Successful pregnancy following a single fresh embryo transfer in a 45-year-old woman whose early follicular phase serum follicle stimulating hormone was 29 mIU/ml

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Summary

Purpose: To determine if a successful pregnancy is possible following in vitro fertilization embryo transfer (IVF-ET) in a woman of advanced reproductive age with diminished egg reserve. *Methods:* In vitro fertilization-embryo transfer with intracytoplasmic sperm injection (ICSI) was performed for a 45-year-old woman with a peak serum follicle stimulating hormone (FSH) level of 29 mIU/ml and a history of failing to conceive in five previous IVF-ET cycles at a younger age. A minimal FSH stimulation protocol was used. *Results:* A fresh transfer of a 7-cell embryo was performed on day 3. A successful pregnancy and delivery ensued. *Conclusion:* This case report establishes a precedent that a successful pregnancy following IVF-ET is possible in a woman whose serum FSH is > 15 mIU/ml, and is age 45. Of course, there is no implication that accomplishing this again in another woman with similar circumstances would be likely.

Key words: Advanced reproductive age; In vitro fertilization; Diminished egg reserve.

Introduction

According to a recent study from a reputable in vitro fertilization (IVF) center when early follicular phase serum follicle stimulating hormone (FSH) level was ≥ 15 mIU/ml, no live pregnancies resulted following a series of IVF embryo transfers (ET) with several embryos of good morphology, irrespective of maternal age [1]. The authors suggested that when the serum FSH attains this level the treatment plan should proceed directly to donor oocytes [1].

However, there is not universal agreement with these conclusions. In fact, one study found in women with even a greater degree of diminished egg reserve, as evidenced not only by serum FSH > 15 mIU/ml but by such reduced ovarian reserve where only a single embryo was transferred, that instead of a zero percent pregnancy rate for the 65% who had a 6-8 cell embryo, the pregnancy rate was approximately 40% per transfer [2]. The women in this study were aged ≤ 39.9 [2]. In another study of women with diminished egg reserve with a mean number of 1.06 embryos transferred, the live delivery rate was 21.7% in women aged 40-42; but there were no live deliveries in 25 embryo transfers in women aged ≥ 43 [3].

Advanced reproductive age seems to be a more important predictor of poor pregnancy rates than early follicular phase elevation of the serum FSH [4, 5]. Most IVF centers find that the pregnancy rate following IVF-ET in women aged ≥ 45 is quite poor even if the early follicular phase serum FSH is normal and even if there are good amounts of metaphase 2 eggs retrieved. Nevertheless, because there are anecdotal reports of successful pregnancies in women ≥ age 45 with elevated serum FSH including a 45-year-old woman who appeared to be in overt menopause, this 45-year-old woman wanted to try IVF with her own eggs [6-8]. She was cautioned that these three cases did not involve IVF and that we had no knowledge of a successful pregnancy following IVF-ET in a 45-year-old woman whose early serum FSH was > 15 mIU/ml that had been published. She was warned that maybe there is some advantage for embryos created from eggs from a 45-year-old woman traversing the fallopian tubes. Nevertheless, she wanted to try with her own eggs and was against donor eggs.

Case Report

The woman described herein had spontaneously conceived at the age of 39 after six months of unprotected intercourse and had delivered a full term normal baby. Her menses were regular but she had not used any contraception since the birth of the child.

She did achieve a spontaneous pregnancy at age 41 but she had a miscarriage. An infertility work-up found an elevated day 3 serum FSH and her infertility specialist advised her that a successful pregnancy with her own eggs was not possible and advised donor oocytes. She was not interested in that treatment option so she sought another option with our group.

The male partner's semen analysis was re-checked with the addition of antisperm antibodies and the hypoosmotic swelling test (HOS) [9]. The sperm concentration was normal at 46.3 x 10^6/ml. Though the percentage of motile sperm was slightly low at 32.0% the motile density was normal at 14.8 x 10^6/ml. However, only 3.2% had rapid linear motion. In addition, and more importantly, the HOS test was low at 46%. It was explained that when the HOS score is < 50% it generally stays

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low and although it allows normal oocyte fertilization and embryo formation the embryos fail to implant [9-14]. The couple was further advised that sometimes the defect can be overcome by avoiding unprotected intercourse exposing the woman only to sperm introduced by intrauterine insemination in which the hypothesized toxic protein factor attached to the sperm was neutralized by treatment of the sperm with the protein digestive enzyme chymotrypsin [15, 16]. However they were also advised that bypassing contact and attachment of supernumerary sperm at the time of fertilization by performing IVF with intracytoplasmic sperm injection (ICSI) would provide a better chance of conception [17].

The woman was 41 ½ years old a half at the initial consult with our practice. She proceeded with IVF-ET using a low dosage minimal stimulation protocol and despite the transfer of several embryos she failed to conceive after five IVF-ET cycles. She had taken a break for one and a half years because of health problems that were initially considered to be possibly related to amyotrophic lateral sclerosis (ALS) but symptoms spontaneously abated. The ALS diagnosis was now considered highly unlikely and she returned to try IVF-ET again. The couple was advised that IVF-ET has been extremely unsuccessful in women aged ≥ 45 throughout the world even in women with normal egg reserve. Nevertheless they wanted to still try again. Donor oocyte or embryos were not considered an option.

At age 43 she attained her highest serum FSH at 29 mIU/ml. Several others had been over 20 mIU/ml. In her last cycle of IVF she did not obtain a day 3 serum FSH but instead the serum levels were obtained on day 5. Her serum estradiol (E2) was 40 pg/ml and the FSH was 20 mIU/ml. She was first given ethinyl estradiol 20 mcg daily (it does not cross-react in the serum E2 assay) [18]. She was started on 150 IU of recombinant FSH beginning on day 10 following the principles of the minimal stimulation protocol [19].

On day 5 she had four antral follicles (a 9 mm and 5 mm in the right ovary and two that were 6 mm in the left ovary). Recombinant FSH at 150 IU was continued at 150 IU for days 10 and 11 and was increased to 225 IU. The serum E2 at that time was 367 pg/ml and two follicles were seen in the left ovary of 14.7 mm and 12.3 mm. By day 14 the serum E2 reached 578 pg/ml. The serum progesterone remained low at 0.8 ng/ml and there was no rise in the luteinizing hormone (LH) at 7 mIU/ml. The follicle sizes were 22.3 mm and 17.3 mm. The next day the serum E2 dropped to 462 ng/ml with a subtle rise in serum progesterone at 1.1 ng/ml but the serum LH did not rise (6.3 mIU/ml). Human chorionic gonadotropin 10,000 units was given. Two eggs were retrieved; one a metaphase II and one a metaphase I. The metaphase II egg was fertilized by ICSI with a semen specimen showing a concentration of only 15 x 10^6/ml and only 14% motility. A 7-cell embryo without fragmentation was transferred on day 3.

This 45-year-old woman conceived this cycle and delivered a live healthy baby.

Discussion

The couple was told at their consult before the sixth IVF cycle that their pregnancy prognosis was extremely poor. This prognosis was predominantly related to the female partner's age of 45, her diminished egg reserve and previous failure to conceive with five previous IVF cycles at a younger age.

As far as a precedent was concerned we did mention the three cases of successful pregnancy in women age 45 and over with elevated serum FSH [6-8]. However, they were advised that we were unaware of precedents with successful pregnancies following IVF-ET in women aged 45 with diminished egg reserve, though we were aware of a successful pregnancy in a 42-year-old who required IVF-ET for tubal factor who appeared to be in overt menopause [20].

One might wonder how many women ≥ 45 advised of very poor prognosis with elevated serum FSH ≥ 15 mIU/ml would even attempt IVF-ET. Unfortunately there have been enough oocyte retrievals and transfers in this circumstance to make us question whether there is something about aging that requires passage of the embryo through the fallopian tubes. This is why this anecdotal case is so important, i.e., establishing that successful pregnancy is possible (though unlikely) in women needing IVF-ET even at the age of 45 with diminished egg reserve.

References

[1] Roberts J.E., Spandorfer S., Fasouliotis 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] Check J.H., Summers-Chase D., Yuan W., Horwath D., Wilson C.: "Effect of embryo quality on pregnancy outcome following single embryo transfer in women with a diminished egg reserve". *Fertil. Steril.*, 2007, *87*, 749.

[3] 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 stimulation hormone using minimal or no gonadotropin stimulation". *Clin. Exp. Obstet. Gynecol.*, 2004, *31*, 183.

[4] Check J.H., Peymer 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.

[5] 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.

[6] Check J.H., Check M.L., Katsoff D.: "Three pregnancies despite elevated serum FSH and advanced age: Case report". *Hum. Reprod.*, 2000, *15*, 1709.

[7] Check J.H.: "Successful pregnancy despite advanced age and elevated serum follicle stimulating hormone levels - A case report". *Clin. Exp. Obstet. Gynecol.*, 2000, *27*, 171.

[8] Katsoff B., Check M.D.: "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.

[9] Check J.H.: "The infertile male - Diagnosis". *Clin. Exp. Obstet. Gynecol.*, 2006, *33*, 133.

[10] Check J.H., Epstein R., Nowroozi K., Shanis B.S., Wu C.H., Bollendorf A.: "The hypo osmotic swelling test as a useful adjunct to the semen analysis to predict fertility potential". *Fertil. Steril.*, 1989, *52*, 159.

[11] Shanis B.S., Check J.H., Bollendorf A., Lurie D.: "Stability of the hypo osmotic swelling test over time". *Arch. Androl.*, 1992, *29*, 263.

[12] Check J.H., Stumpo L., Lurie D., Benfer K., Callan C.: "A comparative prospective study using matched samples to determine the influence of subnormal hypo osmotic test scores of spermatozoa on subsequent fertilization and pregnancy rates following in vitro fertilization". *Hum. Reprod.*, 1995, *10*, 1197.

[13] Katsoff D., Check M.L., Check J.H.: "Evidence that sperm with low hypoosmotic swelling scores cause embryo implantation defects". *Arch. Androl.,* 2000, *44*, 227.
[14] Check J.H., Katsoff D., Check M.L.: "Some semen abnormalities may cause infertility by impairing implantation rather than fertilization". Med. Hypoth., 2001, *56,* 653.
[15] Katsoff D., Check J.H.: "Two methods of achieving pregnancies despite subnormal hypo-osmotic swelling test scores". *Fertil. Steril.,* 1997, *68*, 549.
[16] Check M.L., Katsoff D., Check J.H., Summers-Chase D.: "Effect of treating sperm with low hypo-osmotic swelling test scores with chymotrypsin on pregnancy rates after conventional in vitro fertilization-embryo transfer". *Fertil. Steril.*, 2004, *82,* 741.
[17] Check J.H., Katsoff D., Check M.L., Choe J.K., Swenson K.: "In vitro fertilization with intracytoplasmic sperm injection is an effective therapy for male factor related to subnormal hypo-osmotic swelling test scores". *J. Androl.*, 2001, *22,* 261.
[18] 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.
[19] Check J.H.: "Mild ovarian stimulation". *J. Assist. Reprod. Genet.,* 2007, *24,* 621.
[20] 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.

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