Poor response to ovulation induction is a stronger predictor of early menopause than elevated basal FSH: a life table analysis

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BACKGROUND: During the course of assisted reproduction treatment, a number of women exhibit a ‘poor response’ to ovulation induction, or demonstrate an elevated basal FSH level (>10 IU/l) at a young age. We sought to determine whether these women are at increased risk of early menopause and poor reproductive performance.

METHODS: A retrospective cohort study included 118 ‘poor responders’ with normal basal FSH level (<10 IU/l), 164 women with raised basal FSH (>10 IU/l), and 265 controls, who underwent assisted reproduction treatment between 1987 and 1998. All women were <40 years of age at the time of treatment and had normal menstrual cycles. Participants were sent a postal questionnaire in 2000–2001, seeking information on ovarian function and reproductive performance following cessation of treatment.

RESULTS: After adjusting for age and smoking habits, women with poor response and raised basal FSH levels were more likely to experience symptoms of the peri-menopause [hazard ratios 2.4, 95% confidence interval (CI) 1.52–3.78, and 2.76, 95% CI 1.78–4.29 respectively, \( P = 0.0001 \)]. Poor responders were six times and 23 times more likely to experience the menopause within 10 years of treatment than those with raised basal FSH levels and controls respectively (hazard ratio 5.97 and 23.9, \( P = 0.015 \) and \( P = 0.002 \) respectively). Poor responders and those with raised basal FSH levels have half the chance of spontaneous conception after discontinuation of treatment compared with controls (\( P < 0.007 \)). CONCLUSIONS: Both poor response to ovarian stimulation and raised basal FSH are markers of reduced ovarian reserve and predict an increased risk of early menopause.

Key words: early menopause/IVF/ovarian reserve/poor ovarian response

Introduction

There is wide variation in the age at which natural menopause occurs. In the UK, the median age is 51.7 years (McKinley et al., 1992). The health risks following the menopause are well established. The lifetime risk of a woman developing an osteoporotic fracture is 50% (Cummings et al., 1989), and cardiovascular disease remains the single most important cause of death in post-menopausal women (Bush, 1990; Office for National Statistics, 2001). Women who undergo early menopause are potentially at greater lifetime risk of these complications (Caplan et al., 1994; Pouillès et al., 1994; van der Schouw et al., 1996; Jacobsen et al., 1999; Hu et al., 1999), and may benefit from lifestyle modification and/or pharmacological therapy (Ketola et al., 2000; Hooper et al., 2001; Delmas, 2002).

The prevailing hypothesis on the aetiology of the menopause is exhaustion of the follicle pool in the ovaries (Blocke, 1952; Baker, 1963). The overwhelming majority of oocytes are lost by atresia, a process that begins in early gestation and continues until a few years following menopause (Costoff and Mahesh, 1975). The number of oocytes decreases particularly rapidly in the years immediately preceding the menopause (Richardson et al., 1987; Faddy et al., 1992; Gougeon et al., 1994). This reduction in oocyte numbers in the peri-menopause (so-called reduced ovarian reserve) is accompanied by a rise in serum follicular phase FSH levels (Sherman et al., 1976; Ebbiary et al., 1994). However, basal FSH levels can be highly variable in the peri-menopausal period (Martin et al., 1996) and the value of a single raised FSH level in predicting the onset of menopause is unclear.

Within the UK, 27 151 women underwent 33 884 cycles of assisted reproduction treatment in 1998–1999 (Human Fertilisation and Embryology Authority, 2000). The administration of gonadotrophins to such women has highlighted an
important group who fail to respond to ovulation induction therapy with appropriate follicular development, despite having normal basal FSH levels (<10 IU/l). It has been suggested that this ‘poor response’ to ovulation induction may be an early sign of impaired ovarian reserve, preceding the perimenopausal rise in FSH (Tanbo et al., 1992; Farhi et al., 1997).

We sought to determine whether poor response to ovulation induction or elevated basal serum FSH (>10 IU/l) in women aged <40 years who underwent assisted reproduction treatment can be used as predictors of early menopause and poor fertility outcome.

Materials and methods

A controlled retrospective cohort study was undertaken of women who underwent IVF/ICSI at Guy’s and St Thomas’ Hospital and King’s College Hospital during an 11 year period (1987–1998). The institutional ethics committees of the two participating centres approved the study. All women included were <40 years of age (range 25–39) and had regular menstrual cycles and no climacteric symptoms (i.e. hot flushes, night sweats, vaginal dryness or insomnia) at the time of treatment.

Patients

From a database of ~6000 patients treated between 1987 and 1998, three groups were identified.

Group 1 (poor responders)

Women who had a normal basal FSH level (<10 IU/l) and exhibited a ‘poor response’ to ovulation induction. Poor response was defined as stimulation with our maximum dose of 450 IU of gonadotrophins daily for a minimum of 9 days and either: (i) <4 oocytes obtained at oocyte retrieval, or (ii) cycle cancellation prior to oocyte retrieval because of poor follicular development (<3 follicles of ≥14 mm after 9–12 days of stimulation).

Group 2 (raised FSH)

Women who exhibited an elevated basal FSH level (≥10 IU/l) during the course of their IVF/ICSI treatment and therefore were stimulated with a similar gonadotrophin dose of 450 IU daily.

Group 3 (controls)

A control group composed of women of the same age group who had a normal basal FSH level (<10 IU/l), underwent IVF/ICSI during the same time period, and from whom ≥6 oocytes were obtained at oocyte collection following stimulation with a daily gonadotrophin dose appropriate for their age (150 IU if 25–30 years, 225 IU if 31–35 years or 300 IU if 36–39 years).

Procedure

All women were sent a postal questionnaire and a study information letter signed by the treating consultant in 2000–2001 seeking information regarding current menstrual function (i.e. cycle length and regularity), vasomotor symptoms, past medical and surgical history, hormonal drug treatment, subsequent assisted reproduction treatment and spontaneous pregnancies, and pregnancy outcome. For those with menstrual dysfunction and/or vasomotor symptoms, the date of onset of symptoms was recorded. Those who had undergone uterine and/or ovarian surgery, or who had commenced the oral contraceptive pill or a GnRH analogue or had chemotherapy or radiotherapy for any reason during the follow-up period were excluded from follow-up at the time of surgery or beginning of drug therapy.

The general practitioners of all women who did not reply to the first questionnaire were contacted to confirm the patient’s address. Questionnaires were sent up to three times to a woman’s last known address. Data with respect to gynaecological history, previous pregnancies, cause and duration of infertility, all IVF/ICSI treatment prior to and subsequent to inclusion in the study were obtained from the medical files of patients who returned the questionnaire.

Outcome measures

The main outcome measures were ovarian function, pregnancy rates and pregnancy outcome. Ovarian function was assessed by recording the occurrence of the menopause and/or symptoms of the perimenopause. Menopause was defined as amenorrhoea for ≥12 months (excluding pregnancy and lactation) and/or continuous use of hormone replacement therapy (HRT) for ≥6 months duration prior to completion of the questionnaire. Peri-menopause was defined as the presence of menstrual cycle change [either short (<21 days) or long (>35 days) in women who previously had a regular 25–35 day cycle], and/or vasomotor symptoms (hot flushes or night sweats at a frequency of >1 episode/day). Pregnancy rates and pregnancy outcome were recorded for pregnancies which arose as a result of assisted reproduction treatment, and which occurred spontaneously following cessation of treatment. Pregnancies arising from ovum/embryo donation were excluded from the analysis.

Power calculation and statistical analysis

After identifying all cases in groups 1 and 2 (n = 261 and 258 respectively), a pilot study was undertaken which gave a 50% response rate. Given that the prevalence of early menopause is ~1% and with a response rate of 50%, it was calculated that a control group twice as large as each of the two study groups would be required to give the study a power of 90% to detect a 10-fold increase in the risk of early menopause with a P-value of 0.05. Data analysis was undertaken using Stat A version 5.0 for Windows (StatA Corporation, TX, USA). Baseline characteristics were compared using one-way analysis of variance for means and χ²-test for proportions. Ovarian function was compared using Kaplan–Meier life table (survival) analysis. Adjustment was made for age at the time of treatment and smoking habits using logistic regression analysis. A hazard ratio (i.e. relative risk estimate), 95% confidence intervals (CI) and significance tests were calculated using the Cox regression–Breslow method for ties. Assisted reproduction treatment and spontaneous pregnancy rates were compared using a χ²-test.

Results

Questionnaires were sent to 261 women with poor response, 258 women with raised basal FSH and 520 controls. Replies were received from 118 women with poor response, 164 women with raised FSH and 265 controls (response rates of 45, 64 and 51% respectively).

Baseline characteristics of the three groups of women at the time of treatment were compared (Table I). The mean age of the whole study population at the time of treatment was 34 years. There was a small but statistically significant difference in the mean age between the three groups. Women with poor response and those with raised FSH were on average 1–2 years older than those in the control group (35.6, 34.7 and 33.1 years respectively, P = 0.01). However, there was no significant difference between the three groups with respect to the number of years since menarche, number of children, number of miscarriages and number of previous ovarian stimulations. There was no statistically significant difference in the number of years since menopause, perimenopause and menopause between the three groups. The number of years since menopause was greater in the control group than in the other two groups.

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proportion of women who had a previous pregnancy or mean duration and cause of infertility. Equal proportions of each group received their treatment before or during 1994.

The mean basal FSH level of women in the raised FSH group was $13.6\pm 3.6$ IU/l (range 10–33). There was no significant difference in the mean basal FSH level between women with poor response and controls ($6.7\pm 2.1$ and $6.4\pm 2$ IU/l respectively; two-sample t-test: $P=0.2$, non-significant).

Poor responders produced the least number of oocytes when compared with the other two groups ($P<0.0001$). The mean number of retrieved oocytes was also significantly lower for women with raised FSH compared with controls ($P<0.001$).

### Ovarian function

The follow-up period in the study ranged between 2.8 and 12.7 years (mean 5.6 ± 2.1 years) and the mean follow-up period was similar in the three study groups. During follow-up, 46 women with poor response (39%), 49 with raised basal FSH level (30%) and 41 controls (16%) have developed perimenopausal symptoms. The corresponding numbers for those who developed the menopause were 13 (11%), 3 (2%) and 1 (0.38%) respectively.

After adjustment for age and smoking habits, Kaplan–Meier life table analysis (Figures 1 and 2) showed that both women with poor response (group 1) and raised FSH (group 2) were more than twice as likely as controls to develop symptoms of the perimenopause within 10 years of receiving IVF treatment (hazard ratio 2.40 and 2.76 respectively, $P<0.0001$) (Table II, Figure 1). Moreover, women who exhibited a poor response to ovulation induction were 23 times more likely to become menopausal within 10 years of IVF treatment than controls and nearly six times more likely to reach the menopause within 10 years of treatment than those with a raised basal FSH level (hazard ratio 23.9 and 5.97, $P=0.002$ and 0.015 respectively).

### Table 1. Baseline characteristics of women in the study groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 ($n=118$)</th>
<th>Group 2 ($n=164$)</th>
<th>Controls ($n=265$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>35.6 (3.2)</td>
<td>34.7 (5.3)</td>
<td>33.1 (7.3)*</td>
<td>0.01*</td>
</tr>
<tr>
<td>Previous pregnancy (%)</td>
<td>31</td>
<td>38</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of infertility (years)</td>
<td>6.1 (3.7)</td>
<td>5.6 (3.7)</td>
<td>5.4 (3.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Cause of infertility (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubal</td>
<td>35</td>
<td>42</td>
<td>42</td>
<td>NS</td>
</tr>
<tr>
<td>Non-tubal</td>
<td>65</td>
<td>58</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>33.7</td>
<td>32.2</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Unexplained</td>
<td>27.1</td>
<td>22.6</td>
<td>22.4</td>
<td></td>
</tr>
<tr>
<td>Other (endometriosis or anovulation)</td>
<td>4.2</td>
<td>3.4</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Year of treatment, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987–1994</td>
<td>56 (48)</td>
<td>69 (42)</td>
<td>145 (54)</td>
<td>NS</td>
</tr>
<tr>
<td>1995–1998</td>
<td>62 (52)</td>
<td>95 (58)</td>
<td>121 (46)</td>
<td>NS</td>
</tr>
<tr>
<td>Basal FSH level (IU/l)</td>
<td>6.7 (2.1)b</td>
<td>13.0 (3.6)</td>
<td>6.4 (2.0)</td>
<td>NSb</td>
</tr>
<tr>
<td>Smoking, No. (%)</td>
<td>13 (11)</td>
<td>20 (12.2)</td>
<td>35 (13.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Cancellation rate (%)</td>
<td>30</td>
<td>21</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>No. of oocytes retrieved</td>
<td>1.5 (1.2)a</td>
<td>5.4 (3)b</td>
<td>10.7 (5.1)</td>
<td>&lt; 0.001b</td>
</tr>
<tr>
<td>Pregnancy rate at reference cycle (%)</td>
<td>5.9a</td>
<td>13.6</td>
<td>28</td>
<td>&lt; 0.001a</td>
</tr>
</tbody>
</table>

Values are given as mean (SD) or percentage.

*When compared with the other two groups, Student’s t-test.

bWhen compared with controls, Student’s t-test.

NS = not significant, $P > 0.05$. 529

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![Figure 1](image1.png)

**Figure 1.** Kaplan–Meier survival analysis of perimenopausal symptoms, adjusted for age (35 years) and smoking status.

![Figure 2](image2.png)

**Figure 2.** Kaplan–Meier survival analysis of menopausal status, adjusted for age (35 years) and smoking status.
Women with raised FSH were also more likely to become menopausal during the period of follow-up than controls, although this difference did not reach statistical significance (hazard ratio 2.76, 95% CI 1.78–4.29, P = 0.001) (Table III, Figure 2).

**Total assisted reproductive treatment and pregnancy rates**

Table IV summarizes the total number of IVF/ICSI cycles following entry to the study and the treatment pregnancy rates achieved by the three groups. The three groups underwent similar mean number of IVF/ICSI cycles after fulfilling the criteria for inclusion in the study. Both women with poor response and raised FSH were significantly less likely to achieve a pregnancy than controls. After adjusting for age and smoking habits, the odds ratio (OR) of achieving an assisted reproductive treatment pregnancy when compared with controls was 0.20 (95% CI 0.11–0.39) for poor responders, and 0.47 (95% CI 0.30–0.75) for women with raised basal FSH (P = 0.0001 and 0.002 respectively). In addition, poor responders were significantly less likely to achieve a pregnancy with IVF/ICSI treatment compared with women who had a raised basal FSH level (OR 0.43, 95% CI 0.22–0.8, P = 0.01).

**Spontaneous pregnancy rates**

Fourteen (11.9%) of the women with poor response, 14 (8.5%) of the women with raised basal FSH, and 49 (18.5%) of the women in the control group achieved a spontaneous pregnancy during the period of follow-up. Both women with poor response and raised FSH were half as likely to achieve a spontaneous pregnancy than controls (OR 0.51, 95% CI 0.32–0.86, P = 0.007). Furthermore, after excluding from the analysis those who had a live birth following IVF/ICSI treatment, women with poor response and raised FSH were still less likely to have a spontaneous pregnancy compared with controls (P = 0.003). After adjustment for age and smoking habits, the OR (95% CI) of achieving a spontaneous pregnancy compared with controls was 0.64 (0.32–1.2) for poor responders and 0.44 (0.23–0.85) for those who had a pre-treatment raised basal FSH level.

**Pregnancy outcome**

The total numbers of pregnancies (assisted reproductive treatment + spontaneous) achieved by women with poor response, raised FSH and controls were 33, 59 and 197 respectively. Table V summarizes the outcome of these pregnancies. The lowest live birth rate (66.7%) and highest miscarriage rate (33.3%) were seen in the control group. Women with poor response had a reduced reproductive potential, manifest by lower spontaneous and assisted pregnancy rates, than an age-matched cohort.

**Discussion**

This study demonstrates that both ‘poor response’ to ovarian stimulation and raised basal FSH level are markers of declining ovarian function. Women who exhibit these markers are at increased risk of reaching the menopause earlier and overall have a reduced reproductive potential, manifest by lower spontaneous and assisted pregnancy rates, than an age-matched cohort.

There are two potential sources of bias in the study. First, the overall response rate to the questionnaire was lower in women with poor response than in women with raised basal FSH (45 and 64% respectively, P = 0.01). This study required participation of patients who had left treatment for many years. Thus there was difficulty in obtaining the current address for each woman as it is possible that some have moved since treatment.

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**Table II.** Relative risk of menopause in women with poor response and raised FSH compared with controls, after adjustment for age and smoking habits

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor response</td>
<td>2.40</td>
<td>1.52–3.78</td>
</tr>
<tr>
<td>Raised FSH</td>
<td>2.76</td>
<td>1.78–4.29</td>
</tr>
</tbody>
</table>

CI = confidence interval.

**Table III.** Relative risk of menopause in women with poor response and raised FSH compared with controls, after adjustment for age and smoking habits

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor response</td>
<td>23.93</td>
<td>3.10–185.3</td>
</tr>
<tr>
<td>Raised FSH</td>
<td>9.25</td>
<td>0.9–94.6</td>
</tr>
</tbody>
</table>

CI = confidence interval; NS = non-significant.

**Table IV.** Total IVF/ICSI cycles and pregnancy rates following entry to the study

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 2</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 118)</td>
<td>(n = 164)</td>
</tr>
<tr>
<td>Total no. of IVF/ICSI cycles</td>
<td>186</td>
<td>230</td>
</tr>
<tr>
<td>No. of IVF/ICSI cycles/patient, mean (SD)</td>
<td>1.5 (0.78*)</td>
<td>1.4 (0.7*)</td>
</tr>
<tr>
<td>No. of patients achieving pregnancy</td>
<td>14</td>
<td>38</td>
</tr>
<tr>
<td>No. of IVF/ICSI pregnancies</td>
<td>17</td>
<td>42</td>
</tr>
<tr>
<td>Pregnancy rate per cycle (%)</td>
<td>9.1bc</td>
<td>18.3b</td>
</tr>
<tr>
<td>Cumulative ART pregnancy rate/patient (%)</td>
<td>11.9bc</td>
<td>23.2b</td>
</tr>
</tbody>
</table>

*Not significant, P > 0.05.
*When compared P = 0.01.
*When compared P < 0.001.
ART = assisted reproductive treatment.

**Table V.** Pregnancy outcome (assisted reproductive treatment + spontaneous)

<table>
<thead>
<tr>
<th></th>
<th>Poor responders (n = 33)</th>
<th>Raised FSH (n = 59)</th>
<th>Controls (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Livebirth</td>
<td>22 (66.7)</td>
<td>41 (69.5)</td>
<td>148 (75.1)</td>
</tr>
<tr>
<td>Spontaneous pregnancy loss</td>
<td>11 (33.3)</td>
<td>15 (25.4)</td>
<td>42 (21.3)</td>
</tr>
<tr>
<td>Ectopic</td>
<td>0 (0)</td>
<td>3 (5.1)</td>
<td>7 (3.6)</td>
</tr>
</tbody>
</table>

Values are number (%).
Self-selection was another potential source of bias. This may act in two main ways. First, it is possible that women whose treatment was unsuccessful might be less likely to reply to the questionnaire than those who became pregnant with treatment. This would apply more to women with ‘poor response’, as their assisted reproductive treatment pregnancy rates were lowest. Second, it is possible that women who became menopausal or developed peri-menopausal symptoms following treatment were more likely to reply to the questionnaire than those who remained symptom-free.

We tested the effect of selection bias on our hypothesis by assuming that all women who did not reply to the questionnaire had normal menstrual cycle and were symptom-free when sent the questionnaire. We then included these women in a $\chi^2$-test of the difference in incidence of menopause and/or peri-menopause, comparing first poor responders and controls, and then women with raised FSH and controls. The difference in incidence of menopause and/or peri-menopausal symptoms remained statistically significant ($P = 0.001$ and 0.01 respectively), indicating that selection bias does not invalidate the findings of our study.

Thus, this study supports the hypothesis that poor response and raised basal FSH level are markers of reduced ovarian reserve and predictive of early onset of menopause. Our findings corroborate those of de Boer et al. (2002), who used data from a nationwide Dutch study to estimate the risk of early menopause in poor responders to IVF stimulation and demonstrated that their relative risk is 8–11 times that of normal responders. Nikolau et al. (2002) reported a retrospective study of 12 young non-responders and demonstrated a strong association between lack of response to ovulation induction and early ovarian failure. Although the latter two studies also used normal responders as a control group, unlike our study, they did not report data on pre-treatment basal FSH levels.

Our study also highlights that women who exhibit a poor response to ovarian stimulation and those who had a raised basal FSH level are more likely to suffer climacteric symptoms earlier than controls. Climacteric symptoms can influence daily activities and interfere with physical and psychological comfort. Moreover, these symptoms might be more distressing in younger infertile women (Bryson et al., 2000; Liao et al., 2000; Bloche, 2002). Therefore, sufficient medical attention and appropriate counselling should be made available for these women to limit the adverse effects of such symptoms, particularly in light of recent research suggesting that it is the climacteric symptoms, not the menopausal status, that are associated with higher rates of depressive symptoms at midlife (Bosworth et al., 2001).

Counselling may also be important with regard to the chances of spontaneous conception following failed assisted reproductive treatment and discontinuation of treatment. Our results show that 10% of poor responders and women with a raised basal FSH level will conceive spontaneously within 2–12 years. This proportion is similar to those reported in previous series involving follow-up of couples after assisted reproductive treatment failure (Baram et al., 1988; Bryson et al., 2000). Although the chance of spontaneous conception in the poor prognosis groups appears to be only half that of normal responders, the knowledge that conception can still occur naturally could be important for childless couples who have experienced IVF failure.

To our knowledge, this is the first study which compares the risk of early menopause between women who exhibit poor response to gonadotrophin stimulation despite having a normal basal FSH level and those with a raised basal FSH level. It shows that poor response is a stronger indicator of declining ovarian function than raised FSH. Within 10 years of receiving IVF treatment, 30% of women with ‘poor response’ had become menopausal compared with only 5% of women with raised basal FSH level ($P = 0.015$) and 0.3% of the control group ($P = 0.002$). The proportions of those who developed climacteric symptoms within the same period were 70, 50 and 26% respectively ($P < 0.01$).

In addition to menstrual cycle changes and vasomotor symptoms, a further sign of declining ovarian function is impaired fertility. Women who exhibited poor response to gonadotrophin stimulation achieved a lower pregnancy rate per assisted reproductive treatment cycle and a lower cumulative assisted reproductive treatment pregnancy rate than women with raised basal FSH level (9.2 versus 18.3% and 11.9 versus 23.2% respectively, OR 0.43, $P = 0.01$), providing further evidence that loss of female fertility and onset of menopause are reflections of the same process, namely progressive depletion of the oocyte pool.

It is known that female fertility declines with age (Menken et al., 1986; Margarelli et al., 1996). However, it is also perceived that age per se can be a poor determinant of female fertility, since there is a wide range in the relationship between ovarian reserve and age (Jacobs et al., 1990; Maroulis, 1991). Basal FSH concentration is an indirect estimate of ovarian reserve, being a measure of the magnitude of negative feedback exerted on the pituitary by ovarian inhibin and estradiol secretion (Buckler et al., 1991). Although an elevated basal FSH level has been shown to be a better predictor of poor IVF outcome and reproductive potential than chronological age alone (Toner et al., 1991; Cahill et al., 1994; Scott et al., 1995), the significance of a normal FSH level in the early follicular phase in reflecting the true ovarian reserve and forecasting the risk of early menopause is undefined (Scott et al., 1990; Schipper et al., 1998). In this respect, measuring the clinical responsiveness of the ovaries to gonadotrophin stimulation appears to be a more sensitive and clinically useful tool. In the present study, poor responders and women with raised basal FSH levels were stimulated with a similar daily dose of gonadotrophins. However, the mean number of retrieved oocytes in the two groups was significantly different, reflecting the difference in the degree of oocyte pool depletion between the two groups (Lass et al., 1997). Therefore, it seems reasonable to postulate that ovarian stimulation with gonadotrophins can be regarded as a dynamic test of ovarian reserve, similar to the clomiphene challenge test (Navot et al., 1987; Scott and Hoffman, 1995). Our results support this hypothesis: women with a ‘normal’ basal FSH level who exhibited poor response to a high dose of gonadotrophin stimulation were nearly six times more likely to reach the menopause within 10 years of receiving IVF treatment than those with a raised basal...
FSH level. These findings are in agreement with the small study of Farhi et al. (1997) which described a group of 12 normogonadotrophic women who did not respond to gonadotrophin stimulation and developed ovarian failure within a mean period of 9 months only (range 3–19).

Finally, our study found the highest incidence of pregnancy loss in the poor responders group (33%), although the intergroup difference approached, but did not reach, statistical significance ($P = 0.07$), due to the small number of pregnancies reported in the study. Abnormal chromosome complements are often found in ageing oocytes (Angell et al., 1991; Munné et al., 1995; Magli et al., 1998). It is also believed that primordial follicles which contain oocytes that are predisposed to aneuploidy are recruited predominantly late in reproductive life (Zheng and Byers, 1992). Thus, the risk of aneuploidy increases with declining ovarian reserve. This hypothesis is supported by a case–control study of 78 spontaneously aborted fetuses, which found an association between abnormal karyotype and elevated maternal serum FSH and/or estradiol levels prior to conception (Nasser et al., 1999). In addition, various recent studies (Nikolettos et al., 2000; Levi et al., 2001; El-Toukhry et al., 2002) have reported high miscarriage rates (47–71%) in infertile patients with reduced ovarian reserve. Abnormal meiotic spindle assembly during various phases of meiosis has been demonstrated in ageing oocytes (Battaglia et al., 1996; Steuerwald et al., 2001) and could provide an explanation for this phenomenon.

Infertility is a chronic condition. Consequently, care of the infertile woman should not end with her last IVF attempt. So far, research has focussed mainly on the immediate and short-term prognosis of infertility treatment, with only few studies addressing the risk of reproductive problems occurring well beyond the treatment period such as early onset of climacteric symptoms and menopause. The present study indicates a higher risk of early menopause occurring in poor responders to ovarian stimulation and in those with an elevated basal FSH level compared with normal responders. Indeed poor response appears to be a stronger predictor of such risk and, therefore implies a more profound degree of reduction in ovarian reserve. With such information, more informed counselling programmes, extending long after IVF treatment has ended, should be implemented. Both specialists and general practitioners should be alerted to the possibility of early menopause and its associated health risks in these women.

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References


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