol. However, from our data we have 19 paired cycles which the FSH levels were checked within the same cycle and the outcome was similar to that we reported; with live birth rate of 15.8 (3/19) in cycle started with high FSH and 5.3% (1/19) in cycle started with low FSH.

It is possible, of course, that all of these patients might have had a low inhibin B level, which works independently of the levels of both their FSH and estrodiol. However, this is not routinely measured in our department and therefore is not part of this analysis. These findings nevertheless are rather important because the measurement of FSH and estrodiol are the most commonly used to screen patients prior to treatment and a previous study by Creus et al. (2000) suggested that basal FSH is a stronger predictor of ovarian reserve than inhibins.

We have shown in a previous study that the elevation of the level of basal FSH reflects a reduced ovarian reserve (Abdalla and Thum, 2004). This reduction of ovarian reserve is in fact a permanent condition and it is therefore illogical to presume that if the total number of oocytes in the ovary is reduced that they will miraculously change in number if the level of FSH is reduced. The study, however, shows that there are patients with occult reduced ovarian reserve as evidenced by those who had normal FSH level in their first cycle. These patients had a raised FSH in the second cycle and still responded in the same fashion to the medications; therefore, repeat testing of basal FSH level has no benefit in women with reduced ovarian reserve and in fact it is counterproductive in view of losing reproductive time. This suggestion is in accord with a previous study (Bancsi et al., 2004) showing that repeat measurements of basal FSH levels have no clinical value.

The responsiveness of the ovary is determined primarily by the number of primordial follicles, rather than by mere changes in the hormones. The level of basal FSH, however, is an indirect indication of that reduction in ovarian reserve. This suggestion is in accord with previous studies (Bancsi et al., 2000; Frattarelli et al., 2000) showing that reduced antral follicle count, as related to a reduced quantity of primordial follicles, is a better indicator of ovarian reserve than basal FSH levels. In this study we examined patients who on average had three failed IVF attempts and primary infertility. One may argue that this may skew the results to severe cases and as such the results may not be representative of all patients with elevated FSH; nevertheless there is no evidence to suggest that women with elevated FSH achieve better outcomes in their earlier rather than their latter attempts. Furthermore, this study does provide evidence that in a good controlled situation with an equal number of failed attempts, the chances of conception and implantation are no different whether the FSH was high or low.

In our view, cycling women with reduced ovarian reserve deserve to be treated; they do have a reasonable chance of achieving a pregnancy (Abdalla and Thum, 2004). What is important is that they are informed of their lower chance to achieve a pregnancy compared to their counterpart with normal ovarian reserve. Continued hunting for a change in the level of basal FSH is rather counterproductive, as they may be waiting for many months for that change in the level of FSH to occur, during which time they are getting older and nearer to their menopause. It would therefore be appropriate to treat them if they are normally cycling with the full knowledge that their chances of achieving a pregnancy are not particularly high.

References


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