

Case Reports

Live delivery following transfer of a single frozen-thawed embryo derived from a 42-year-old woman with marked decreased oocyte reserve

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Summary

Purpose: To determine if live birth is possible in a woman of older reproductive age and who has markedly decreased oocyte reserve following frozen embryo transfer of an oocyte fertilized by intracytoplasmic sperm injection of testicular sperm.

Methods: Ethinyl estradiol followed by ovarian stimulation with gonadotropins was used and a mature follicle was attained. Following oocyte retrieval 34 hours later, intracytoplasmic sperm injection of testicular sperm was performed. The embryo was cryopreserved.

Results: A live delivery of a full-term baby ensued. Following subsequent frozen embryo transfer, the baby was diagnosed with Down's syndrome and subsequently died.

Conclusion: This is the first report of a live delivery following frozen embryo transfer in a woman of advanced reproductive age with marked decreased oocyte reserve.

Key words: Ovarian failure; Frozen embryo transfer; Testicular sperm.

Introduction

There are data suggesting that women have only approximately 5,000 oocytes remaining when they are in their late thirties [1]. At the time of menopause there are still approximately 1,000 oocytes remaining but of poor quality. Decreased egg reserve may manifest in a continuum where an euestrogenic woman goes from increased day 3 FSH levels and is still able to stimulate multiple follicles with gonadotropins but less than her age peer group with normal baseline serum FSH [3], to stimulation of ≤ 4 follicles causing cancellation of IVF retrieval in many IVF centers, to only stimulating one follicle with minimal or no gonadotropins [4], to even euestrogenic women who become estrogen deficient when given follicle stimulating drugs [5], to estrogen deficient women who are resistant to stimulation with follicle stimulating drugs but can attain a mature follicle by lowering their gonadotropins exogenously [6-16].

Depending on how many follicles are still left, this latter group can develop mature follicles almost every month following treatment but sometimes only once every four months [7]. Finally, there are estrogen-deficient women who cannot develop a mature follicle or raise their estradiol significantly and these women are in overt menopause.

Though several anecdotal cases have been published demonstrating successful pregnancies in women despite

approaching the end of the continuum toward menopause [6-16], it was not clear whether their oocytes would withstand the rigors of in vitro fertilization or whether the absence of exposure to certain tubal substances would compromise successful embryo implantation. A case of successful pregnancy following IVF-ET in a woman with estrogen deficiency and high FSH has been reported [17]. This woman was in her mid-30s. Another similar successful case was reported in a 42-year-old woman [18]. Both women needed IVF because of tubal factor [17, 18].

The question next arises as to whether embryos from women close to overt menopause can withstand the rigors of embryo freezing. An interesting case involving frozen embryo transfer in a woman of advanced reproductive age is described.

Case Report

A 42-year-old woman with primary infertility sought help in achieving pregnancy. She had a history of amenorrhea for 14 months and was estrogen-deficient as evidenced by failure to have menses following 14 days of 10 mg medroxyprogesterone acetate. A normal functioning uterus was established by demonstrating menses with estrogen and progesterone replacement. A diagnosis of ovarian failure was made on the basis of serum estradiol (E_2) < 10 pg/ml with serum FSH of 83 mIU/ml. Previous attempts to stimulate her with exogenous gonadotropins up to 450 IU per day had failed.

The couples' case was also complicated by the fact that the husband had had a previous vasectomy, and despite surgical reversal, there were very few sperm in the ejaculate and they were all tailless sperm.

The patient desired therapy aimed at inducing ovulation, then performing oocyte retrieval followed by testicular sperm aspiration with intracytoplasmic sperm injection (ICSI). She was treated with 0.02 to 0.04 mg ethinyl estradiol daily to lower her sperm FSH (as previously described [6, 7]) but she failed to attain a rise in serum estradiol spontaneously or with low-dose gonadotropins. The decision was made to lower the serum FSH then try high-dose gonadotropins while maintaining the ethinyl estradiol. The FSH decreased to 14 mIU/ml and then 225 IU of human menopausal gonadotropins (Repronex®) were used daily in the morning and 225 IU of recombinant FSH (Follistim®) were used in the evening. After 11 days of stimulation a follicle with an average diameter of 19 mm was attained and the serum estradiol reached 248 pg/ml. She then received 10,000 IU HCG and the oocyte was retrieved 34 hours later. The sperm was collected by both aspiration and biopsy. The motile sperm was 0% in both samples and the respective concentrations were 0.28 million/ml in the former and 0.19 million/ml in the latter. The oocyte fertilized following ICSI, but for personal reasons the embryo was cryopreserved. The frozen embryo was thawed and subsequently transferred nine months later. The transfer occurred when the embryo was 72 hours old and assisted embryo hatching was performed prior to transfer [20]. A simplified freezing protocol using propanediol as the cryoprotectant [1, 2] with a one-step thawing procedure was used [19]. The embryo had seven blastomeres and < 25% fragmentation.

The woman conceived and delivered a full-term baby with Down's syndrome but, the baby died within a month because of abnormal organ development.

Discussion

At menopause there are approximately 1,000 oocytes remaining compared to approximately 25,000 at age 37.5 [21]. Generally these oocytes are considered to be of poor quality. Thus despite several previous anecdotal reports of successful pregnancies despite imminent ovarian failure, or even what was considered overt menopause, it was not clear how fragile these oocytes are and whether they could withstand artificial removal from the follicle during IVF and unnatural exposure to sperm during oocyte insemination [6-16]. However, anecdotal support that successful pregnancy under these conditions was possible was provided in a report of a 32-year-old woman needing IVF for tubal factor who was in imminent ovarian failure [17].

It is well known that oocytes from women over the age of 41 result in a significantly reduced chance of successful implantation even if the transferred embryos appear normal. The poor quality oocyte seems to be related both to nuclear abnormalities (especially non-disjunction of chromosomes leading to aneuploidy) and also to cytoplasmic senescence [21]. There are data suggesting that despite a similar paucity of oocytes, there is a greater chance of successful pregnancy if the oocytes are provided by younger (≤ 39) women [22]. Similar conclusions were reached for women with decreased oocyte reserve undergoing IVF-ET [23]. Thus it was not clear whether a woman older than 41 with elevated day 3 serum FSH and diagnosed with imminent menopause could be successful with IVF-ET. A precedent was set, however, with a case of a 42-year-old woman needing IVF for tubal factor [18].

The case described here established some additional precedents. The case showed that a successful pregnancy can be achieved in a woman of advanced reproductive age in imminent ovarian failure even under the most difficult circumstances with intracytoplasmic sperm injection. Furthermore this is possible even with non-motile testicular sperm. Finally the case shows that the embryos are hearty enough to withstand embryo freezing and thawing.

Prior to undergoing therapy for follicle stimulation and oocyte retrieval the couple was advised of the options of donor oocytes, donor embryos or adoption. However, they only wanted to try with their own gametes. Though their baby only lived for a few months due to complications of Down's syndrome, they were very appreciative of the short time they had with their daughter. Even though they were told that the trisomy abnormality may have been age-related, the couple wanted to try again with their own egg rather than try any of the aforementioned options. The woman is presently undergoing IVF with ICSI again.

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