

Successful pregnancy with frozen embryo transfer into a gestational carrier from eggs obtained from a woman in premature menopause

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Summary

Purpose: To describe a unique case of a successful gestational carrier pregnancy in a woman with premature ovarian failure using her own oocyte. **Methods:** Despite amenorrhea, failure to have menses to progesterone withdrawal and resistance to gonadotropin stimulation, ovulation induction was attempted by restoring down-regulated follicle stimulating hormone (FSH) receptors by lowering the elevated serum FSH and allowing stimulation by endogenous or exogenous gonadotropins. Oocyte retrieval was attempted if a mature follicle was obtained. GnRH antagonist was used to prevent premature oocyte release. Tapering prednisone was used for the first five days of the cycle due to patient's history of autoimmune disease (vasculitis and Crohn's disease). IVIG was given 8/2003 for vasculitis. **Results:** The patient underwent a total of 19 attempted retrievals during continuous natural cycles from 3/2003 to 2/2007. Oocyte retrieval required traversing the uterus with the retrieval needle because of ovarian position after multiple surgeries for bilateral endometriomas and Crohn's disease. Empty follicle syndrome was encountered in four retrieval attempts. In 15 attempts, an oocyte was obtained. The sole attempt at natural fertilization failed. ICSI and assisted hatching were used in all subsequent attempts, and were successful in all but one attempt which led to a 3 pronuclei embryo which was discarded. The first four single embryos retrieved (7, 4, 6 cells and morula) were all A1 or A2 and transferred fresh to the patient, but no pregnancy resulted. All subsequent embryos were cryopreserved. The transfer of four embryos (6-cell and 7-cell and 3-cell and 8-cell) in two cycles to two different gestational carriers resulted in a successful delivery of a full-term healthy female infant 3.3 kg. Genetic testing confirmed maternal identity to be the patient, not the carrier. **Conclusions:** This is the first reported case of a successful gestational carrier pregnancy after reversing ovarian failure, inducing ovulation, and transferring a frozen-thawed embryo.

Key words: Frozen embryo; Ovarian failure; Gestational carrier.

Introduction

There are studies suggesting that even if normal embryos are transferred as a result of in vitro fertilization (IVF) in regularly menstruating women of any age, the prognosis for pregnancy is extremely poor, if day 3 follicle stimulating hormone (FSH) is elevated [1-7]. This opinion is markedly intensified if the woman is in apparent menopause as evidenced by amenorrhea, estrogen deficiency, and elevated serum FSH.

Recently an editorial was published entitled "A 59-year-old woman gives birth to twins - when should a fertility specialist refuse treatment?". The editorial described several cases of infertility in which women were willing to take significant health risks to achieve pregnancy against great odds and where the infertility specialist was willing to try to help the women [8]. Another editorial article described IVF in women who were willing to undergo great expense to fulfill their dreams [9].

The present case report describes a woman who was advised that the odds of her conceiving (and for that matter even ovulating) were extremely remote and that the mode of treatment would be extremely risky and yet she, a very intelligent physician, wanted to take her chances to fulfill her dream of having a child with her genetic material.

Case Report

A 34-year-old physician consulted us for primary infertility and premature ovarian failure in January, 2003. She had a history of severe endometriosis and fistulizing Crohn's disease, including a rectovaginal fistula. In 1989 she had a left oophorectomy for a 12 cm endometrioma with associated extremely elevated CA-125 level (1243 units/ml) and in 2002 had an 8 cm right ovarian endometrioma removed leaving very little ovarian tissue. Her serum FSH following surgery was increased to 38.6 mIU/ml.

She also had other surgical procedures. In 1989 she had a total colectomy/ileostomy and a Hartmann pouch for her Crohn's disease. In 1990 she had to redo the ileostomy because of a stricture and she also had adhesiolysis related to her Crohn's disease.

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Her medical history included a grand mal seizure as a result of an allergic reaction and vasculitis as a side-effect of Infliximab. Her medications included prednisone 10 mg daily, ranitidine 150 mg twice daily, loperamide 2-4 mg daily, metronidazole 250 mg 3x/day, folic acid 1 mg daily, various vitamins including vitamin B12 (1000 U) s.c. monthly and TPN 2x/week.

Related to her various surgeries her right fallopian tube was occluded and she was told if she wanted to conceive that it would not be possible through artificial insemination with donor sperm (she was single and did not have a male partner) and that she would need IVF.

She attempted IVF in another institution and they started her on leuprolide acetate 20 units daily followed by 300 units once daily of recombinant FSH and 300 units of human menopausal gonadotropin. At this time despite her day 3 serum FSH of 38.6 mIU/ml she was still menstruating approximately every 28-35 days (but did occasionally skip menses). Nevertheless after a week's worth of 600 units daily of FSH her serum estradiol (E2) dropped from 28.5 pg/ml to zero and her IVF cycle was cancelled. This was in November, 2002.

She had a spontaneous menstrual cycle the end of December, 2002 but had very few spontaneous menstrual cycles over the next five years.

From doing a computer search on premature ovarian failure (PubMed 1966-2002) the patient was aware that we had published a technique for inducing ovulation even in women in apparent premature ovarian failure who were unresponsive to gonadotropins [10-16]. She was also aware that we had published case reports of successful pregnancies following in vitro fertilization-embryo transfer in two women with premature ovarian failure with tubal factor [17, 18].

Pelvic sonography however found the right ovary to be located very high in the pelvis and the ovary was inaccessible by transvaginal needle. Abdominal ultrasound (US) suggested that the ovary was in a deep location and was covered by bowel thus it did not seem accessible by abdominal guided US either.

The woman was willing to have general anesthesia and an abdominal laparotomy if we could induce her to mature a follicle but our IVF center, though university and hospital based, is a free standing IVF center not physically connected to an operating room. We suggested that we could monitor her cycle and she could request the retrieval with laparotomy be performed at the facility that attempted her first IVF cycle since they were hospital based. However they rejected the proposal. The patient then had a failed attempt at J-pouch and simultaneous attempt to move the ovary to a more accessible location (4/2003) by expert colorectal surgeons.

Our IVF group then concluded that it would be possible to retrieve an egg if there was a transuterine approach but we explained this could be risky because we could puncture her bowel. As a gastroenterologist she believed that the needle was too thin to cause any serious damage even if it did hit the bowel. She would also take extra IV antibiotics for the egg retrievals.

Four of the five physicians in our facility agreed to do her egg retrievals and one physician declined. However, that physician subsequently agreed to do two of the 19 egg retrievals she had when it fell on the weekend in which that doctor was on call. The only time the woman did not take her IV antibiotics for seven days (the medication never arrived from the pharmacy), and instead took PO antibiotics, she developed a pelvic abscess (this was after her 6th retrieval attempt) requiring hospital admission and six weeks of IV zosyn; she never had

another episode. Also, during stimulation a 3.5 cm ovarian cyst developed 12/2006 and resulted in acute hydronephrosis of the right kidney with resulting severe pain. This resolved without complications after cyst drainage via the same transuterine approach.

The woman had follicular maturation using ethinyl estradiol to lower elevated serum FSH levels associated with low E2 levels (E2 < 20 pg/ml). When a follicle was finally recruited as evidenced by a rise in serum estradiol, the follicle was allowed to develop naturally and when an 18 mm diameter follicle associated with a serum E2 of 200 pg/ml or more was reached, 10,000 IU of human chorionic gonadotropin (hCG) was given. The attempted egg retrieval was performed 34 hours later. In addition, when she was able to be off prednisone for her Crohn's disease, a prednisone taper (40, 30, 20, 10, 5 mg) was given for the first five days of the cycle. A single dose GnRH antagonist 250 mcg s.c. was added to prevent endogenous LH surge and oocyte release.

Alternatively, once the serum E2 began to rise thus helping to keep the FSH from increasing (and thus down regulating FSH receptors), a boost of a low-dose (usually 75-150 IU per day) FSH drug was given and antagonist daily was added to keep the LH:FSH ratio low. The woman was single and the eggs were fertilized with donor sperm.

Out of the 15/19 retrievals resulting in an oocyte, three were completely natural cycles with one dose of antagonist, or also taking ethinyl estradiol to lower the elevated serum FSH. Intracytoplasmic sperm injection and assisted embryo hatching were performed for 14/15, after the very first successful natural cycle oocyte retrieval resulted in failure of natural fertilization. Minimal stimulation or natural cycles with boost protocols were used for the rest of the IVF cycles (combination of ethinyl estradiol, rhFSH, GnRHa, prednisone as described above). The woman failed to conceive following four single embryo transfers of 4-cell, 6-cell, 7-cell, and 14 cell morula stage (the abscess cycle) embryos on day 3.

The woman decided that any subsequent embryos formed would be frozen for transfers to a gestational carrier that she would obtain in the future since she thought that she may have a compromised uterus or immune system. She was able to fertilize and freeze nine single/2 pronuclear embryos. She thawed two 2 pronuclear embryos that had been frozen for two and a half years (at age 35 and 36 years) and transferred a 6-cell and a 7-cell day 3 embryo with < 25% fragmentation to a gestational carrier. She did not become pregnant (just a chemical pregnancy).

She then thawed two more embryos that had been frozen one and a half years before (at age 37 and 38 years) and transferred a 3-cell and an 8-cell embryo with no fragmentation to another (different) gestational carrier and a singleton pregnancy was conceived. A healthy 3.3 kg baby girl at 38 weeks' gestation was successfully delivered. Because of fear of losing the pregnancy she did not have the gestational carrier undergo chorionic vilus sampling or amniocentesis. However, quadruple screens adjusted for the patient's age (not the carrier's) and high level US for signs of genetic abnormality done at 20 weeks of gestation were normal. The baby underwent maternity testing by the DNA Diagnostic Center, using DNA fingerprinting with the Power Plex 1.2 system by Promega Corp., Madison WI, confirming maternity with 99.99% probability to be our patient.

Other pertinent tests that had been performed on this woman was a chromosome analysis showing a normal 46XX karyotype, and fragile X PCR was negative. Hysteroscopy done 4/2007 for increased CA-125 (> 200), dysmenorrhea, and

menometrorrhagia showed severe uterine adhesions and endometrial polyps. Lysis of the adhesions and polypectomy were successful, with resolution of symptoms and marked reduction in CA-125 to 40 units/ml. The patient is presently well, maintained on hormone replacement therapy with continuous estradiol 20 mcg daily and medroxyprogesterone 10 mg daily for the first two weeks of each month.

Discussion

The cathexis for this extremely intelligent physician was to have a child with her own genetic background. However, she was advised by a reproductive endocrinologist at an academic medical university center that even though she was still menstruating at the time of that appointment it would not be possible for her eggs to result in a pregnancy. That reproductive endocrinologist quoted even recent studies claiming extremely poor or no pregnancies even with normal appearing embryos transferred once the serum FSH was elevated let alone a woman in actual ovarian failure [7]. A second opinion from another reproductive endocrinologist at an academic medical university center agreed that pregnancy was highly unlikely but they were willing to attempt the one IVF cycle with extremely high dosage gonadotropins. When she failed to raise her serum E2 at all (it plunged to zero) despite several days of high dose gonadotropin, they too considered that she would need donor eggs to become pregnant. A third reproductive endocrinologist at an academic medical university center with expertise in premature ovarian failure/high FSH cancelled her consultation appointment, refusing even to see her as "nothing could be done". A fourth reproductive endocrinologist, and national expert in premature ovarian failure, expressed sympathy, but agreed it was futile.

The patient did her own computer search and in contrast to the opinions expressed by the previously consulted experts she found many articles concerning not only achieving pregnancies in younger women with high day 3 serum FSH but even live deliveries in women in apparent menopause with the aforementioned techniques.

At her consult at our facility her consulting physician was confident that she could be made to ovulate and that these eggs would probably be of good quality. However, our head surgeon and co-director of the IVF program strongly believed that the safest way to retrieve the eggs would be through a laparotomy. The importance of a pregnancy with her own genetic material was so great that she was willing to go through major surgery. Unfortunately, however, our IVF facility is not in the operating room and she could not find an IVF center that performs retrievals in the operating room willing to take her case, even if she did attain a mature follicle with our technique.

When she returned asking if we could consider another alternative to a laparotomy we said that we could retrieve the eggs by placing the retrieval needle through the uterus but that could be extremely risky. Nevertheless this highly motivated and informed physician was willing to take the risk of puncturing her bowel or other complications.

Thus with the expense of 19 oocyte retrievals and a gestational carrier, the risks that she was willing to take, and the successful outcome that she achieved, her case should be added to the group described willing to risk poverty to attain their dreams and willing to take significant medical risks [8, 9]. This woman was undaunted by the development of an abscess after one cycle and the development of an ovarian cyst which we drained with a retrieval needle that had caused ureteral obstruction and hydronephrosis.

This case report is unique. Although there are two other cases of women in apparent ovarian failure achieving a pregnancy following IVF-ET, this is the first one that was achieved by transferring frozen-thawed embryos from a woman whose apparent ovarian failure was reversed through suppression of elevated serum FSH, with theoretical restoration of down-regulated FSH receptors followed by mild FSH stimulation. This is also the first case of successful pregnancy achieved by a woman in premature ovarian failure using her own eggs but transferring embryos to a gestational carrier.

This case report is not intended to level criticism against the physicians who refused treatment. Physicians devote a great deal of time and money into acquiring their degree and it is not fair to insist that they take risks that could jeopardize their continuance of providing health care. If a complication occurs despite the presence of informed consent, a woman may still litigate. Even in the presence of a complication the individual patient may not sue but the family could litigate or some peer-review board could censure the treating physician stating that the case should have never been tried.

Thus one take-home message from this case is that a highly motivated patient with a dream does not have to accept rejection by the first or second opinion but can continue a search for a physician willing to work with her if that physician thinks that there is a possible chance of the dream being achieved. A careful explanation of the potential complications and the estimate of success must first be provided.

One of the best ways to accomplish this is to do what the patient did and perform a computer search to see if there have been any successful precedents for this type of case. In this circumstance, the patient was not only a physician but she had training in reproductive endocrinology. Even non-physicians however, are very computer savvy today and frequently can gain this information through the internet.

Nevertheless, even though our patient first went to colleagues with whom she had trained, they told her that her eggs were not of good quality and told her point blank she would need donor eggs. I do not believe that they did due diligence by not at least making her aware of contrasting conclusions from the ones they quoted that were the basis of their opinions. The second physician could be criticized for not reviewing the literature sufficiently to realize that the usage of high dosage gonadotropin stimulation is not the best choice for this type of patient but to be fair the emphasis on how important low-dose FSH

regimens are for this type of woman has only recently been emphasized [19, 20].

One of my associates had the right to refuse to perform egg retrieval on this patient for fear of complications and possible jeopardy to her future career. I greatly appreciate my other associates who despite agreeing that risk did exist, but realizing that this patient would not accept donor eggs or donor embryos, were willing to take some personal risks to provide this woman a chance to fulfill her dreams. The one associate never officially changed the refusal to do the egg retrieval, so the other physicians retrieved the eggs when it was the objecting physician's weekly turn for IVF-ET. However that physician was willing to perform the procedure twice on weekends rather than make other associates come in on their weekend off work. It was in fact the physician who had refused to do egg retrievals that did the transfer to the second gestational carrier which proved to be the conception cycle.

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