Excessive follicular response to controlled ovarian stimulation in a woman with menopausal FSH levels: Case report

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A suspected poor responder to controlled ovarian stimulation (COS), with menopausal levels of follicular phase serum FSH, required coasting due to an excessive ovarian response. A 27 year old woman was referred to our Fertility Centre for ovum donation following repeated elevated, early follicular phase FSH levels (34.3, 27.1, 20.3 IU/l). Further investigations revealed the presence of antiovular antibodies and a trial of COS, with the additional use of prednisolone, was proposed in view of her regular 28 day cycle. As 23 follicles were noted and an oestradiol level of 10 461 pmol/l following 7 days of stimulation with 450 IU of recombinant FSH per day, gonadotrophins were withheld for 9 days. Ten oocytes were retrieved and two grade I embryos were transferred. Pregnancy did not occur and she developed mild ovarian hyperstimulation syndrome. During a second cycle, multiple follicular development was again observed with an oestradiol level >13 200 pmol/l, despite a lower dose of gonadotrophin, and coasting was required for 4 days. Nineteen oocytes were collected, of which nine fertilized and cleaved. Two grade I embryos were replaced, leading to a singleton pregnancy. This patient subsequently had a vaginal delivery of a normal male baby at term. Young women with regular menstrual cycles and grossly elevated FSH levels may benefit from further investigation of autoantibodies and their ovarian response to exogenous gonadotrophins.

Key words: antibodies/corticotherapy/FSH/infertility

Introduction

Serum FSH levels increase as ovarian reserve declines and a rise in early follicular levels of FSH is believed to indicate a reduced reproductive potential (Kligman et al., 2001) even in regularly menstruating and ovulating women (Ahmed Ebbiary et al., 1994). Early follicular FSH levels have been shown to be a useful predictor of fertility potential during ovulation induction and the presence of an elevated FSH level in regularly menstruating women, with otherwise unexplained infertility, is associated with a poor outcome compared with those with normal FSH levels and unexplained infertility (Cameron et al., 1988; Flood et al., 1989; Tinkanen et al., 1999). Cahill et al. (1994) observed early follicular FSH levels to provide an independent and more powerful prediction of ovarian responsiveness than age, with women with elevated FSH levels requiring consistently more gonadotrophin stimulation than women >40 years with FSH levels in a ‘normal’ range. An association with autoimmune premature ovarian failure (POF) has been suggested in regularly menstruating women who have an elevated FSH level following the detection of a higher incidence of ovarian antibodies in their peripheral circulation (Ahmed Ebbiary et al., 1994).

This case describes a young woman with markedly elevated basal FSH levels, regular menses, ovarian antibodies and infertility who responded excessively to controlled ovarian stimulation (COS) and required ‘coasting’ for the prevention of ovarian hyperstimulation syndrome (OHSS) and subsequently had a live birth.

Case report

A 27 year old woman was referred to our Fertility Centre for ovum donation following three significantly elevated basal serum FSH levels of 34.3, 27.1 and 20.3 IU/l. She gave a 6 year history of unexplained infertility with a regular 28 day cycle, proven tubal patency and normal pelvic pathology at laparoscopy and a normal semen analysis. She had received no prior hormone treatment for fertility. A repeat early follicular (day 3) hormone profile was performed which showed an FSH level of 42 IU/l, LH level of 5.9 IU/l and oestradiol (E₂) level of
111 pmol/l. Thyroid function tests were normal. A transvaginal ultrasound performed on day 15 of the menstrual cycle showed an anteverted, normal-sized uterus with an endometrium of 8 mm and normal-sized ovaries with a 12 mm follicle in the right ovary. An autoantibody screen was performed which showed the presence of antiovarian antibodies. The remainder of the autoantibody profile was negative and included: antinuclear antibodies (ANA), gastric parietal cell, smooth muscle, liver/kidney microsomal, mitochondrial reticulin and thyroid microsomes.

In view of her regular cycle, it was decided to proceed with a trial of COS for IVF using a long GnRH analogue protocol and a maximum 450 IU of a recombinant FSH per day. Prednisolone (10 mg BD) was commenced at the same time as the GnRH analogue. A repeat autoimmune screen was performed 3 weeks after commencing the GnRH analogue, just prior to starting ovarian stimulation, no antiovarian antibodies being found. An ultrasound was performed on the 8th day of stimulation when 20 follicles between 10 and 17 mm in diameter were identified. The serum oestradiol and FSH levels were 10461 pmol/l and 137.9 IU/l respectively. Gonadotrophin administration was withheld for a total of 9 days until the oestradiol level returned to 6938 pmol/l, in accordance with the Centre’s protocol for avoidance of severe OHSS. The level of serum FSH was 10.4 IU/l. HCG (10 000 IU s.c.) was given and oocyte retrieval was performed 36 h later. Ten oocytes were retrieved, of which six fertilized and developed to the two-pronuclear (2PN) stage. Two grade I 4-cell embryos were transferred 48 h later with progesterone (Cyclogest pessaries: 108 mg BD) as luteal support. A pregnancy did not follow and the prednisolone was gradually reduced and stopped. Mild, early onset, OHSS developed (Navot et al., 1992).

Seven months later, a second cycle of COS for IVF was undertaken using a similar protocol of long down-regulation, prednisolone and 300 IU of a recombinant FSH daily. The serum FSH level taken 3 months prior to treatment was 38.8 IU/l, antiovarian antibodies not being detected. Gonadotrophins were withheld for 4 days due to an excessive ovarian response by day 11 with 25 follicles between 10 and 20 mm in diameter and an E2 level >13 200 pmol/l. Nineteen oocytes were retrieved, of which nine fertilized and developed to the 2PN stage. Two grade I 4-cell embryos were transferred 48 h later, giving rise to a singleton pregnancy. OHSS did not develop. The pregnancy continued uneventfully and a healthy male was delivered vaginally at term.

### Discussion

This case is of particular interest in that, despite the well-documented observations that elevated, early follicular phase, FSH levels in a young, infertile woman with regular menses have a poor response to COS, dosing was required to reduce the possibility of severe OHSS, as determined by the high number of follicles and elevated E2 levels. Also of interest was the detection of antiovarian antibodies and the use of corticosteroid therapy in an IVF attempt.

Increasing levels of early follicular phase serum FSH is a characteristic of reproductive ageing and is in common usage for the determination of diminished ovarian reserve (Cahill et al., 1994; Sharif et al., 1998). It has been suggested that young women with otherwise unexplained infertility, who have increased basal FSH levels, have poor outcomes compared with those with a normal FSH and unexplained infertility (Flood et al., 1989) and an impaired response to COH has been observed (Cameron et al., 1988; Scott et al., 1989). Ahmed Ebbiary et al. (1994) showed these women to have endocrine and follicular growth patterns characteristic of the menopause and concluded that a gradual rise in plasma FSH indicates a reduced reproductive potential regardless of chronological age and may represent a stage of menopausal transition consequent on POF. However, in this particular case, an excessive follicular response was observed following 8 days of stimulation, albeit that an initial high dose of gonadotrophin was used. Of note in this case was the presence of antiovarian antibodies. Autoimmune abnormalities are believed to play a role in reproductive failure and antiovarian antibodies have been found to be an independent marker associated with unexplained infertility (Luborsky et al., 2000). Serological evidence of ovarian autoimmune disease may be a marker for those patients who are good candidates for COS using glucocorticoids as immunosuppressive agents in an ovarian stimulation regime (El-Roiey et al., 1987; Barbarino-Monnier et al., 1995) and in this particular case prednisolone was given at the commencement of GnRH analogues. This immuno-suppression may explain the observed unexpected response to COS seen by day 8 in the first cycle and again by day 11 of the second cycle and it would have been interesting to observe the response to COS without the use of prednisolone. In a case report by Barbarino-Monnier et al. (1995), when prednisolone was given during a third IVF cycle where ovarian autoimmunity was present, a greater number of oocytes was retrieved with fewer units of gonadotrophin. This patient, however, differed in that the FSH level was ‘normal’.

There are several documented causes of elevated levels of FSH other than a diminished ovarian reserve resulting in a perimenopausal state. Technical laboratory errors should be considered, including the presence of heterophilic antibodies that can interfere with the FSH immunoassay giving falsely elevated levels of FSH (Cahill et al., 1992; De Konig et al., 2000). Perez Mayorga et al. (2000) have shown that the ovarian response to FSH stimulation is dependent upon the FSH receptor genotype with a less active FSH receptor requiring higher levels of FSH for normal function. Different isoforms of FSH have been described with differing receptor binding/immunoactivity (Zambrano et al., 1999). FSH binding inhibitors or FSH antibodies may also affect the ovarian response to FSH (Meyer et al., 1990). In a recent paper, Lambalk (2003) discussed the differential diagnosis of elevated basal levels of FSH and suggests the need to differentiate between the various causes during the diagnostic fertility workup. Inhibin levels, which are believed to decrease secondary to follicular exhaustion, lead to a monotropic FSH rise and could have provided further information regarding the ovarian reserve of this patient. However, they are not currently routinely available at our hospital and were consequently not performed.
Certainly this case reflects the need for further investigations into any young patient with a regular menstrual cycle and elevated FSH levels with respect to the detection of ovarian autoantibodies and the need to differentiate among the possible causes of an elevated FSH. If antibodies are detected, the use of prednisolone may be considered in an attempt to improve the ovarian response to COS and the choice of a trial of COS should be offered before discussing ovum donation. This patient will require follow-up for POF.

References


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Excessive follicular response to COS