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ORIGINAL ARTICLE

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Does Ovarian Hyperstimulation Syndrome influence embryo quality and thereby the outcome of a frozen embryo replacement cycle ? – A preliminary observation

Anuradha **BS, *Thankam R* Varma,**

Institute of Reproductive Medicine and Women's Health, Chennai - 600 037.

OBJECTIVE(S) : To study whether the embryos derived from a cycle where the patient suffered from ovarian hyperstimulation syndrome (OHSS) are influenced or affected because of the hyperstimulation syndrome.

METHOD(S) : In this prospective observational study 34 frozen embryo replacement (FER) cycles were analyzed. A comparative analysis was made of FER cycles when frozen embryos were derived from non-OHSS cycles (n=22) with FER cycles when frozen embryos were derived from OHSS cycles (n=12).

RESULTS : The pregnancy rate in the OHSS group was 8.33%, whereas, in the non-OHSS group it was 18.18%. This difference was not statistically significant as the number of patients in the study was small.

CONCLUSION(S) : The pregnancy rate was not significantly different statistically in OHSS and non-OHSS cycles. However until further larger studies are done, embryo cryopreservation with FER can be considered a cost effective option for OHSS patients.

Keywords : ovarian hyperstimulation syndrome, embryo cryopreservation, frozen embryo replacement, pregnancy rates

Introduction

Frozen embryo replacement is indicated in patients who have surplus embryos after transfer in a fresh cycle. It is also indicated in patients who have ovarian hyperstimulation syndrome (OHSS) as a preventive strategy to avoid severe life threatening OHSS. Our study attempts to check whether the altered biochemical milleu in which eggs develop in an OHSS cycle has an influence on the quality of the embryos produced. The embryo quality can be judged best by the ability of the embryos to survive a free thaw process and finally produce a pregnancy.

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Correspondence :
Dr. Anuradha BS
Institute of Reproductive Medicine and Women's Health
A Unit of Madras Medical Mission
4 A, 5th Floor, Dr. J. J Nagar, Mogappair, Chennai - 600 037.
Tel. 91-44-26565513 / 26565514 Email : mmmirm@yahoo.com

The potential benefits of embryo freezing are that it provides an opportunity to achieve a pregnancy without needing multiple egg retrievals, reduces the risk of multiple pregnancy, enables transfer in a natural cycle, and enables better organization of donor programs.

Methods

This is a prospective study of 34 patients who underwent frozen embryo replacement (FER) between September 2003 and May 2004. The subjects were categorized in two groups based on whether they suffered from OHSS (n=12) or not (n=22) when the embryos were frozen. Five of the 12 patients in the OHSS group and 6 of the 22 in the non-OHSS group had polycystic ovarian syndrome.

During freezing, embryos were exposed to increasing concentrations of cryoprotective medium (propanediol and sucrose) at room temperature. Cryovials loaded with the embryos were equilibrated at room temperature before being cooled at a rate of of -2^0C/minute until -7^0C.

They were held for 5 minutes, manual seeding was performed, and they were held for a further 5 minutes. Cooling was continued at a rate of –0.3^{0}C/minute until –30^{0}C. Cryovials were then plunged into liquid nitrogen. While thawing, the cryovials were warmed in a 30^{0}C water bath for 30-90 seconds and then held for 5 minutes at room temperature before removing the embryos. Embryos were taken through decreasing concentrations of cryoprotective medium. Specimens were washed thoroughly and incubated until intrauterine transfer [1]. The couple's consent for thawing and for replacement was taken. When the endometrium was at least 8 mm thick, trilaminar, and with good subendothelial blood flow on doppler study, 50 mg of micronised progesterone was given intramuscularly which was continued daily till the day of the pregnancy test done 16 days after the FER. It was further continued upto 10 weeks if pregnancy resulted. Embryo thawing was done on the day following the progesterone injection if they were frozen at the pronuclear stage, 2 days after the injection if they were frozen on day 2 (4 cell stage) and 3 days after if they were frozen at the 8 cell stage or compact stage.

The data were tabulated and statistically analyzed. Students t-test was applied to find if there was any significant difference in the mean values of all the continuous variables between the two groups and it was found that none of the variables had any significant difference. Chi-square test of association was used to find if there was any significant association between OHSS and the outcome. The association was not statistically significant. The chi-square value was 0.600 and P value 0.438.

Results

The means were calculated for each parameter in the two groups and were found comparable as shown in Table 1. There was one ongoing pregnancy in the 12 patients of OHSS group and there were four pregnancies in the 22 patients of the non-OHSS group with pregnancy rates of 8.33% and 18.18% respectively. Although not statistically significant (Chi-square value 0.600, P value 0.438) due to the small numbers studied, this could prove to be a significant observation if larger numbers of FER cycles are compared. Of the 12 patients with OHSS, 10 had moderate and two had severe OHSS. One with severe OHSS got pregnant in the FER cycle. Severity of OHSS did not have any significant influence on the outcome as more the number of eggs collected more the number of embryos to choose from and greater the chance to have two or three embryos of best quality for transfer.

In the OHSS group, one transfer was done in the natural cycle and 11 in the assisted cycles. This is comparable to two transfers in the natural cycles and 20 in the assisted cycles in the non-OHSS group.

Table 1. Comparison between OHSS and Non-OHSS groups who underwent frozen embryo transfer.

Parameter	OHSS (n=12)	Non-OHSS (n=22)	P value
Mean age (years)	30.83	32.45	0.392
Mean body mass index	25.45	26.32	0.462
Mean day of freezing	3.50	3.07	0.642
Mean day of transfer	16.83	17.65	0.368
Mean freeze-thaw interval (minutes)	8.75	6.77	0.397
Mean embryos thawed	4.91	4.36	0.253
Mean embryos survived	3.33	3.13	0.484
Mean E_2 on the day of transfer (pg/mL)	597.00	428.56	0.108
Mean progesterone on the day of transfer (ng/mL)	22.52	24.12	0.789
Mean number of days of progesterone supplementation before transfer	2.00	2.60	0.188
Mean number of embryos transferred	3.25	3.18	0.809
Mean endometrial thickness on day of transfer (mm)	9.95	9.85	0.827

Discussion

The implications of the high estradiol concentrations and the large number of oocytes in OHSS on the outcome of assisted reproduction are controversial in world literature. In an analysis of 581 IVF cycles Meniru and Craft in 1997 showed that although the mean fertilization rate of approximately 60% was similar in all groups the proportion of retrieved oocytes that produced embryos of a quality suitable for transfer or cryopreservation fell significantly in OHSS.

A case has been reported from Bournhall clinic by Akagbosu et al [2] where two wives of a Muslim with severe male factor infertility had simultaneous ovulation induction for TESA and ICSI. Of them one wife developed OHSS and only one of the 27 retrieved oocytes got fertilised while the other wife who had a normal response to ovarian stimulation, had normal fertilization following ICSI and delivered a live born infant. The wife who had suffered from OHSS, had a normal response in a later cycle of IVF- ICSI, had normal fertilization rate but no pregnancy. The authors concluded that the only variable that determined the different rate of fertilization in the simultaneous ICSI cycles appears to be oocyte quality. While the results of FER cycles after the decision to freeze all embryos following OHSS are generally satisfactory, it is important to counsel couples about the possible detrimental effects of OHSS on oocyte quality. Aboulghar et al [3] have reported a significantly lower oocyte maturity and quality resulting in lower fertilization rate in an OHSS group following ovulation induction for IVF or ICSI.

We have not analyzed the morphology or number of oocytes produced in each patient in our study.We have done analysis with the frozen embryo replacement cycle only.However, this helps us to have comparable endometrial receptivity in the two groups under study.The mean number of embryos thawed was 4.91 per cycle in the OHSS group and 4.36 per cycle in the non-OHSS group. The slightly greater number of embryos thawed in the OHSS group was probably due to their survivability compared to the normal stimulation group. However, the number of embryos finally transferred was comparable in the two groups at 3.33 embryos per patient in the OHSS group and 3.13 embryos per patient in the non-OHSS group. The poorer pregnancy rates in the OHSS group of patients despite transferring an equal number of embryos with comparable endometrial preparation is noticeable although not statistically significant because of the smaller number of patients studied. Serhal et al [4] showed that the outcome of ICSI is dependent on the quality of oocytes retrieved. While normal fertilization and early embryo development were achieved in oocytes with abnormal cytoplasm morphology, the resulting embryos failed to demonstrate the same implantation potential as those derived from oocytes with normal cytoplasm [4] .

On the contrary, unlike the low pregnancy rates of 8.33% observed in our set of patients with FER in OHSS cycles, Pattinson et al [5] have reported a pregnancy rate after thaw transfer of 25.2% per transfer, with a cumulative pregnancy rate per patient after additional thaw transfers of 40.6%. They have concluded that cryopreservation of all embryos and delayed ET in patients at risk of OHSS result in a lower incidence of severe OHSS. Oocyte quality, fertilization rates and cryosurvival of frozen embryos are equal to those for patients who have normal stimulation profile and subsequent thaw embryo replacement results in satisfactory pregnancy [5].

Another self controlled clinical study by Fabregues et al [6] included 22 patients who developed severe OHSS during their first IVF or ICSI cycle and had a second ART attempt at the same center when OHSS did not develop. They observed that the oocyte yield and the number of metaphase II oocytes were significantly higher in patients with OHSS than in the control cycles. Fertilization rates were similar in both the groups of ART cycles but the number of viable embryos was significantly higher in OHSS cycles. Implantation and pregnancy rates were similar. They concluded that oocyte quality is not compromised in severe OHSS cycles irrespective of whether patients had or did not have PCOS [6]. Despite all the controversies, cryopreservation of all embryos and subsequent replacement of the frozen thawed embryos in a later natural or hormonally prepared cycle would be a cost effective and safe option. It should be noted that such a strategy only prevents late onset OHSS and early onset OHSS is not totally avoided.

Until further larger studies are available cryopreservation of all embryos will continue to be a safe and economic option for patients to prevent late onset OHSS. However it would be wiser for clinicians to counsel couples about the possible detrimental effects of the altered biochemical milieu on oocyte quality, and thereby on embryo quality, its survivability and final outcome of pregnancy rates.

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