

In vitro fertilization (IVF) outcome in women in overt menopause attempting to induce follicular maturation by follicle stimulating hormone (FSH) receptor down-regulation

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Summary

Purpose: To determine the frequency of ovulation induction, obtaining oocytes leading to embryos, and pregnancy rates per embryo transfer in women with premature menopause. **Materials and Methods:** Prospective observational study of women hoping to have in vitro fertilization-embryo transfer (IVF-ET) with their own oocytes despite being in menopause. Ethinyl estradiol was used to lower follicle stimulation hormone (FSH) and restore sensitivity of follicles to mild FSH stimulation. **Results:** Three of five women had a live baby. Only one woman failed to induce ovulation and thus failed to have an embryo to transfer. One woman conceived two times and delivered a live healthy baby twice. The live delivered pregnancy rate per transfer was 20% (4/20) with generally one or occasionally two embryos transferred. The pregnancy rate per retrieval was 9.3% (4/43). **Conclusions:** These data can help other women in this circumstance to decide on IVF with their own eggs or switch to donor eggs.

Key words: Premature menopause; Embryo transfer; Restoration of FSH receptors; Ethinyl estradiol.

Introduction

Over the last 30 years, it has become clear that by lowering elevated serum follicle stimulation hormone (FSH), ovulation induction can be achieved much more frequently than expected in women who appear to be in overt menopause [1-5].

The most frequently used method to induce ovulation in this population is by lowering the high serum FSH with ethinyl estradiol (which has the advantage over estradiol (E2) of not contributing to the serum E2 levels, thus allowing better follicular monitoring) [6]. However, ovulation induction has also occurred by lowering the serum FSH with gonadotropin releasing hormone agonists, e.g., leuprolide acetate, or antagonists (cetorelix) [3, 7, 8].

Anecdotal reports of reversal of apparent menopause with subsequent pregnancy achieved by in vitro fertilization-embryo transfer (IVF-ET) have also been reported [9-11]. IVF is expensive. The objective of this study was to determine the efficacy of IVF-ET in women with premature ovarian failure. Knowing that previous precedents for success by anecdotal reports may help a woman to decide to try IVF when needed if there is a severe tubal or male factor, (although the women appear to be in menopause) if ovulation is induced. Others, before spending the money, would like to have some idea of the success rate to decide whether to spend the money or consider other options, e.g., donor oocyte or adoption.

Materials and Methods

A prospective observational study was performed on couples with either tubal factor or male factor where the female partner was in apparent menopause and desired IVF-ET with the female partner's own oocytes. Additional inclusion criteria were: age \leq 42, serum E2 $<$ 20 pg/ml, serum FSH $>$ 20 mIU/ml, amenorrhea $>$ one year. The treatment rendered was ethinyl estradiol 20 mcg per day was given. The woman was monitored by serial serum levels of E2, LH, FSH, and occasionally progesterone (P) plus ultrasound to evaluate follicular size and endometrial thickness. When serum FSH approached normal, mild stimulation with FSH may have been given. Human chorionic gonadotropin 10,000 units was given when there appeared to be at least one mature follicle. Details of methodology have been previously published [12, 13].

Results

There were five couples enrolled. Patient 1 failed to increase her E2 at all (remained $<$ 20 pg/ml) in two attempts and dropped out of study. Patient 2 developed a mature follicle in 24 of 28 attempted cycles. She formed one embryo in 13 of 24 cycles (54.1%). Her first four cycles resulted in single embryos, but she failed to conceive after four fresh embryo transfers.

Her Crohn's disease exacerbated and she was treated with cyclophosphamide, precluding any more transfers to herself. She decided to stockpile cryopreserved embryos until

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she acquired a gestational carrier. She proceeded with 24 more attempted IVF with cryopreservation cycles. Oocyte retrieval occurred in 20 cycles. A single two pronuclear embryo was created and cryopreserved nine times. Six of the nine cryopreserved embryos were thawed and two embryos were transferred to a gestational carrier twice and she conceived on her third attempt and delivered a live healthy baby. The gestational carrier by choice had only one embryo transferred in cycle 1 and cycle 2, but allowed two in the third cycle, which was successful. Thus one of ten embryos formed resulted in a live baby. This patient was part of the observational study, but her case report has already been published [14]. She has three embryos left and is planning to transfer them again to a gestational carrier.

Patient 3 made a mature follicle in five of nine cycles leading to oocyte retrieval. She had a total of four embryos. She failed to conceive with one embryo transfer x 2 but she was successful with a two-embryo transfer following her fifth oocyte retrieval (and third embryo transfer).

Patient 4 had ten oocyte retrievals leading to nine embryo transfers. There were a total of 12 embryos created. She conceived and delivered a healthy baby following single embryo transfer on her third attempt. She returned for baby 2 and formed one or two embryos in six of seven oocyte retrieval cycles. She conceived and delivered a healthy baby a second time from oocyte retrieval number 10 with two embryos transferred.

Patient 5 had 6 initiated cycles and four of them led to oocyte retrieval. She had two embryo transfers of one embryo each. However, she failed to conceive.

Overall the live delivered pregnancy rate per transfer was 20% (4/20). Overall, the live delivered pregnancy rate per retrieval was 9.3% (4/43). The live delivered pregnancy rate per initiated cycle was 6.1% (4/65).

Discussion

IVF-ET is generally a very expensive procedure, especially related to the cost of gonadotropins and the cost of the IVF-ET procedure itself. IVF-ET also has certain risks, especially ovarian hyperstimulation syndrome (OHSS).

More expensive than IVF-ET is the cost of being a donor oocyte recipient, with extra costs of donor fees frequently leading to prices twice as high as a regular IVF-ET cycle.

The cost of medication in described techniques to induce ovulation in women in apparent menopause is only a fraction of normal price for medication with normal IVF-ET because hardly any (or none at all) gonadotropins are used. Because there is generally only one or two oocytes, the price of IVF-ET could be considerably lowered by a given IVF center when faced with this type of problem. There obviously is no risk of OHSS.

There does not appear to be any age time-line for successful pregnancy from donor oocytes [15]. With this information as to success rates and a cost analysis, a given

couple can decide to try IVF with their own oocytes or try donor oocytes. It should be noted that though highly successful, some women fail to conceive even with donor oocytes. One woman (not part of this series because she did not have IVF-ET) had failed to conceive despite four cycles of transferring embryos derived from donor oocytes. She spent USD 120,000.00 without success. She was made to ovulate three times out of four initiated cycles with ethinyl estradiol despite two years of amenorrhea with serum E2 < 20 pg/ml and a serum FSH initially 125 mIU/ml but one time getting to 185 mIU/ml. She was successful with just intercourse alone in her fourth ovulation induction cycle with luteal phase P support. IVF was not suggested because she had patent fallopian tubes and her husband's semen parameters were normal [16].

This study also confirms that the technique to induce ovulation in women in apparent premature menopause by lowering FSH and theoretically restoring down-regulated FSH receptors making the follicle more sensitive to FSII stimulation, seems to be an effective technique in that there is no question that the frequency of ovulation in these women far exceeds what would have been expected just fortuitously.

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