

IVF Outcome: Advanced Female Age, Low Egg Reserve

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Introduction

Fecundity decreases with advancing reproductive age especially related to meiosis errors leading to embryos with aneuploidy. For many years, there has been an opinion from some of the pioneers of infertility treatment and in vitro fertilization-embryo transfer (IVF-ET) that diminished oocyte reserve (DOR), as determined by elevated day 3 serum FSH levels, was associated with a marked decrease in pregnancy rates following IVF-ET [1-3]. However, not all studies agree that DOR markedly diminishes success with IVF-ET. Our own studies found that utilizing a technique known as an FSH receptor up-regulation technique for controlled ovarian stimulation, which is a type of mild FSH stimulation technique, produces live delivered pregnancy rates (LDPRs) that are reasonable [4-7]. One study, using the day 3 serum FSH as the method to determine DOR found that women age <35 are 80% as likely to have a live delivery compared to women with normal oocyte reserve (NOR), 70% in women aged 36-39, and 50% in women aged 40-42 [5].

The aim of the present study was not only to determine the relative effect of DOR vs NOR on IVF success with fresh day 3 embryo transfer according to DOR based on serum AMH levels <1 ng/ml vs NOR (AMH>1ng/ml) in women aged 40-42, but also to determine the impact of very low serum AMH (<0.5ng/ml).

Materials and Methods

This study evaluated the outcome of IVF-ET in women aged 40-42 according to 4 sera AMH ranges: 1. < 0.5 ng/ml, 2. 0.5 to <1ng/ml, 3. 1 to <5ng/ml, and 4. >5ng/ml. A mild ovarian stimulation technique called the follicle stimulating hormone (FSH) receptor up-regulation technique was used for patients with diminished oocyte reserve (DOR)

with a gonadotropin releasing hormone antagonist (GnRHa) [7]. For women with sera AMH levels of >1ng/ml, a conventional GnRHa protocol was used with 225 to 300 IU FSH per day. In all instances, fresh embryos were transferred in the retrieval cycle unless there was a problem with too thin of an endometrium in which case all embryos were cryopreserved and transferred in a subsequent (frozen ET) cycle. LDPRs were calculated for the patient's first transfer (fresh or frozen). LDPRs were also calculated according to sera AMH levels per oocyte harvest defined as a live delivery from any of the embryos created in that 1 oocyte retrieval whether the transfer occurred from the first fresh ET cycle or from a subsequent frozen ET as long as they were from that oocyte retrieval. The normal ovarian reserve (NOR) group was considered to have serum AMH <5ng/ml. Another group with superior ovarian reserve (SOR) was also evaluated who had a serum AMH >5ng/ml.

Results

The results are seen in Table 1. There was a total of 419 oocyte retrievals in women with sera AMH levels <5 ng/ml. There were only 12 with sera AMH >5ng/ml. Thus, of the total number of oocyte retrievals in this age group (431), only 3% had a high serum AMH level and were considered the SOR group. For women aged 40-42, at least in our treatment group (there may be a bias for referrals for DOR) using < 1ng/ml for serum AMH as the cut off, 250 of 419 with serum AMH <5ng/ml had DOR (about 60%).

Though there were no significant differences in LDPR in the 3 groups with serum AMH <5ng/ml, there was a trend for the NOR group to have a 50% higher LDPR per first transfer compared to the combined DOR group. For the SOR group, though only consisting of 12 cases, there was a trend for the LDPR per first transfer to be three-fold higher than the DOR group vs DOR combined group. The SOR group had a 3-fold higher LDPR (50%) than the DOR group. There was no difference between the LDPR per harvest in the 2 low



serum AMH groups. However, this study did not evaluate whether lower serum AMH levels lead to fewer ETs. Thus, the actual LDPR per oocyte retrieval may have been somewhat lower in the very low vs low AMH group.

Table 1: LDPR in women ages 40-42 by AMH level following IVF according to sera AMH ranges.

AMH Level ng/ml	<0.5	0.5 to <1.0	1.0 To <5.0	>5-0
Number of Retrievals	136	114	169	12
Number of Embryo transfers	136	114	169	12
Number of pregnancies	43	42	54	6
Number of clinical pregnancies	30	30	43	5
PR per % clinical per transfer	22.1	26.3	25.4	41.7
Live delivered	17	16	29	33.3
Live delivered PR % delivered per 1st transfer	12.5	14	17.2	33.3
LDPR per harvest	14.0%	14.90%	18.90%	50.00%

Discussion

These results show that women aged 40-42 with DOR, evidenced by low serum AMH levels, do not have any negative impact in achieving a live delivery following IVT-ET compared to women with NOR as evidenced by serum AMH 1 to <5ng/ml. Thus, if IVF is needed for procreation, a woman aged 40-42 may choose to use her own oocytes rather than donor eggs (as is so frequently recommended by infertility specialists to this group) as long as these LDPRs are acceptable. We have hypothesized that the very poor outcome by others mentioned in the introduction may have been related to the use of too much FSH stimulation which could possibly down regulate key FSH dependent enzymes or cytokines needed for successful implantation or to create a euploid embryo [1-8].

Thus, it is possible that the experience may differ in other IVF centers if they do not follow the tenets of the FSH receptor up-regulation technique [8]. Some women in the DOR group were considered to be in overt menopause [9]. There have been some studies suggesting that women with serum AMH >5 ng/ml have lower LDPRs per transfer. We disagree [10]. Our studies not only show that women with serum AMH >5 ng/ml do not have lowered LDPRs per embryo transfer, but, in fact, have even have higher LDPRs per harvest [10]. This is supported in this study by the outcome of the 12 women aged 40-42 with serum AMH >5ng/ml.

It should be noted that this study evaluated only women intending to have a day 3 transfer as opposed to a blastocyst transfer or a transfer of a blastocyst with pre-implantation genetic testing for aneuploidy (PGT-a) to gain more understanding of the impact of DOR in addition to advanced reproductive age. We generally discourage blastocyst transfer or PGTa because some embryos will result in a normal pregnancy if transferred on day 3 but not make it on extended culture to attain a blastocyst stage.

However, it should be noted that only cycles resulting in day 3 transfers were included. The majority of oocyte retrievals did lead to a day 3 transfer, but some oocyte retrievals failed to obtain an egg, and some eggs did not fertilize, and some had fertilized eggs, but the zygote did not reach day 3. Thus, the actual pregnancy rate per oocyte retrieval may have been somewhat lower because this study did not evaluate whether lower sera AMH levels could lead to a lower chance of a day 3 embryo transfer being produced.

Author Contributions

Jerome H Check designed the study and wrote 70% of the manuscript. Brooke Neumann, Carrie Wilson, and Donna Summer had equal contributions in gathering and collecting the data. Michael Sobel performed 60% of the oocyte retrieval and transfers and made 30% of the decision during the patients monitoring cycles (Jerome Check did 70%). Donna Summer was 1 of the 2 embryologists. All authors made some additions or corrections of the 1st rough draft of the manuscript.

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Institutional Review Board Statement

Retrospective studies do not require IRB approval from our institution.

Informed Consent Statement

All patients on the initial visit are asked to sign a consent that their data can be used for possible studies. Those not consenting (which is rare) are flagged and not used.

Data Availability Statement

Available from Carrie Wilson at carrie.wilson@ccivf.com

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Conflicts of Interest

None

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