

Physicians should be more open-minded about performing in vitro fertilization-embryo transfer in women with diminished oocyte reserve and consider the couple's wishes and desires

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Summary

Purpose: By presenting anecdotal cases of women who conceived with IVF-ET despite very poor odds, this editorial hopes to make some of the infertility specialists to be more optimistic about the prognosis for pregnancy in women with diminished oocyte reserve. **Methods:** Description of case reports where despite poor odds the couples elected to still attempt IVF-ET which appeared to be needed for conception to be possible. **Results:** Five cases are presented where the couple was willing to deplete their financial resources to achieve a pregnancy with IVF-ET using their own gametes and were eventually successful. **Conclusions:** Physicians should restrain from being dogmatic and present all options to patients not merely the physicians' preference. It is embarrassing for a physician to insist that successful pregnancy is impossible only for the patient to prove that physician wrong. After receiving proper data patients should be allowed greater input into their treatment decision.

Key words: Diminished oocyte reserve; Finances; Patients' rights; In vitro fertilization.

Introduction

There have been several studies in the past suggesting that an increased day 3 serum follicle stimulating hormone (FSH) is associated with extremely poor pregnancy rates [1-5]. However, pregnancy rates have improved considerably in the field of in vitro fertilization (IVF) since these previous publications so the question is do these conclusions still apply in the modern era of IVF. Recently, however, data from one of the foremost IVF centers in the world concluded that if the day 3 serum FSH was ≥ 15 mIU/ml there would be no pregnancies at any age despite the transfer of multiple normal embryos [6].

With all these negative studies concerning the ability to conceive if the serum FSH is elevated even in normal menstruating women, women needing IVF-ET (who are facing an immense expense) might be less willing to undergo the IVF procedure even if that were the only way to achieve a pregnancy.

One might think that if it is difficult to achieve a pregnancy in menstruating women with decreased oocyte reserve it would be a lot more difficult to attain a pregnancy with the egg reserve so low that the woman appears to be in overt menopause (amenorrhea, elevated serum FSH, estrogen deficiency and failure to respond to exogenous gonadotropins). Nevertheless, ovulation induction and pregnancies have been achieved without IVF-ET in women in apparent menopause especially in women aged ≤ 39 [7-12]. However the estimated live delivery rate has been quoted as 8% in aggressively treated patients treated for a maximum of four cycles. Thus the success rate with IVF-ET would be expected to be extremely low. However some women have achieved success despite very low odds and despite lack of third party insurance coverage or being in good financial condition to bear the costs. Nevertheless they sacrificed their life savings to attempt to have a baby with their own genes. Some of these cases are described below.

Case 1

A 32-year-old woman with a tubal problem (bilateral fimbrial agglutination) related to a Chlamydia infection sought to have IVF-ET [13]. She came from Alabama to New Jersey because she was told she was in imminent ovarian failure due to a day 3 serum FSH of 44 mIU/ml and the failure to raise the serum estradiol (E2) level past 52 pg/ml despite several days of high dose exogenous gonadotropins.

Despite the very low odds that were quoted and her limited finances she wanted to try the method of lowering the elevated gonadotropins with ethinyl estradiol followed by low-dose gonadotropins. She had one mature oocyte in two consecutive cycles and she conceived and had a full-term live normal baby.

She tried again after the delivery but seemed to now be in overt ovarian failure and was unable to generate a dominant follicle.

Comment

This couple despite markedly limited finances and poor odds wanted the opportunity to try to achieve a pregnancy with their own gametes. Because of the lack of oocytes and therefore marked work reduction for the embryologist we were able to reduce the cost to one-third of the normal price. Because they had to work they drove 1000 miles back and forth during her stimulation phase.

For personal reasons they did not want to ever consider donor oocyte. They were willing to gamble on a fixed amount of money that they have saved to give them a chance to fulfill their dream.

Case 2

A 41-year-old woman was told that she was nearing ovarian failure. Her serum E2 was 119 pg/ml on day 3 and she was told by another IVF center that serum E2 levels > 50 pg/ml on day 3 prognosticate poor pregnancy rates [2].

She was advised that even though we have had pregnancies in women with elevated day 3 serum FSH and/or high serum E2 levels on day 3 [7-13], the prognosis for women age 40 or greater is markedly reduced [8, 14, 15].

Nevertheless she wanted to try to conceive with her own oocytes. The first cycle she was treated with ethinyl estradiol to lower the elevated serum FSH and to try to increase the length of the follicular phase [16, 17]. Clomiphene citrate was then given and the oocyte retrieved was deemed mature but it did not fertilize [17].

The next cycle the day 3 serum FSH was 17.4 mIU/ml and the serum E2 was 85.2 pg/ml. With ethinyl estradiol therapy the serum E2 dropped to 43.6 pg/ml but the FSH increased to 20.9 mIU/ml. Staying on the ethinyl estradiol the serum E2 was 250 pg/ml. She was given 10,000 units of human chorionic gonadotropin (hCG) and a mature egg was retrieved. A 4-cell embryo with 25% fragmentation was transferred three days later and resulted in a live normal baby [17].

Comment

Advanced reproductive age is much more of a negative factor for conception than the serum FSH. Based on our IVF studies a woman aged 40 has 70% as much of a chance of conception as women \leq aged 39 and the levels drop to 40% at age 41-43 then plummet to 10% at 44 and are extremely rare at age \geq 45 [15].

Nevertheless there have been pregnancies recorded without IVF-ET in women aged 45 and even 46 with elevated day 3 serum FSH [18, 19]. These two women still had fairly regular menses. However, there was even one woman aged 45 who was in overt menopause with estrogen deficiency, amenorrhea for six months, and a serum FSH of 43 mIU/ml who had ovulation restored by lowering the high serum FSH with ethinyl estradiol [20]. The interesting thing about this case was that the sperm count was so low (3.0×10^6 /ml with 20% motility) that IVF with ICSI was suggested but she did not want to spend the money for such low odds. However, miraculously she successfully conceived after two cycles of intrauterine insemination and delivered a full-term perfectly normal child [20].

Case 3

A 43-year-old woman with primary infertility of five years duration had decreased ovarian egg reserve as manifested by a day 4 serum FSH of 9 mIU/ml and a serum E2 of 55 pg/ml with a total of four antral follicles seen.

She had a previous hysterosalpingogram that showed the right fallopian tube to be patent but the left tube was blocked and showed a hydrosalpinx. She was advised that a unilateral hydrosalpinx could impair fertility even with IVF-ET, and that salpingectomy significantly improves the chance of pregnancy [21-23]. However, she was on medical assistance and the insurance would not cover this procedure for infertility purposes. She was advised that because of the cost to perform the procedure and the risk of laparoscopy considering her bowel resection for colon cancer, that we would suggest doxycycline 200 mg/day from day one of the IVF cycle until embryo transfer.

She was also advised that the majority of the IVF centers believe that decreased ovarian egg reserve is associated with a poor prognosis even if normal appearing embryos are transferred. She was also advised that our own data did not show such a poor prognosis in women aged \leq 39 since a study on pregnancy rates in women with decreased egg reserve allowing only single embryo transfer found a 40% clinical pregnancy rate per transfer with a miscarriage rate of 15% in the 65% who transferred an embryo with 6-8 blastomeres [24]. However in another study of marked decreased egg reserve where an average of 1.06 embryos were transferred, though the live delivery rate for women aged 40-42 was 21.5%, there were no live pregnancies in women aged \geq 43 [25]. Nevertheless, in our regular IVF program the pregnancy rates of 43-year-olds are similar to 42-year-olds with a big plummet at age 44. Our patient was reminded that she had just turned age 43.

Despite the seemingly poor odds not only related to advanced reproductive age but decreased egg reserve and the presence of a hydrosalpinx she decided to try IVF-ET with her own eggs. She of course was advised that even if she used donor eggs, the hydrosalpinx could impair success [22]. Financially, though, she had no choice (plus it was a lot less risky) to hope that a longer course of antibiotics would negate the adverse effect of the hydrosalpinx on embryo implantation.

We charge 50% less for mild stimulation IVF because of considerably less work for the embryologists [26]. In fact, she was stimulated with only five days of highly purified urinary FSH at 75 IU/day. Only one dominant follicle was developed and one metaphase II oocyte was retrieved. The peak serum E2 level was 251 pg/ml.

The egg fertilized and cleaved to an 8-cell embryo that had good symmetry and < 25% fragmentation. She conceived and delivered a healthy full term baby.

Comment

This woman with very meager financial means was willing to become even more impoverished to achieve her dream of a baby with her and her husband's gametes. She was even willing to undergo even greater expense and risk having surgery for the hydrosalpinx despite the risk of bowel perforation.

Successful cases like this one re-emphasize the importance of allowing patients to make their own choices as long as they are provided the appropriate information to make that choice. The patient was even willing to undergo surgery but we convinced her not to take the risk; however we would have performed the salpingectomy if that was still her final decision. We advised her that she could have three IVF cycles for the price of the one operation and that it was not an absolute fact that the hydrosalpinges would impair embryo implantation especially with a more prolonged course of antibiotics.

Case 4a

A 33-year-old woman presented with a four and a half year history of infertility. She went to one infertility center who upon initial evaluation performed a clomiphene challenge test which she did not pass. On the basis of this test she was advised that she would require donor oocytes.

She went for a second opinion to another infertility center that also suggested the donor oocyte program but was willing to try IVF-ET with her own eggs if she wished. However, despite normal fallopian tubes and normal semen analysis in her husband this center suggested she lose no time and go directly to IVF-ET.

She was placed on a traditional ovarian hyperstimulation protocol and had three failed attempts. She only had three, four and four oocytes retrieved resulting in transfers of two embryos, the first and second time and none on the third. After the third cycle the IVF center said they would do no more IVF with her own oocytes and that she must proceed to donor oocytes.

Since the couple did not want donor oocytes they came to our IVF center knowing that we have no problem in trying IVF-ET with women with diminished egg reserve, especially if they are young. However, we believe it is because of using minimal gonadotropin stimulation [26].

In the first IVF cycle at our facility her peak E2 reached 307 pg/ml and she had one metaphase II oocyte retrieved. She had a transfer on day 3 of just a 4-cell embryo without fragmentation and did not conceive.

She was advised that 4-cell embryos only have a 3.8% chance of implantation but that did not mean that she would not make embryos in subsequent cycles with more blastomeres [24].

In cycle 2 at our center (but number 5 for her) she attained a serum E2 of 443 pg/ml on the day of hCG injection. She had three metaphase II eggs retrieved; three fertilized but only one cleaved to day 3 when an 8-cell embryo with < 25% fragmentation was transferred. She did not conceive.

Encouraged by the improvement in embryo quality she tried again and attained a peak serum E2 of 776 pg/ml. Though two eggs were retrieved only one was mature. One fertilized the first day, the second fertilized on the second day and two embryos with six and five blastomeres with < 25% fragmentation were transferred but she did not conceive.

She still wanted to try again. In cycle 4 with our center (but 7 IVF cycles altogether) her peak serum E2 was only 244 pg/ml and only one metaphase II egg was retrieved. She transferred one 8-cell embryo with ≤ 25% fragmentation. She conceived in this cycle and delivered a full term healthy baby. She was 34.5 years old when she conceived. All four cycles used intracytoplasmic sperm injection in view of failed fertilization in cycle 3 at the previous center.

Comment

The couple had only a moderate income – she was a probation officer and her husband a teacher. Nevertheless, they were willing to sacrifice their money to have their dream of a child with the wife's and the husband's genes.

After delivery her menses resumed three months later and they tried on their own for four months without success. They have returned to our IVF center again to try once more a minimal stimulation protocol and IVF with intracytoplasmic sperm injection.

Case 4b

Similar to case 4a there was a 37-year old-woman with secondary infertility who failed to conceive despite ten cycles of follicle maturing drugs and intrauterine insemination. She was advised to do IVF-ET and had a traditional COH protocol. However, only one egg was retrieved and the IVF center told her they would not do another cycle with her own oocytes but would gladly use donor oocytes in her body.

She wanted her own genes so she came to our IVF center. We performed natural to minimal COH and in cycles 2-7 she failed to fertilize any oocytes in three of the six cycles and only transferred four embryos total in the other three cycles.

She still wanted to keep trying with her own oocytes. In her eighth IVF cycle (7 with our center) she transferred one 7-cell embryo without fragmentation. She conceived monochorionic diamniotic twins [27]. She successfully delivered full term twin girls. Though her day 3 serum FSH had been as high as 17 mIU/ml she had a level of 10 mIU/ml on the cycle of conception.

Comment

One does not always have to expect that it will take so many cycles to achieve a successful pregnancy as in cases 4a and 4b. One woman with diminished oocyte reserve achieved three live deliveries (singleton each time) in four IVF attempts over an 8-year time period [28]. However, it would not be fair to merely present to the couple the example of this very fortunate couple without mentioning that some women had to undergo many IVF cycles before achieving a success. Couples must also be advised that they could go through many IVF cycles and still not be successful.

Case 5

A 37-year-old woman with primary infertility traveled 3000 miles from California to New Jersey to see if it was possible to make her ovulate despite the diagnosis of premature menopause [29]. She had not had a menstrual period for one year. After 50 days of amenorrhea her physician diagnosed premature menopause on the basis of a serum E2 of 20 pg/ml, a serum FSH of 120 mIU/ml and failure to have menses following progesterone withdrawal. Furthermore, her failure to stimulate a rise in serum E2 despite gonadotropin therapy convinced the consulting physician that there was complete absence of eggs rather than the production of defective FSH by a possible FSH secreting pituitary tumor.

The woman's husband, a physician, ran a computer search and found that ovulation induction and pregnancies have been recorded in women in apparent menopause by restoring down-regulated FSH receptors in the few remaining follicles by lowering the chronically elevated serum FSH through the use of ethinyl estradiol [7-12].

They came from California to New Jersey for a consult and she was treated with ethinyl estradiol. Her monitoring was performed in California and we directed her case by telephone. She attained a dominant follicle of 17 mm with a serum E2 of 314 pg/ml (ethinyl estradiol does not cause any increase in serum E2), released the egg and was treated with vaginal progesterone suppositories in the luteal phase at 200 mg twice daily. She did not conceive that cycle. She ovulated again with the same technique but did not conceive in cycle 2.

They requested if she formed a mature follicle on cycle 3 to fly to our center to do single egg retrieval and in vitro fertilization. However, her serum E2 only rose to 32 pg/ml.

The infertility specialists in California who were monitoring her advised her that although they were impressed that she was able to ovulate two times despite apparent menopause, that even if she did ovulate she would not conceive because her oocytes were of poor quality based on previous studies [1-6]. She called and stated that although she believed our data that a pregnancy is possible with even her oocytes she wanted to expedite the process and that she is not uncomfortable with the donor oocyte process. So that was her next step. For convenience she would have the transfer of embryos derived from donor oocytes in California.

Unfortunately she failed to conceive despite the transfer of 12 high quality embryos over four donor egg cycles. She reconsulted us at age 40 stating that she would like to try donor oocyte at our IVF center.

We prepared her uterus for donor oocytes with estrogen since she was estrogen deficient. The estrogen treatment allowed her to ovulate again (thus now 3 of 4 times). She was supported with progesterone but it was not expected that she would become pregnant with her own oocytes after failing with four donor oocyte attempts. However she did become pregnant and delivered a full term healthy baby.

Comment

This couple had a better financial situation than the other couples illustrated in this editorial. However, they were feeling the "sting" after spending \$120,000 for four failed donor oocyte cycles. Yet they were willing to pursue more financial depletion to attain her goal of having a baby with her husband's sperm. In her case the desire to carry and delivery a baby was more important than her own genes. Surprisingly in the end she was rewarded with both.

Discussion

All of the reported women were willing to undergo the expense of IVF despite the fact that the number of embryos transferred would be quite low and with the knowledge that in the opinion of the majority of infertility specialists the odds of success were quite small. Some were advised that pregnancy with their own eggs was impossible. However, these anecdotal reports proved the naysayers wrong and strongly suggest that even when the oocyte reserve of a younger woman is comparable to the number of oocytes in women over the age of 45, the quality of the eggs are more analogous to their age peers. Thus these women should not be denied attempts at oocyte retrieval of their own oocytes as long as they have been properly advised of the far greater likelihood of success with donor oocytes.

Case 5 is really fascinating. Here was a woman who was willing to travel 3000 miles to do IVF if a mature follicle could be achieved but yet was able to be convinced to do donor oocytes because of the much greater likelihood of success. However, she found out that donor oocytes are not guaranteed to work either. When faced, though, with the suggestion of using a gestational carrier with transfer of embryos derived from donor oocytes and her husband's sperm or adoption as her only two options, she chose instead to pursue more donor oocyte cycles despite the immense expense already incurred with her four previous failed donor oocyte cycles.

She was hoping that another IVF center might identify some correctable factor that would enable her to attain her dream of carrying and delivering a baby. Other than the estrogen treatment her only other treatment was progesterone supplementation which she continued through the first trimester.

Case 5 exemplifies the fact that if a 40-year-old woman with extremely high serum FSH (actually her serum FSH was as high as 180 mIU/ml at some point during her attempts at donor oocyte) and estrogen deficiency can get pregnant with her own oocytes physicians should not advise younger patients with an even greater egg reserve that they should have IVF-ET performed with their own oocytes merely because one day 3 FSH was elevated at least one time.

Cases 4a, 4b, and 5 illustrate that despite repeated failures to conceive despite embryo transfer that successful pregnancy is certainly still possible without changing the gametes or uterus. As long as couples are advised that the repeated failures reduce the odds of success of the next one, and they are re-advised of other options that may be more effective, they should still be given the opportunity to try more attempts under the conditions that they prefer.

It is hard to believe with the plethora of studies dating back to 1984 describing techniques to increase the chance of ovulation even in women in apparent premature ovarian failure, and the demonstration of quite adequate pregnancy rates in women with diminished oocyte reserve, that many physicians only make the couple aware of the negative but not the positive studies. Some of these articles have been written in the same main infertility journals where the negative studies are being quoted [7, 8, 20, 24, 26].

Reproductive endocrinologists/infertility specialists should not be politicians in being able to lure patients into a therapy that better suits the treating physician and not the couple. These physicians should be aware that their reputation as an expert will be marred if a woman advised that only donor oocytes would be successful, goes to another infertility specialist and conceives with her own oocytes. Even if the woman is unsuccessful she may be very disappointed with the IVF center quoting her studies biased for negative results without presenting other studies with positive results. This is especially important if the positive studies present reasons why the negative studies failed – especially because of the use of a high FSH dosage-controlled ovarian hyperstimulation protocol [26].

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