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Research Article

A Study to Determine the Reason for Lower Pregnancy Rates in Younger Women with Diminished Oocyte Reserve-less Chance of Implanting *vs.* Fetal Demise

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Abstract

Most studies find lower live-delivered pregnancy rates (LDPRs) following *in vitro* fertilization-embryo transfer (IVF-ET) in women with diminished oocyte reserve (DOR) vs. normal oocyte reserve (NOR) even in a younger population. How much of a discrepancy may depend on the degree of oocyte depletion in the DOR group and the follicular stimulation protocol. Some fertility specialists favor an FSH receptor up-regulation technique as the protocol to attain the maximum LDPRs in women with DOR. The objective of this study was to compare chemical, clinical, and LDPRs following IVF-ET to determine if the main time of embryo loss is very early, as evidenced by the largest discrepancy occurring in attaining even a chemical pregnancy, and/ or a large discrepancy between a chemical pregnancy and attaining a clinical pregnancy (ultrasound evidence of a gestational sac) or later losses as evidenced by showing a greater loss rate from clinical evidence of pregnancy to live delivery in those with DOR compared to NOR. Overall, the DOR group, with a mean serum anti-Mullerian hormone (AMH) level of 0.42 ng/mL, had 50% as much chance to have an LDPR/transfer as women with NOR (AMH of 4.66) despite the same number of day 3 embryos transferred. The main reduction in LDPRs occurred from embryo transfer failing to attain a positive clinical pregnancy in the DOR group. The least discrepancy was from attaining a clinical pregnancy to live delivery. Thus, for NOR from positive pregnancy test 59% of this younger age group will have a live delivery *vs.* 50% for DOR. Thus, the reduction in LDPRS/transfer in young women with DOR vs. NOR seems mostly very early so the DOR group does not even attain a positive serum beta human chorionic gonadotropin level. This suggests that this inferiority in attaining a live delivery may be related to aneuploidy involving large chromosomes or a marked decrease in the mitochondrial DNA of the embryo.

Introduction

Some *in vitro* fertilization-embryo transfer (IVF-ET) centers report very low live-delivered pregnancy rates following IVF cycles in women of all ages who have diminished oocyte reserve (DOR) [1-3]. These low live-delivered pregnancy rates (LDPRs) were found in these studies despite the transfer of embryos that appeared normal by morphologic criteria [3]. Many other IVF centers advise women with DOR, including younger women, that their fertility prognosis is very poor with their eggs and recommend donor egg programs [3]. Not all infertility specialists agree. Though most infertility specialists believe that younger women with DOR are less likely to achieve a live delivery than peers with normal oocyte reserve (NOR), nevertheless, the LDPRs from a given IVF-ET cycle are sufficiently adequate to allow the women with DOR to try to conceive with her eggs. This may especially apply to younger women with DOR [4].

One reason for lower LDPRs was the use of high FSH dosage stimulation protocols that may have downregulated FSH receptors responsible for making certain enzymes or cytokines that are needed for successful embryo implantation. Evidence to support this concept is based on much better outcomes when the stimulation protocol emphasizes up-regulation of the FSH receptor rather than down-regulation [5,6].

Theoretically, the somewhat lower LDPR with DOR *vs.* NOR following IVF-ET could be related to either higher rates of aneuploidy or decreased mitochondrial DNA if the embryos are euploid [7]. The objective of this study was to try

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to determine at what stage the pregnancy rate decreases in a younger population with DOR following embryo transfer of day 3 embryos- failure of the embryos to implant or early death after implantation may favor aneuploidy, especially of the larger chromosome which rarely leads to live deliveries and lower rates of even yielding a positive serum beta-human gonadotropin (B-HCG) level or marked diminished mitochondrial DNA [5-7]. However, if most of the decrease in LDPRs per transfer occurs after a clinical pregnancy is achieved, this could favor that most losses could be related to aneuploidy of the smaller chromosomes, e.g., numbers 13,16,18, 21 and 22.

Thus the objective of this study was to determine from the time of fertilization when the drop in fecundity occurs to determine if the decrease in fertility is more related to severely abnormal embryos (aneuploidy of large chromosomes or marked reduced mitochondrial DNA), leading to failure to even attain a positive pregnancy test or embryos that lead to very early losses (chemical pregnancies before there is even ultrasound, evidence of pregnancy), or pregnancy losses after ultrasound evidence of pregnancy which may favor losses related to trisomy of smaller chromosomes.

Materials and methods

Women age ≤ 35 undergoing *in vitro* fertilization-embryo transfer (IVF-ET) were divided into 2 groups: those with serum anti-mullerian hormone (AMH) levels <1 ng/mL and those whose AMH levels were >1 ng/mL. They agreed to have a day 3 ET, and no more than 2 embryos were transferred.

Women with DOR were stimulated with an FSH receptor uptake technique that varied according to the degree of DOR, and in general, did not use more than 150 IU follicle stimulating hormone (FSH), unless cetrorelix or ganirelix were given when an extra 75 IU could be used [6]. Gonadotropin injections were not given if serum FSH was > 13 mIU/mL in which the patients were monitored until endogenous FSH dropped to 12 mIU/mL or less by rising endogenous estradiol, (E2) [6]. If endogenous serum E2 was not rising, or there was a history of a short follicular phase, 20 mcg of ethinyl estradiol was given. Women in apparent overt menopause were included as long as they attained one mature follicle.

A chemical pregnancy was considered if there was a rise in the serum Beta human chorionic gonadotropin (B-HCG) levels x 2 and the serum HCG level exceeded 100 mIU/mL. A clinical pregnancy was considered if there was ultrasound evidence of pregnancy 4 weeks from embryo transfer.

Since this study was merely an observational one evaluating the normally accepted clinical practice of this type of patient, and since ethical standards were observed using the least expensive, most successful treatment option to solve the infertility problem taking into consideration the couple's wishes this study did not need approval by the Institutional Review Board of Cooper Medical School of Rowan University. The study was entirely retrospective.

Results

There were 67th day 3 ETs evaluated in women with DOR *vs.* 209 for normal oocyte reserve (NOR). A positive pregnancy blood test was found in 37.3% with DOR *vs.* 54.5% with NOR. The clinical pregnancy rate (PR) per transfer was 25.4% for DOR *vs.* 45.9% for NOR. The live delivered PR/transfer was 19.4% *vs.* 38.3% respectively. Thus, a woman with NOR had an 83% chance of progressing from a clinical pregnancy to fetal viability *vs.* 76% for DOR. Therefore, women with DOR were 92% as likely to progress from a clinical pregnancy to live delivery as women with NOR.

There were 1.7 *vs.* 1.8 embryos transferred leading to an implantation rate of 18.6% *vs.* 32.3%. The mean serum anti-mullerian hormone (AMH) levels were 0.42 ± 1.27 *vs.* 4.66 ± 4.16 ng/ml.

Discussion

Embryos resulting from women with DOR are 68.4% as likely to survive long enough to achieve a chemical pregnancy compared to women with NOR. A woman with DOR has an 80% as much chance of positive pregnancy test to a clinical pregnancy compared to a woman with NOR. The overall miscarriage rate with DOR once a gestational sac was found was 23.5% *vs.* 16.7% for NOR.

Thus, it would seem that the inferiority of eggs from women from DOR *vs.* NOR is mostly manifested early, so the largest discrepancy is first to achieve a positive pregnancy test. Once a chemical pregnancy is achieved 59% with NOR will have a live delivery *vs.* 50% with DOR.

Thus, at least when using the FSH receptor up-regulation technique for DOR, the live-delivered PRs are 50% as likely to occur following day 3 ETs in this younger age group. This information is needed for the women to decide on proceeding with IVF-ET (if this was needed for tubal or male factor) *vs.* donor oocytes.

It should be remembered that for many couples the use of donor oocytes is not an option because of religious doctrines, e.g., some patients of the Muslim, Catholic, or Orthodox Jewish faiths [8]. In fact, in one study of Sunni Muslims who went against the Islamic "future" that inhibits third-party gamete donations despite Islamic religious prohibitions subsequently in a large percentage of the patients expressed guilt about their decision but expressed

the dilemma of causing marital unhappiness by not bearing a child [9]. This group would likely have persisted with their gametes if the results of this study were known to them and they were not advised that donor eggs were the only option [9].

It should be noted that this discrepancy difference could be less if the cohort did not have severe DOR or were not even included in this study if there was a temporary reversal of the menopausal state as evidenced by attaining a mature follicle. The mean serum AMH for the DOR group for this study was 0.47 ng/mL and about 30% of the patients were considered to be in overt menopause [10].

Evidence to support the concept that if aneuploidy is the cause for early losses that it is more likely related to abnormalities with larger rather than smaller chromosomes is supported by very low incidence of trisomies 13,18, or 21 following non-invasive pre-natal testing in women with DOR age 39.5 or younger as opposed to women > age 39.5 [11].

These have been case reports of women with DOR who failed to fertilize oocytes despite intracytoplasmic sperm injection, who were not only successful in creating embryos with the use of calcium ionophore for artificial oocyte activation but conceived in their first cycle, including a 43-year-old woman who had twins [12,13]. At present, we are conducting research to evaluate whether oocyte activation could improve embryo quality by either improving melogly function to inhibit aneuploidy or improving mitochondrial DNA in women with DOR even those who have no problem in fertilization.

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All patients used in this study gave written permission when they enrolled as patients so that their results could be used for research studies.

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