

Successful pregnancy following in vitro fertilization embryo transfer in a 46-year-old woman with diminished oocyte reserve as evidenced by a high day 3 serum estradiol

J.H. Check, R. Chern, J. Amui

*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, NJ (USA)*

Summary

Purpose: To establish a precedent that a successful pregnancy is possible following in vitro fertilization-embryo transfer (IVF-ET) even in a 46-year-old woman with diminished egg reserve. **Methods:** Mild ovarian stimulation was used to stimulate multiple follicles in a woman whose diminished oocyte reserve was manifested by elevated day 3 serum estradiol and top normal serum follicle stimulating hormone (FSH). **Results:** She conceived on her third IVF-ET attempt. She delivered a healthy full term baby girl. **Conclusions:** This is believed to be the first case report of a successful pregnancy in a woman of this advanced age with diminished oocyte reserve using her own oocytes. It establishes a precedent showing others in similar circumstances that a pregnancy is at least possible though unlikely.

Key words: Diminished ovarian reserve; Live deliveries; Advanced reproductive age; In vitro fertilization-embryo transfer.

Introduction

Even in recent times there are some infertility specialists that conclude that an elevated day 3 serum follicle stimulating hormone (FSH) at any age is associated with very poor pregnancy rates even with in vitro fertilization-embryo transfer (IVF-ET) [1, 2]. However, our own data suggest that an elevated day 3 serum FSH level in younger women up to age 42 does not necessarily forebode a terrible prognosis as long as one avoids high dosage controlled ovarian hyperstimulation [3, 4].

However, advanced reproductive age particularly \geq age 43 (and especially \geq age 45) is associated with a poor fertility prognosis even when using mild ovarian hyperstimulation in the setting of diminished oocyte reserve [5-7]. Even in women with normal FSH at age 45 pregnancy rates approach zero [8].

Nevertheless, there are case reports of successful pregnancies at age 45 despite elevated day 3 serum FSH levels including a 45-year-old woman in overt ovarian failure (who only took 2 treatment cycles to conceive as did another 45-year-old with a short follicular phase) [9, 10]. There is also one case report of a successful conception in a woman age 46 with an elevated day 3 serum FSH.

When one determines ovarian reserve by measuring the day 3 serum FSH one should also measure the serum estradiol (E2). In the presence of the usual low serum E2 on day 3 the main inhibitor of FSH release from the pitu-

itary is inhibin B which is dependant on the number of antral follicles selected for the present cycle which in turn reflects the state of ovarian reserve. Early follicular recruitment with an increased E2 could lower the FSH release from the pituitary and give the physician/patient false security about the number of antral follicles. In fact high FSH can drive follicular maturation faster. Since stimulation of the dominant follicle for this month's cycle began in the luteal phase of the preceding cycle, a woman with diminished oocyte reserve is more likely to have a short follicular phase [10-12]. Some researchers have claimed that a serum E2 over 50 pg/ml on day 3 has the same poor prognosis as a high day 3 serum FSH [13].

The case described here we believe is the first report of a successful pregnancy following IVF-ET in a 46-year-old with diminished oocyte reserve as manifested by an elevated day 3 serum E2.

Case Report

At age 41 a woman who wanted to become pregnant came under our care. She had only one child, age 5, who had been conceived on her first cycle of unprotected intercourse. However she failed to conceive again after one and a half years of trying to have another child. Infertility investigation revealed bilateral damaged fallopian tubes that were not repairable with surgery and thus IVF-ET was recommended. However the couple could not afford it so they decided to forego having another child.

Unfortunately their son developed acute lymphocytic leukemia at age 8. He attained remission but the mother was faced with the reality that the remission could cease and she would lose her son thus with the exacerbation she wanted to have another child. Furthermore, there was the possibility that

Revised manuscript accepted for publication September 8, 2010

the next time a bone marrow transplant could be needed. She thought she might facilitate the process by storing cord blood. Thus despite the expense, she decided to try IVF-ET. She was 45 at this time.

She was advised that at age 45 the quality of the oocytes are so low that pregnancies rarely occur. Nevertheless, though rare, successful pregnancies have occurred. The couple decided to give it three attempts. Possibly decreasing her prognosis even further was that she was found to have a serum E2 over 50 pg/ml on day 3 with a top normal serum FSH.

She failed to conceive following her first two attempts despite the transfer on day 3 of four embryos (a 5-cell, 7-cell, 8-cell, and morula with little fragmentation) in cycle 1 but only formed one embryo (a 7-cell) in cycle 2. She had been treated with mild ovarian hyperstimulation in cycles 1 and 2.

For cycle 3 she was now age 46. She was reminded that successful pregnancies at this age are extremely rare (an even worse prognosis than age 45) but she wanted to try again despite the expense. The dosage of FSH was increased to 300 IU per day started on day 3. She transferred four embryos (two 8-cell embryos and two 9-cell embryos) and conceived that cycle. She delivered a healthy baby girl at 39 weeks by cesarean section.

Discussion

Faced with the reality of possibly losing their only child, this couple who had wanted a second child – but could not afford IVF-ET which was needed for a tubal factor problem – now wanted to proceed with IVF-ET.

When faced with somewhat lower chances of conception (about 50% less per cycle) at age 41, despite wanting a second child, their decision was that related to the expense with no guarantees they could be depleting education funds for their boy's future. Thus they elected not to proceed.

Then faced with new circumstances they now wanted to proceed despite the expense with IVF. They were willing to try a third time despite failing twice with the transfer of five good quality embryos despite the two previous failures, and now with further age advancement and the possibility of diminished oocyte reserve as evidenced by a serum E2 of 69 pg/ml on day 3.

An editorial was written entitled "In vitro fertilization is expensive: when should a couple be advised to stop trying with their own gametes and seek other options? Review of three cases" [14]. Indeed this case should be added to that collection of anecdotal successes.

Despite low odds, what helped the woman to decide to try a third cycle was the knowledge that some women achieved a pregnancy in a short time with diminished egg reserve and advanced age of ≥ 45 including a woman in overt menopause [15] and a 46-year-old with elevated day 3 serum FSH [16].

References

- [1] Roberts J., 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] 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., 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.
- [4] Check J.H.: "Mild ovarian stimulation". *J. Assist. Reprod. Genet.*, 2007, 24, 621.
- [5] 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.
- [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 stimulation hormone using minimal or no gonadotropin stimulation". *Clin. Exp. Obstet. Gynecol.*, 2004, 31, 183.
- [8] Manken J., Trussel J., Larsen U.: "Age and infertility". *Science*, 1986, 233, 1389.
- [9] Check J.H., Check M.L., Katsoff D.: "Three pregnancies despite elevated serum FSH and advanced age: Case report". *Hum. Reprod.*, 2000, 15, 1709.
- [10] 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.
- [11] Check J.H., Adelson H., Lurie D., Jamison T.: "The effect of the short follicular phase on subsequent conception". *Gynecol. Obstet. Invest.*, 1992, 34, 180.
- [12] Check J.H., Liss J.R., Shucoski K., Check M.L.: "Effect of short follicular phase with follicular maturity on conception outcome". *Clin. Exp. Obstet. Gynecol.*, 2003, 30, 195.
- [13] Scott R.T. Jr., Hofmann G.E., Oehninger S., Muasher S.J.: "Inter-cycle variability of day 3 follicle-stimulating hormone levels and its effect on stimulation quality in in vitro fertilization". *Fertil. Steril.*, 1990, 54, 297.
- [14] Check J.H.: "In vitro fertilization is expensive: when should a couple be advised to stop trying with their own gametes and seek other options? Review of three cases". *Clin. Exp. Obstet. Gynecol.*, 2008, 35, 5.
- [15] Check J.H., Check M.L., Katsoff D.: "Three pregnancies despite elevated serum FSH and advanced age: Case report". *Hum. Reprod.*, 2000, 15, 1709.
- [16] 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.

Address reprint requests to:
J.H. CHECK, M.D., Ph.D.
7447 Old York Road
Melrose Park, PA 19027 (USA)
e-mail: laurie@ccivf.com