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A Study to Determine the Impact of Diminished Oocyte Reserve (DOR) on Pregnancy Outcome in Women of Advanced Reproductive Age

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ABSTRACT

Background: *Both advancing age and diminished oocyte reserve (DOR) have a negative impact on fecundity.*

Objective: *To determine what effect diminished oocyte reserve (DOR), as determined by low anti-Mullerian hormone levels, has on live delivered pregnancy rates following in vitro fertilization embryo transfer (IVF-ET) in women aged-40-42.*

Design: *This was a retrospective study.*

Materials and Methods: *A retrospective study was performed in women aged 40-42 undergoing IVF-ET with DOR or normal ovarian reserve (NOR). The women were divided into two groups based on egg reserve: DOR (anti-mullerian hormone (AMH) level <1 ng/ml) and normal oocyte reserve (NOR) (serum AMH ≥ 1ng/ml). A type of mild ovarian stimulation protocol, known as the FSH receptor up-regulation technique, was used for women with DOR.*

Setting: *University-associated private practice IVF center*

Results: *The live delivered pregnancy rate (LDPR) was 12.6% for the DOR group and 12.9% for normal oocyte reserve (NOR).*

Conclusion: *Since the LDPRs were the same for women aged 40-42 with DOR compared to NOR, a low serum AMH should not be a deterrent for performing IVF-ET in women aged 40-42. If this LDPR is not acceptable, then one could consider the use of donor eggs.*

Keywords
Diminished ovarian reserve, Normal ovarian reserve.

Introduction
An FSH receptor up-regulation technique has been utilized by our reproductive endocrinology/infertility group for over 40 years to restore FSH sensitivity in antral follicles leading to ovulation and successful deliveries even in women in apparent premature menopause [1,2]. Live deliveries using this technique have been achieved through natural intercourse, intrauterine insemination (IUI), or in vitro fertilization (IVF) [1-3]. Studies from our IVF center have found that the live delivered pregnancy rate (LDPRs) in women aged ≤ 39 with diminished oocyte reserve (DOR) following IVF-ET range anywhere from 50-75% as likely to achieve a live delivery as women with normal oocyte reserve (NOR), depending on the average age of the woman in the study, the degree of DOR, and whether women in overt menopause were included or not [2-4]. The present study evaluated the impact of

DOR on LDPRs in women aged 40-42 with NOR vs women of comparable age with DOR group undergoing IVF-ET.

Methods

Women aged 40-42 having IVF-ET were divided into two groups based on their serum anti-mullerian hormone (AMH) levels (<1 ng/mL, for DOR and ≥ 1 ng/mL for NOR). As long as an embryo cleaved to day three, and there were at least four blastomeres, even with poor morphology, the 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 was given, when the extra 75 IU could be added [2]. Gonadotropin injections were not given if serum FSH was >13 mIU/mL in which case the patients were monitored until endogenous FSH dropped to 12 mIU/mL or less by the rising endogenous serum estradiol (E2) [2]. If endogenous serum E2 was not rising, or there was a history of a short follicular phase (ovulation before day 9), 20 mcg of ethinyl estradiol was given [4-6]. Women in apparent overt menopause were included as long as they attained one mature follicle [4,7,8]. Conventional oocyte insemination was used for fertilization of the oocytes unless there was a male factor problem or history of poor or failed fertilization when intracytoplasmic serum injection (ICSI) was performed.

A chemical pregnancy was considered if there was a rise in the serum beta human chorionic gonadotropin (hCG) levels twice and the beta hCG exceeded 100 mIU/mL. It should be noted that this group of women differ from some of our previous publications in that DOR was determined by a low serum AMH, not by an increased day three serum FSH [9]. We have found low AMH to be a better predictor of DOR than high FSH [1].

Results

The results are summarized in Table 1. There were 111 ETs in women with DOR vs. 101 with NOR. A positive pregnancy test (chemical) was found in 32.4% in women with DOR vs. 30.7% with NOR. A gestational sac at four weeks from oocyte retrieval was seen in 27.9% with DOR vs. 23.8% with NOR. The LDPRs per transfer were 12.6% with DOR vs. 12.9% with NOR. The average number of embryos transferred was 1.7 with DOR vs. 2.4 with NOR. The implantation rate was 18.3% with DOR vs. 11.3% with NOR.

Table 1: Pregnancy outcomes in diminished ovarian reserve versus normal ovarian reserve.

	Diminished ovarian reserve	Normal ovarian reserve
Total embryo transfers	111	101
Chemical pregnancy	32.4%	30.7%
Gestational sac	27.9%	23.8%
Live delivered pregnancy rate	12.6%	12.9%
Implantation rate	18.3%	11.3%
Average number embryos transferred	1.7	2.4

Conclusions

Interestingly, DOR in women aged 40-42 does not seem to diminish the chance of a live delivery compared to age peers with NOR, following IVF-ET, at least when the FSH receptor uptake technique is used for ovarian stimulation for women with DOR. In a previous publication from our group where a day three FSH ≥ 12 mIU/mL was the criteria for selection for DOR, the LDPRs for women 40-42 with DOR was 9.9% which was only 50% as good as women 40-42 with NOR with a LDPR of 22% [3].

We are not sure with the data presented here why women aged 40-42 with NOR have dropped their LDPRs in half compared to our publication with a different set of patients. Nevertheless, what is the most important information that one can take away from this study is that if a couple needs IVF-ET because of severe male factor problems or damaged fallopian tubes, a woman should not be denied IVF-ET because of DOR as long as she is aware of the success rate for her age group.

The use of donor oocytes is not acceptable to all patients. One 42-year-old woman, who was not the least bit wealthy, and who was in total menopause, was willing to drive from North Carolina to New Jersey for monitoring, and then would drive back the same day so she would not lose her job. Even though she failed to conceive following her first transfer of a single embryo in her first IVF-ET cycle, she returned for a second cycle. She was rewarded with a full-term healthy baby following another single embryo transfer [4]. Another woman aged 42 with regular menses, but a very elevated day three serum FSH level, was found to make a mature dominant follicle without stimulation, but she failed to release the egg in cycle one, despite an LH surge, and in cycles two through four with treatment with human chorionic gonadotropin (hCG) as well as leuprolide acetate [10,11]. Thus, we suggested IVF-ET, but she could not afford it. However, she was willing to try something experimental. She was the first case where we tried an injection of granulocyte colony stimulating factor (G-CSF). She released the egg and had a successful live delivery [12]. Interestingly, this woman returned at age 46.5 in overt menopause and wanted to conceive again. By restoring down-regulated FSH receptors by suppressing very elevated serum FSH with ethinyl estradiol, she once again achieved a mature follicle and released the egg with G-CSF and hCG [12]. She was our first case of treating the luteinized unruptured follicle syndrome with G-CSF [13].

The results show for women aged 40-42 there is about a 20% loss rate from chemical to clinical pregnancy. The greatest loss rate was from the development of a gestational sac by transvaginal sonography (clinical pregnancy) to a live delivery, which was over 50%. This was most likely related to aneuploidy. Many IVF centers may recommend pre-implantation genetic diagnosis for aneuploidy (PGT-a). It is the authors' view that performing PGT-a for this age group is not in the patient's best interest because they will be paying extra money for the procedure. Furthermore, PGT-a may decrease the chance of a live delivery based on some embryos

that would result in a live delivery if transferred on day 3 may not survive in vitro to day five. Also, the trophectoderm biopsy may lower the chance of any given embryo leading to a successful delivery by damage from the procedure. In other words, PGT-a could lead to a higher LDPR per transfer to report to the Society of Assisted Reproductive Technology but result in a lower chance of delivery of a healthy baby by a woman of advanced reproductive age following IVF-ET.

The one exception is where a couple is unwilling to terminate a pregnancy for trisomy 21, 18, or 13 at the time of delivery in women conceiving at age 40, 41 and 42. The risk of a baby making it to term with a trisomy 21 is 1.2% (19/1533) at age 40, 1.8% at age 41 (19/1022) and 3.4% at age 42 (25/725). This risk of trisomy 18 is much less: age 40-0.5%, 41-0.4% at 42-0.7%. Trisomy 13 is the rarest of all the newborn trisomies age 40-0.15%, 41-0%, 42-0.01% [14]. Thus, women who would not terminate a live fetus based on the aforementioned study could decide whether the risk of a live delivery with a baby with physical abnormalities related to aneuploidy of 1.9% (29/1533) at age 40, 1.3% at 41 (13/1022) and 4.2% (31/723) at age 42 is worth the extra cost and possible reduction in success rate to perform PGT a and thus not transfer an embryo with aneuploidy.

Statement of Ethics

All patients on their initial visit are asked to sign a statement that their results may be included in research studies, but their anonymity will be maintained. Generally, 99% sign the statement. Those who do not, their chart is flagged and not used in research studies. Cooper Medical School of Rowan University does not require IRB approval for retrospective studies. Performing a mid-luteal vaginal ultrasound in part of our standard procedure.

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