

Successful pregnancy with spontaneous ovulation in a woman with apparent premature ovarian failure who failed to conceive despite four transfers of embryos derived from donated oocytes

J.H. Check, B. 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 & Infertility, Camden, N.J. (USA)

Summary

Purpose: To show that successful pregnancy is possible in a woman in apparent premature ovarian failure despite a serum follicle stimulating hormone (FSH) > 100 pg/ml.

Methods: The high serum FSH was lowered with ethinyl estradiol. Progesterone (P) supplementation was to be used if ovulation was achieved.

Results: Successful ovulation x2 was achieved by using .02 mg ethinyl estradiol. Progesterone vaginal suppositories (200 mg) twice daily were used in the luteal phase. Unfortunately pregnancy was not achieved. The couple elected to try donor oocytes after failing to ovulate on the third cycle. The patient spontaneously ovulated and conceived immediately after failing to become pregnant with four donor-oocyte transfers.

Conclusions: The suspicion was that the graduated dosage of estrogen used for the donor-oocyte cycles suppressed the FSH allowing her to respond to endogenous gonadotropins.

Key words: High FSH; Natural pregnancy; Donor oocytes.

Introduction

Recently two reports in major infertility journals have advocated that women with elevated day 3 follicle stimulating hormone (FSH) should proceed directly to donor oocytes because of an extremely poor prognosis even in women of all ages with regular menses who can still stimulate several oocytes/cycle [1, 2]. However, this strong suggestion was criticized in two letters-to-the-editor because both manuscripts failed to reference other data showing a reasonably good prognosis with in vitro fertilization (IVF) in women up to age 39 and maybe even up to age 42 with elevated day 3 serum FSH levels [3-7]. In fact, reasonably good 6-month pregnancy rates have been recorded in women aged ≤ 39 with elevated day 3 serum FSH without the use of IVF-embryo transfer (ET) [8].

If pregnancy has failed despite several cycles of ovulation induction and progesterone support or the failure to achieve ovulation, many will choose donor oocytes. Most IVF centers should expect a 50% success rate per transfer. Thus if one failed to achieve a pregnancy in four donor oocyte cycles the odds that this may have been related merely to bad luck is 1:16. At this point the main conclusion might be that there is some uterine factor responsible for the refractory infertility. Thus a frequent recommendation at this point would be to consider a gestational carrier.

The case presented will show that this woman spontaneously conceived and successfully completed the first trimester of the cycle after failing to conceive despite four donor oocyte embryo transfer cycles.

Case Report

A 37-year-old woman with primary infertility presented with a history of oligomenorrhea and vasomotor symptoms after stopping oral contraceptives at age 36. Prior to her consult at our infertility center, she had a serum estradiol (E2) and FSH obtained after 50 days of amenorrhea. The serum E2 was 20 pg/ml and the serum FSH was 120 mIU/ml. The endometrial thickness on ultrasound was 2 mm. Her physician diagnosed her with premature ovarian failure. Other important laboratory studies were positive tests for rheumatoid factor and antinuclear antibodies. She was advised by her reproductive endocrinologist that her only chance for pregnancy would be through the use of donor oocytes.

However after searching the internet and performing a computer search the couple realized that there have been reports of actual therapy aimed at restoring down-regulated FSH receptors on the ovarian granulosa cells with restoration of ovulation and even pregnancy [9, 10]. Thus she flew from California to New Jersey to try these therapies because her preference was to conceive with her own oocytes.

In her first treatment cycle her last spontaneous menstrual cycle had been 66 days before. Her serum E2 was < 10 pg/ml and the serum FSH was 123 mIU/ml. One week after starting 0.02 mg ethinyl/estradiol daily (which does not increase serum E2 levels) her FSH dropped slightly to 95.0 mIU/ml but her serum E2 increased to 53 pg/ml. A week later her serum E2 increased to 89 pg/ml. The serum FSH dropped to 48.2 mIU/ml

Revised manuscript accepted for publication November 18, 2005

and a follicle with an average diameter of 11.5 was seen in the right ovary. Four days later the serum E2 rose to 138 pg/ml and the serum FSH was 57.5 and the follicle averaged 17 mm in diameter. Two days later the serum E2 was 156 pg/ml. Five days later the serum E2 was 314 pg/ml and the serum P was 14.2 ng/ml. She did not conceive this cycle.

The same regimen was used the next cycle and she attained a serum E2 of 161 pg/ml, and the serum FSH had suppressed to 2.9 mIU/ml. Because of vacation no more follow-up from that cycle occurred but she did show evidence of ovulation by a temperature chart and did use 200 mg progesterone supplementation twice daily by vaginal suppositories (as she also did in cycle 1).

She went for genetic testing in California and she was advised that she had a somewhat greater risk of having a child with fragile X syndrome. For that reason, she elected to postpone treatment for at least four months when her schedule would allow egg retrieval and pre-implantation genetic diagnosis of the embryo(s). The IVF was to be done at the California center and they would try gonadotropin stimulation. However she failed to stimulate a rise in serum E2 even though the drugs were not started until the serum FSH was suppressed to 1.6 mIU/ml.

Another cycle of ethinyl estradiol only was tried but this time her E2 rose from < 10 pg/ml to only 32 pg/ml and the cycle was aborted.

She decided to forego achieving a pregnancy with her own oocytes and instead to proceed with donor oocytes. However, despite four transfer cycles of three embryos each time she failed to conceive.

For each of the cycles she had been on a graduated estrogen regimen which would have kept her serum FSH down although it was not measured. She spontaneously ovulated the next cycle and with progesterone support she has successfully completed her first trimester.

Discussion

There are reports of women with apparent ovarian failure who have conceived in one or two cycles of IVF-ET using ethinyl estradiol to lower FSH and restore FSH receptors, and allow the follicles to respond to endogenous and/or exogenous gonadotropins [11, 12].

There are examples of women with extremely high gonadotropin or advanced reproductive age who have also conceived very quickly with this type of therapy [13-15].

However sometimes it takes several cycles before success is achieved [16]. It is easier to be more patient when expensive IVF-ET is not being performed, such as a 45-year-old woman with elevated baseline serum FSH who conceived on her 14th cycle of therapy [17] or a woman in apparent ovarian failure with a serum FSH of 164 mIU/ml who was finally successful in her 10th cycle of therapy [18]. Some women, however, are willing to undergo multiple cycles of IVF with a transfer of only a single embryo each time and not switch to donor oocyte, e.g., a woman who finally succeeded on her 8th IVF cycle and delivered monochorionic-diamniotic twins [19].

There are several purposes for reporting this case. One is to show that pregnancy with the woman's own oocyte is possible despite apparent ovarian failure and a serum

FSH > 100 pg/ml. It makes the other case reported with the circumstances seem less of a miracle [18].

Another purpose of presenting this case was to encourage women who want a child with their own oocytes not to give up too quickly. As exhibited by this case, donor oocytes are not always a quick solution. We suspect the reason for failure with donor oocytes was merely fortuitous.

Though conception was "spontaneous" we suspect that it was aided by lowering her serum FSH in the preceding cycles using a graduated estradiol regimen.

References

- [1] Roberts J., Spandorfer, Fsouls S.J., Kashyap S., Rosenwaks Z.: "Taking a basal follicle-stimulating hormone history is essential before initiating in vitro fertilization". *Fertil. Steril.*, 2005, 83, 37.
- [2] Kolibianakis E., Zikopoulos K., Camus M., Tounaye H., Van Steirteghem A., Devroey P.: "Modified natural cycle for IVF does not offer a realistic chance of parenthood in poor responders with high day 3 FSH levels, as a last resort prior to oocyte donation". *Hum. Reprod.*, 2004, 19, 2545.
- [3] Check J.H.: "'History' of elevated serum FSH and ovarian response [letter-to-the-editor]". *Fertil. Steril.*, 2005, 84, 260.
- [4] Check J.H.: "Modified natural cycle IVF for poor responders [letter-to-the-editor]". *Hum. Reprod.*, 2005, 20, 2661.
- [5] Shanis B., Check J.H., O'Shaughnessy A., Summers D.: "Improved pregnancy rates (PRs) in older patients or those with elevated baseline FSH levels with short flare or clomiphene-hMG hyperstimulation protocols". In: Aburumieh A., Bernat E., Dohr G., Feichtinger W., Fischl, Huber J., Muller E., Szalay S., Urdl W., Zech H. (eds.). IX World Congress on In Vitro Fertilization and Assisted Reproduction, International Proceedings Division, Monduzzi Editore, 1995, 279.
- [6] Check J.H., Nazari P., Check M.L., Choe J.K., Liss J.R.: "Prognosis following in vitro fertilization-embryo transfer (IVF-ET) in patients with elevated day 2 or 3 serum follicle stimulating hormone (FSH) is better in younger vs older patients". *Clin. Exp. Obstet. Gynecol.*, 2002, 29, 42.
- [7] Check M.L., Check J.H., Wilson C., Choe J.K., Krotec J.: "Outcome of in vitro fertilization-embryo transfer according to age in poor responders with elevated baseline serum follicle stimulating hormone using minimal or no gonadotropin stimulation". *Clin. Exp. Obstet. Gynecol.*, 2004, 31, 183.
- [8] Check J.H., Peyer M., Lurie D.: "Effect of age on pregnancy outcome without assisted reproductive technology in women with elevated early follicular phase serum follicle-stimulating hormone levels". *Gynecol. Obstet. Invest.*, 1998, 45, 217.
- [9] Check J.H., Chase J.S.: "Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotropin therapy". *Fertil. Steril.*, 1984, 42, 919.
- [10] Check J.H., Nowroozi K., Chase J.S., Nazari A., Shapse D., Vaze M.: "Ovulation induction and pregnancies in 100 consecutive women with hypergonadotropic amenorrhea". *Fertil. Steril.*, 1990, 53, 811.
- [11] Check J.H., Summers D., Nazari A., Choe J.: "Successful pregnancy following in vitro fertilization-embryo transfer despite imminent ovarian failure". *Clin Exp Obstet. Gynecol.*, 2000, 27, 97.
- [12] Check M.L., Check J.H., Choe J.K., Berger G.S.: "Successful pregnancy in a 42-year-old woman with imminent ovarian failure following ovulation induction with ethinyl estradiol without gonadotropins and in vitro fertilization". *Clin. Exp. Obstet. Gynecol.*, 2002, 29, 11.
- [13] Check J.H., Nowroozi K., Nazari A.: "Viable pregnancy in a woman with premature ovarian failure treated with gonadotropin suppression and human menopausal gonadotropin stimulation. A case report". *J. Reprod. Med.*, 1991, 36, 195.
- [14] Check J.H., Check M.L., Katsoff D.: "Three pregnancies despite elevated serum FSH and advanced age". *Hum. Reprod.*, 2000, 15, 1709.

- [15] Katsoff B., Check J.H.: "Successful pregnancy in a 45-year-old woman with elevated day 3 serum follicle stimulating hormone and a short follicular phase". *Clin. Exp. Obstet. Gynecol.*, 2005, 32, 97.
- [16] Check J.H., Chase J.S., Wu C.H., Adelson H.G.: "Ovulation induction and pregnancy with an estrogen-gonadotropin stimulation technique in a menopausal woman with marked hypoplastic ovaries". *Am. J. Obstet. Gynecol.*, 1989, 160, 405.
- [17] Check J.H.: "Successful pregnancy despite advanced age and elevated serum follicle stimulating hormone levels - case report". *Clin. Exp. Obstet.*, 2000, 27, 171.
- [18] Check M.L., Check J.H., Kaplan H.: "Pregnancy despite imminent ovarian failure and extremely high endogenous gonadotropins and therapeutic strategies: Case report and review". *Clin. Exp. Obstet. Gynecol.*, 2004, 31, 299.
- [19] Katsoff B., Check J.H.: "Monochorionic-diamniotic twins resulting from the transfer of a single embryo in a woman with decreased egg reserve: A case report". *Clin. Exp. Obstet. Gynecol.*, 2005, 32, 141.

Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)

