Successful pregnancy following in vitro fertilization-embryo transfer despite imminent ovarian failure

J. H. Check, *M.D., Ph.D.*; **D. Summers,** *M.S.*; **A. Nazari,** *M.D.*; **J. Choe,** *M.D.*

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, New Jersey (USA)

Summary

There have been previously published several anecdotal cases of women in apparent or imminent ovarian failure who subsequently ovulated and became pregnant. Many of these women had been treated with estrogen. A series of cases were reported where women with hypergonadotropic hypogonadism who failed to stimulate despite gonadotropin therapy were able to ovulate when treated with pharmacologic doses of estrogen alone or in combination with human menopausal gonadotropins. Presented herein is a case of a woman with imminent ovarian failure with tubal disease who failed to stimulate with gonadotropins alone but was successful with estrogen and gonadotropins. We believe this is the first successful case of hypergonadotropic hypogonadism to conceive by in vitro fertilization.

Key words: Down-regulated receptors; Elciated gonadotropins, Estrogen, Twins.

Introduction

Pregnancy rates (PRs) in women with elevated serum follicle stimulating hormone (FSH) levels during the early follicular phase are notoriously poor following in vitro fertilization-embryo transfer (IVF-ET) even in women with fairly regular menses [1]. In fact, there are data suggesting that if the early follicular phase FSH level is elevated in one cycle, then subsequent PRs are poor in subsequent cycles even if the FSH level is normal in those cycles [2]. A similar poor prognosis is ascribed to women whose serum day 3 FSH is in the normal range related to stimulation of a dominant follicle with suppression of FSH by high serum estradiol (E_2) levels at that time [2]. The reason for poor PRs may be related both to paucity and poor quality of oocytes retrieved [1-4]. Thus, most patients are advised to use donated oocytes under these circumstances.

For some couples the choice of donor oocytes is not acceptable for religious or personal reasons. They frequently want to try IVF despite the significantly decreased chance of conception. Described herein is a case report of a woman with oligomenorrhea and bilateral fimbrial damage with very high serum FSH levels (except when she occasionally had early follicular recruitment of a dominant follicle), who successfully achieved a pregnancy following IVF-ET. Though she could not be considered actually menopausal because she occasionally had menses, her hormone levels and responses to follicle stimulating drugs suggested that she could be considered as having imminent rather than incipient ovarian failure. We believe this to be the first such case report in the world literature.

Revised manuscript accepted for publication February 18, 2000

Case Report

The patient presented at age 32 desiring IVF because of fimbrial agglutination that failed to respond adequately to prior fimbrioplastomy. Her past medical history was also positive for a right ovarian-cystectomy for a dermoid cyst with bivalving of the left ovary. Postoperatively there was a complicating infection of her left ovary. Seven years after her surgery for the dermoid she developed pelvic inflammatory disease and was treated with antibiotics for a chlamydia infection. Her menstrual cyles were regular at this time and she was placed on oral contraceptives.

Eight years later at age 30 she stopped her oral contraceptives for the purpose of conceiving. Her cycles for the next year varied from 20 to 33 days. She sought help from a fertility specialist who found the semen analysis to be normal and the fallopian tubes to be patent by hysterosalpingogram. She was treated with clomiphene citrate up to 150 mg plus dexamethasone 0.5 mg daily but failed to ovulate. Her menstrual cycle extended to 50 plus days and her menses were induced by progesterone (P). She changed fertility specialists and was found to have a serum E_2 level of 227 pg/mL on day 3 of the cycle and a serum FSH of 3.9 mIU/mL. She was started on pure FSH (Metrodin) in her next cycle despite a baseline FSH level of 44 mIU/mL. The gonadotropins were stopped after a few days with a peak serum E_2 of 52 pg/mL. She sought the opinion of another fertility specialist who told her she was in incipient menopause and that her only option would be donor oocytes or adoption. Another fertility specialist also shared the same opinion and that "if there were any eggs left they would be genetically damaged". In the next cycle a clomiphene challenge test was performed; the day 3 serum FSH level was 20 mIU/mL and she was told nothing further could be done with her eggs.

Because she may have been fortuitously on a cycle where oocytes may have been recruited on her initial visit (day 5 serum FSH of 5 mIU/mL and serum E_2 of 38 pg/mL), she was started on a modified luteal phase leuprolide acetate (LA) protocol (0.5 mg LA started on the 7th day of medroxyprogesterone acetate) controlled the ovarian hyperstimulation regimen. After 10 days of 0.5 mg LA, 300 IU of human menopausal gonado-

tropin (hMG) and 300 IU of pure-FSH was started, but despite 40 ampules (3,000 IU) her serum E_2 measured only 24 pg/mL. The cycle was aborted.

She was placed on oral contraceptives for one cycle as part of the microdose flare protocol [5]. Her baseline serum FSH was 5 mIU/mL and the serum E_2 <20 pg/mL. Despite 7,500 IU pure-FSH and hMG there were no mature follicles on ultrasound and the peak serum E_2 level was 78 pg/mL. The cycle was aborted.

The controlled ovarian hyperstimulation (COH) regimen was modified to use estropipate (ogen) 2.5 mg twice daily from day 5. The short flare protocol was followed [6, 7]. She formed three follicles and her serum E_2 reached 265 pg/mL, but retrieval was canceled because of spontaneous oocyte release.

The combined use of estropipate with the microdose flare allowed the retrieval of one oocyte in the next cycle (peak serum E_2 reached was 398 pg/mL). No pregnancy ensued following ET of one embryo. The next cycle the LA was again diluted 1:20 and was used for only four days (day 3-6). Estropipate was also used from day six. After 6,750 IU of gonadotropins (equally split between hMG and pure-FSH) the patient attained a serum E_2 of 691 pg/mL and she had two oocytes retrieved and two embryos transferred three days later; assisted embryo hatching was performed. A twin pregnancy was established but at eight weeks only one viable pregnancy was found. The patient successfully delivered a normal full-term baby.

Three months following delivery the patient had amenorrhea and estrogen deficiency. She had failed to develop any functioning follicles (i.e., increase her serum E_2 >20 pg/mL) despite six treatment cycles similar to the therapy that was successful a year before.

Discussion

There have been previous data that do not support the belief that once the early follicular serum FSH becomes elevated, pregnancies will not occur based on the supposition that even if ovulation occurs, the oocytes are defective [7]. A viable PR of 15.0% (6/40) per transfer was reported following IVF in women whose baseline serum FSH was >18 mIU/mL [7]. These cases were from 1992 statistics so the PR/transfer was not that much lower than PRs for the normal IVF population at that time [7].

In fact, a previous study of women with hypergonadotropic amenorrhea (minimum of 12 months) with estrogen deficiency (who would certainly fit most clinicians' definition of overt menopause) were found to have a 19% PR and an 8% viable PR following six months of therapy that did not include assisted reproductive technology [8]. Recently, a study of euestrogenic infertile women (age 39 or less) with elevated baseline serum FSH levels (mean 19 mIU/mL) found the 6-month clinical PR following conventional therapy to be 46% and the viable PR 35% [9].

A reasonable assumption is that when a certain critical number of follicles are no longer recruited per cycle as a reflection of an overall waning of total oocytes left in the ovary, the lower level of inhibin produced leads to a rise of serum FSH at least at times in the cycle when the estrogen levels are the lowest. In the early stages, a reasonable number of oocytes can be produced by COH techniques as previously described (clomiphene-hMG or short flare) [7] or by more potent recently described COH protocols, e.g. micro-dose flare protocol [5]. The women are likely to be euestrogenic at this time.

As the number of oocytes drops further, the number of mature follicles that can be generated may become sufficiently low so that the number of embryos available for transfer is less than the desired amount for IVF. The patient at this stage could be euestrogenic or hypoestrogenic. Next, the patient may be at a stage when only with specialized therapy will any mature follicles form and this will usually be only one follicle or two at most and this could happen possibly only intermittently or rarely [8]. This group typically fails to respond to gonadotropins alone, but may respond to high dose estrogen alone [8] or with high dose estrogen followed by gonadotropins [10]. Finally, a stage is reached of true menopause when no mature follicles are produced any more.

A case was previously described where the exaggerated rise of serum gonadotropins following therapy with fertility drugs appeared to cause a pseudomenopause [11]. Merely stopping the follicle stimulating drugs allowed her to form three mature sized follicles with a serum E_2 of 868 pg/mL [11]. Possibly, the use of follicle maturing drugs had a similar adverse effect on the patient described herein since she was still having menstrual cycles prior to starting follicle stimulating drugs. However, the patient in the present case report did not spontaneously recruit follicles after stopping follicle stimulating drugs.

Previous studies found that some women with hypergonadotropic amenorrhea and estrogen deficiency failed to respond to gonadotropin therapy alone but did form mature follicles if high dose estrogen therapy was used prior to starting gonadotropins [10]. It was not clear whether the mechanism responsible for the success involved lowering the serum gonadotropin which allowed restoration of down-regulated gonadotropin receptors or whether estrogen in some way primed the gonadotropin receptor [10]. This previous observation encouraged us to add estrogen to the therapy of this patient and then use gonadotropins; the patient now responded to gonadotropin therapy. Estropipate was used instead of ethinyl estradiol [8, 10] because the latter was not tolerated (nausea). The possibility does exist, however, that the estrogen treatment had nothing to do with her sudden response to gonadotropins; there may have been fortuitous recruitment of follicles at that time which just were not present previously.

Though pregnancies have been previously recorded with elevated baseline FSH levels following IVF [7], this case is unique in that with the very high gonadotropins and the initial resistance of high dose gonadotropin therapy, we believe this to be the first successful case report of pregnancy following IVF in a woman so far advanced in the continuum of incipient ovarian failure to overt menopause (where there are no functional follicles left). Following delivery she was no longer able to stimulate any follicles even with the same therapy. We are not aware of any successful pregnancies following IVF

reported in the literature with baseline serum FSH levels >25 mIU/mL (where this represents a value at least twice as high as the maximum normal value for the assay); thourgh obviously there is always the possibility of unreported cases. We suspect that the overall success rate of IVF in such advanced cases will be extremely low and patients should be appropriately counseled and enlightened as to the very high success rates following the use of donor oocytes.

Based on previous studies in euestrogenic females with elevated baseline serum FSH levels where patients ≤39 years old had a clinical and viable 6-month pregnancy rate of 46% and 34.6%, respectively (10.1% and 7.6% per cycle) compared to 10.5% and 5.3% (1.9% and 0.9% per cycle) in women ≥40 ($p<.05$) [11], advanced age seems to significantly retard PRs in women with hypergonadism. One hypothesis that would explain these findings is that with natural age-related ovarian failure, the better oocytes are recruited in the younger years leaving behind poorer quality oocytes. In contrast, in at least some younger patients, e.g., the patient described, partial ovarian destruction, e.g., surgery, leaves fewer oocytes remaining, but still with a normal ratio of good to poor quality oocytes. Some younger patients, however, who undergo a more rapid rate of atresia, e.g., with chromosomal abnormalities (Turner's syndrome or Turner's variant) may also have a high percentage of defective oocytes with the same poor prognosis as the older patient.

This case serves to at least provide a precedent that a successful outcome is at least possible for women with such high baseline FSH levels who are so close to overt menopause. When this woman seeked infertility consultation with our group, we could only advise her that we were willing to try but we were unaware of any previous successes in other similar cases. Furthermore, this case suggests a different therapy than traditional protocols be used for cases such as this, i.e., the use of an estrogen not cross-reacting with serum estradiol concomitant to the stimulation with gonadotropins.

References

[1] Toner J. P., Philput C. B., Jones G. S., Muasher S. J.: "Basal follicle-stimulating hormone level is a better predictor of in vitro fertilization performance than age". *Fertil. Steril.*, 1991, *55*, 784.

[2] Scott R. T. Jr., Hofmann G. E., Oehninger S., Muasher S. J.: "Intercycle variability of day 3 follicle-stimulating hormone levels and its effect on stimulation quality in in-vitro fertilization". *Fertil. Steril.*, 1990, *54*, 297.

[3] Munne S., Alikani M., Tomkin G., Grifo J., Cohen J.: "Embryo morphology, developmental rates, and maternal age are correlated with chromosome abnormalities". *Fertil. Steril.*, 1995, *64*, 382.

[4] Lim A. S. T., Tsakok M. F. H.: "Age-related decline in fertility: a link to degenerative oocytes?". *Fertil. Steril.*, 1997, *68*, 265.

[5] Schoolcraft W., Schlenker T., Gee M., Stevens J., Wagley L.: "Improved controlled ovarian hyperstimulation in poor responder in vitro fertilization patients with a microdose follicle-stimulating hormone flare, growth hormone protocol". *Fertil. Steril.*, 1997, *67*, 93.

[6] Garcia J. E., Padilla S. L., Bayati J., Baramki T. A.: "Follicular phase gonadotropin-releasing hormone agonist and human gonadotropins: a better alternative for ovulation induction in invitro fertilization". *Fertil. Steril.*, 1990, *53*, 302.

[7] 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 F., Huber J., Muller E., Szalay S., Urdl W., Zech H., editors. "Proceedings of the IX World Congress on In Vitro Fertilization and Alternated Assisted Reproduction". 1995 April 3-7; Vienna (Austria). Bologna (Italy), Monduzzi, 1995, 279.

[8] 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.

[9] Check J. H., Peymer M., Lurie D.: "The effect of age on pregnancy outcome without assisted reproductive technology in women with elevated early follicular phase sera follicle stimulating hormone levels". *Gynecol. Obstet. Invest.*, 1998, *45*, 217.

[10] Check J. H., Chase J. S.: "Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotroping therapy". *Fertil. Steril.*, 1984, *42*, 919.

[11] Check J. H.: "Multiple follicles in an unstimulated cycle despite elevated gonadotropins in a perimenopausal female". *Gynecol. Obstet. Invest.*, 1992, *33*, 190.

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