

## CASE REPORT

# Three pregnancies despite elevated serum FSH and advanced age

J.H.Check<sup>1</sup>, M.L.Check and D.Katsoff

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Camden, New Jersey, USA

<sup>1</sup>To whom correspondence should be addressed at: 7447 Old York Road, Melrose Park, PA 19027, USA. E-mail: laurie@ccivf.com

**Although the transfer of fertilized donor oocytes is the most efficacious mode of conception for infertile women with hypergonadotrophism associated with incipient or apparent ovarian failure, there are many individuals who, for religious, ethical, or personal reasons, would prefer to try to conceive with their own oocytes. The three cases presented here represent extremes to date for (i) highest serum FSH concentration in a woman with incipient ovarian failure ( $n = 2$ ), and (ii) the oldest woman with apparent overt ovarian failure ( $n = 1$ ) to have successful pregnancies. All three cases were treated for only a short time with pharmacological dosages of ethinyl oestradiol with luteal phase support with progesterone. The peak FSH (mIU/ml) in cases 1 and 2 was 143 and 127 respectively. The precedents set in these cases can help physician-patient consultation when patients enquire whether there is a certain critical FSH concentration above which pregnancy is not possible or an age over which successful pregnancy could not be achieved even if ovulation despite ovarian failure was possible.**

*Key words:* oestrogen/ovarian failure/reversal

### Introduction

It has been known for decades that elevated early follicular phase follicle stimulating hormone (FSH) concentrations predict a paucity of follicles (Goldenberg *et al.*, 1973; Lenton *et al.*, 1988). There have been data presented that suggest that once the serum FSH is elevated, the oocytes released each month are most likely to be defective (Muasher *et al.*, 1988; Fenichel *et al.*, 1989; Scott *et al.*, 1989; Tanbo *et al.*, 1989; Ahmed Ebbiary *et al.*, 1994). Donor oocyte programmes are frequently recommended. However, there are data suggesting that euoestrogenic women 39 years old or younger with elevated serum FSH concentrations can achieve approximately a 45% 6 month pregnancy rate following therapy aimed at correcting follicular maturation abnormalities and luteal phase

defects plus male and cervical factors (Check *et al.*, 1998). The mean FSH for this aforementioned study was 19 (Check *et al.*, 1998). However, the older group ( $\geq 40$  years) did not fare as well with a 10% 6 month pregnancy rate (Check *et al.*, 1998).

Pregnancies in women with hypergonadotrophism and oestrogen deficiency are much less common. Anecdotal reports of pregnancies despite apparent ovarian failure have appeared. Though some apparently occurred without any therapy (Alper *et al.*, 1986; Shanis and Check, 1992), most cases involved women who were on some form of oestrogen replacement (Polansky and DePapp, 1976; Shangold *et al.*, 1977; Shapiro and Rubin, 1977; Szlachter *et al.*, 1979; Ohsaiva *et al.*, 1985; Check *et al.*, 1989a, 1990c). Some ovulations and pregnancies followed human menopausal gonadotrophin (HMG) therapy (Johnson and Peterson, 1979; Tanaka *et al.*, 1982; Fleming *et al.*, 1984; Check, 1990a). Some women failed to ovulate with HMG alone, but were successful when oestrogen and HMG were combined (Check and Chase, 1984; Check *et al.*, 1989b, 1990c, 1991).

When counselling patients it is sometimes of benefit to know extreme limits. Women seeking help with infertility might be more willing to try a particular avenue of treatment, even if the odds of success are quite low, as long as a precedent exists. The purpose of this manuscript is to describe three cases that may represent the women with the highest documented concentrations of serum FSH (cases 1 and 2) and the oldest woman with ovarian failure (case 3) to have successful deliveries using their own gametes.

### Case report

#### Case 1

A 36 year old gravida 1, para 1 presented with a 3 year history of infertility. She still had menses but they varied from a 1 to 4 month interval. On initial presentation, while the serum oestradiol was  $< 20$  pg/ml (Diagnostic Products Corp RIA, Los Angeles, CA, USA), the serum FSH was 143 mIU/ml (Bayer Immunol. EIA, Tarrytown, NY, USA). Her last menstrual cycle had started 47 days prior to the initial visit. Subsequently her FSH was recorded at 101.4 mIU/ml while the luteinizing hormone (LH) was 54.3 mIU/ml and the serum oestradiol 29 pg/ml. A magnetic resonance imaging (MRI) scan failed to find evidence of a pituitary tumour. She was placed on 20  $\mu$ g ethinyl oestradiol and she responded by achieving a mature follicle on her first cycle of therapy. Ethinyl

oestradiol was used rather than other oestrogens because it does not cause a rise in serum  $17\beta$  oestradiol). She conceived on her second cycle with a dominant follicle of 18 mm average diameter and serum oestradiol of 294 pg/ml; her FSH decreased to 6 mIU/ml. She successfully delivered vaginally at full term. She had also been supplemented with progesterone vaginal suppositories in the luteal phase which was increased to 400 mg with the diagnosis of pregnancy plus the addition of oral micronized progesterone 100 mg  $\times 4$ /day.

### Case 2

A 35 year old woman presented with primary infertility and oligomenorrhoea with intervals between menses of more than 2 months but less than 3 months. She was diagnosed previously at another reproductive endocrine practice with incipient ovarian failure based on an early follicular phase serum FSH of 22 mIU/ml while the serum oestradiol was  $<20$  pg/ml. By history she was positive for anti-ovarian antibodies. She had also failed to achieve a rise in her serum oestradiol above 50 pg/ml despite two cycles of clomiphene citrate (50 mg  $\times 5$  days and 100 mg  $\times 5$  days) and two cycles of HMG therapy.

On her initial presentation, 36 days from her last menses, her FSH was 105 mIU/ml and LH was 89 mIU/ml. Menses were induced with medroxyprogesterone acetate (MPA) 10 mg and ethinyl oestradiol 0.02 mg. Her day 3 serum FSH was 69 mIU/ml while the serum oestradiol was 56 pg/ml. After 4 days of continued ethinyl oestradiol therapy (0.02 mg), the serum oestradiol increased to 671 pg/ml with an 18.3 mm dominant follicle. After follicle collapse she was treated with progesterone vaginal suppositories 100 mg twice daily plus oral oestradiol 2 mg. She failed to conceive. Her day 3 FSH for her next cycle was 127 mIU/ml and the serum oestradiol was 45 pg/ml. She was treated with 0.04 mg ethinyl oestradiol and by day 14 the serum oestradiol increased to 185 pg/ml and the FSH was down to 16 mIU/ml. She was given 75 IU of HMG for 2 days and the follicle increased to a 13.6 mm diameter and the serum oestradiol was 254 pg/ml. She was increased to 225 IU HMG for 1 day and given 10 000 units human chorionic gonadotrophin (HCG) the following evening (she was unable to return for blood or ultrasound tests on the day of HCG injection). The oocyte was released by day 19 and she was supplemented with progesterone vaginal suppositories 100 mg twice daily and oral oestradiol 2 mg. She conceived in this cycle and had a successful full-term delivery.

### Case 3

A 45 year old woman with primary infertility of 5 years duration sought help. Her last menstrual period was 6 months previously. She had a serum FSH concentration drawn 3 months prior to her initial visit and it was 35 mIU/ml. Two attempts to induce menses with MPA 10 mg for 13 days failed to induce menses. Her serum oestradiol upon presentation was 15 pg/ml and her serum FSH was 43 mIU/ml. Her husband's semen analysis was considerably subnormal at a concentration of  $3.3 \times 10^6$ /ml with only 20% motility. They were not interested in IVF with intracytoplasmic sperm injection.

She was placed on ethinyl oestradiol 0.02 mg per day and she was monitored by serial serum FSH and oestradiol.

The serum FSH gradually decreased to a concentration of 17 mIU/ml by day 18 with the serum oestradiol reaching 212 pg/ml, and on ultrasound a follicle with an average diameter of 18.3 mm was found. She was given 10 000 units of HCG and an intrauterine insemination (IUI) was performed 40 h later. She was given extra progesterone supplementation 100 mg  $\times 2$ /day of vaginal suppositories but she failed to conceive. During the luteal phase, the ethinyl oestradiol was stopped and 4 mg oral oestradiol was given. She failed to conceive and the progesterone and oral oestradiol were stopped and 0.02 mg of ethinyl oestradiol was given once again. On day 11 she attained a serum oestradiol of 236 pg/ml with a serum FSH of 11 pg/ml and had one dominant follicle measuring 19.2 mm. Following IUI, progesterone vaginal suppositories were again administered and she conceived during that cycle. She delivered a full-term healthy baby.

### Discussion

Certainly, the large majority of patients presenting with findings similar to cases 1, 2 and 3 would be unsuccessful in achieving pregnancies. Thus, in general, the most appropriate recommendation for these individuals would be to consider using donor oocytes. However, there are some couples who, for religious, financial, or for personal reasons, either would never consider the donor oocyte programme, or would only do so if they are sure they have exhausted any chance of conception with their own gametes.

The three cases described here represent, we believe, in cases 1 and 2, women successfully conceiving with the highest serum FSH concentrations recorded to date, and in case 3 the oldest woman with apparent overt menopause to ovulate and have a normal pregnancy. The importance of reporting these cases is that if a patient with hypergonadotrophism requests fertility help and desires pregnancy with their own gametes, they should not be denied such treatment because of the belief that their high concentration of serum FSH precludes any chance of successful conception, or that their age (at least up to 45 years) makes pregnancy with their own gametes impossible. Instead they should be advised that although conception is highly unlikely, and that donor oocytes would be far more efficacious, nevertheless, at least two natural pregnancies were recorded with serum FSH concentrations  $>100$  mIU/ml and another with very advanced age and apparent overt ovarian failure.

The authors have a second reason for wanting to present these cases besides the establishment of upper limits for concentration of serum FSH and age with elevated FSH for the achievement of successful pregnancies. There are no controlled studies that determine the mechanism for ovulation despite elevated FSH and oestrogen deficiency. Though most ovulations have occurred with women on oestrogen therapy, it is not clear if the ovulation could have occurred fortuitously independent of oestrogen.

However, the possibility exists that oestrogen treatment may increase the likelihood of ovulation despite hypergonadotropic hypogonadism. One hypothesis is that it may improve the sensitivity of the FSH receptor. Another hypothesis is that the

woman's chronic FSH elevation leads to down-regulation of the FSH receptors in the few remaining follicles, leading to the inability to respond to either endogenous or exogenous FSH. However, by lowering the serum FSH, the FSH receptors are restored and the follicles can now once again respond to gonadotrophins.

The distinction between the two hypotheses of how oestrogen therapy may help to facilitate ovulation despite hypergonadotrophism is clinically important because if actual lowering of the elevated FSH concentrations is critical, then better results would be likely to occur if a pharmacological dosage of oestrogen is used rather than a physiological replacement dosage. There are some anecdotal published reports that support the importance of actually lowering the serum FSH. There is some evidence that lowering the serum FSH by the use of the gonadotrophin-releasing hormone agonist leuprolide acetate can improve the chances of ovulation without the use of exogenous oestrogen (Check *et al.*, 1988, 1990b,c). Another case report suggested the same conclusions in a different manner by demonstrating that a woman who developed ovarian failure after taking follicle stimulating drugs to 'strengthen' her ovulation was able to form multiple follicles and generate a serum oestradiol >800 pg/ml with her own endogenous gonadotrophins merely by stopping these drugs and allowing her FSH concentrations to decrease spontaneously (Check, 1992).

Furthermore, the frequency of induced ovulations in a series of 100 consecutive patients with ovarian failure with a minimum of 1.5 years of amenorrhoea by using pharmacological dosages of ethinyl oestradiol in the majority and leuprolide acetate in a minority seemed to be too frequent and too consistent (especially with 19% achieving pregnancies) to be explained by mere spontaneous ovulation, as is sometimes seen in women on oestrogen replacement (Check *et al.*, 1990c). Based on the relative paucity of published case reports of pregnancies resulting soon after oestrogen replacement, despite a high percentage of these patients being so treated, there appeared to be better success when higher dosages of oestrogen are used.

It is unlikely (because of the dearth of successful pregnancy cases) that a prospective study could be performed comparing efficacy of pharmacological dosages versus physiological replacement dosages of oestrogen for hypergonadotrophic hypogonadism. Even if such a study could be performed, and a pharmacological dosage of oestrogen proved no better than physiological replacement, there is an advantage of using ethinyl oestradiol as the type of oestrogen. In contrast to most other oestrogen preparations, ethinyl oestradiol does not falsely raise the serum oestradiol concentrations when performing most assays for serum oestradiol. Thus it allows for monitoring by simple blood analysis to determine if a follicle is recruited and to allow timing of intercourse, potential boosting of oocyte maturation by using exogenous gonadotrophins, and determining where to add luteal phase support with extra progesterone. Cases 1 and 3 achieved mature follicles with just ethinyl oestradiol and case 2 did not have a boost of gonadotrophins until maturation was significantly advanced (and it is not clear that the gonadotrophin boost was essential).

The relatively quick success of these patients with very inexpensive therapy allows the treating physician at least to advise a couple not interested in using donor oocytes or adoption that, although a successful outcome is unlikely, there does not appear to be a ceiling on the FSH concentration where conception in a woman with incipient ovarian failure is not possible. Furthermore, they can be advised that there is at least one precedent for temporary reversal of apparent overt menopause with successful delivery in women up to the age of 45 years.

## References

- Ahmed Ebbiary, N.A., Lenton, E.A., Salt, C. *et al.* (1994) The significance of elevated basal follicle stimulating hormone in regularly menstruating infertile women. *Hum. Reprod.*, **9**, 245-252.
- Alper, M.M., Jolly, E.E. and Garner, P.R. (1986) Pregnancies after premature ovarian failure. *Obstet. Gynecol.*, **67**, 59s-62s.
- Check, J.H. (1992) Multiple follicles in an unstimulated cycle despite elevated gonadotropins in a perimenopausal female. *Gynecol. Obstet. Invest.*, **33**, 190-192.
- Check, J.H. and Chase, J.S. (1984) Ovulation induction in hypergonadotropic amenorrhea with oestrogen and human menopausal gonadotropin therapy. *Fertil. Steril.*, **42**, 919-922.
- Check, J.H., Wu, C.H. and Check, M.L. (1988) The effect of leuprolide acetate in aiding induction of ovulation in hypergonadotropic hypogonadism: a case report. *Fertil. Steril.*, **49**, 542-543.
- Check, J.H., Chase, J.S. and Spence, M. (1989a) Pregnancy in premature ovarian failure after therapy with oral contraceptives despite resistance to previous human menopausal gonadotropin therapy. *Am. J. Obstet. Gynecol.*, **160**, 114-115.
- Check, J.H., Chase, J.S., Wu, C.H. *et al.* (1989b) Ovulation induction and pregnancy with an oestrogen-gonadotropin stimulation technique in a menopausal woman with marked hypoplastic ovaries. *Am. J. Obstet. Gynecol.*, **160**, 405-406.
- Check, J.H. (1990a) Ovulation and successful pregnancy in a woman with ovarian failure after hypophysectomy and gonadotropin therapy. *Am. J. Obstet. Gynecol.*, **162**, 775-776.
- Check, J.H. and Adelson, H.G. (1990b) Case report: opposite responses to the addition of leuprolide acetate to human menopausal gonadotropin therapy in two perimenopausal women. *Int. J. Fertil.*, **35**, 343-346.
- Check, J.H., Nowroozi, K., Chase, J.S. *et al.* (1990c) Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropic amenorrhea. *Fertil. Steril.*, **53**, 811-816.
- Check, J.H., Nowroozi, K. and Nazari, A. (1991) Viable pregnancy in a woman with premature ovarian failure treated with gonadotropin suppression and human menopausal gonadotropin stimulation: a case report. *J. Reprod. Med.*, **36**, 195-197.
- Check, J.H., Peymer, M. and Lurie, D. (1998) Effect of age on pregnancy outcome without assisted reproductive technology in women with elevated early follicular phase serum follicle-stimulating hormone concentrations. *Gynecol. Obstet. Invest.*, **45**, 217-220.
- Fenichel, P., Grimaldi, M., Olivero, J-F. *et al.* (1989) Predictive value of hormonal profiles before stimulation for *in vitro* fertilization. *Fertil. Steril.*, **51**, 845-849.
- Fleming, R., Hamilton, M.P.R., Barlow, D.H. *et al.* (1984) Pregnancy after ovulation induction in a patient with menopausal gonadotrophin concentrations after chemotherapy. *Lancet*, **1**, 399.
- Goldenberg, R.L., Grodin, J., Rodbard, D. *et al.* (1973) Gonadotropins in women with amenorrhoea: the use of follicle-stimulating hormone to differentiate women with and without ovarian follicles. *Am. J. Obstet. Gynecol.*, **116**, 1003-1012.
- Johnson, T.R. Jr and Peterson, E.P. (1979) Gonadotropin-induced pregnancy following 'premature ovarian failure'. *Fertil. Steril.*, **31**, 351-352.
- Lenton, E.A., Sexton, L., Lee, S. *et al.* (1988) Progressive changes in LH and FSH and LH:FSH ratio in women throughout reproductive life. *Materials*, **10**, 35-43.
- Muasher, S.J., Oehninger, S., Simonetti, S. *et al.* (1988) The value of basal and/or stimulated serum gonadotropin concentrations in prediction of stimulation response and *in vitro* fertilization outcome. *Fertil. Steril.*, **50**, 298-307.

- Ohsaiva, M., Wu, M.C., Masahashi, T. *et al.* (1985) Cyclic therapy resulted in pregnancy in premature ovarian failure. *Obstet. Gynecol.*, **66**, 64s-67s.
- Polansky, S. and DePapp, E.W. (1976) Pregnancy associated with hypergonadotropic hypogonadism. *Obstet. Gynecol.*, **47**, 47s-51s.
- Scott, R.T., Toner, J.P., Muasher, S.J. *et al.* (1989) Follicle-stimulating hormone concentrations on cycle day 3 are predictive of *in vitro* fertilization outcome. *Fertil. Steril.*, **51**, 651-654.
- Shangold, M.M., Turksoy, R.N., Bashford, R.A. *et al.* (1977) Pregnancy following the 'insensitive ovary syndrome'. *Fertil. Steril.*, **28**, 1179-1181.
- Shanis, B.S. and Check, J.H. (1992) Spontaneous ovulation and successful pregnancy despite bilateral streaked ovaries. *Infertility*, **15**, 70-77.
- Shapiro, A.G. and Rubin, A. (1977) Spontaneous pregnancy in association with hypergonadotropic ovarian failure. *Fertil. Steril.*, **28**, 500-501.
- Szlachter, B.N., Nachtigall, L.E. and Epstein, J. (1979) Premature menopause: a reversible entity? *Obstet. Gynecol.*, **54**, 396-398.
- Tanaka, T., Sakuragi, N., Fujimoto, S., *et al.* (1982) HMG-HCG therapy in patients with hypergonadotropic ovarian anovulation: one pregnancy case report and ovulation and pregnancy rate. *Int. J. Fertil.*, **27**, 100-104.
- Tanbo, T., Dale, P.O., Abyholm, T., *et al.* (1989) Follicle-stimulating hormone as a prognostic indicator in clomiphene citrate/human menopausal gonadotrophin-stimulated cycles for *in vitro* fertilization. *Hum. Reprod.*, **4**, 647-650.

Received on January 12, 2000; accepted on May 4, 2000