

Embryos from Women Who Hyperrespond to Controlled Ovarian Hyperstimulation Do Not Have Lower Implantation Potential as Determined by Results of Frozen Embryo Transfer

J.H. Check, B. Katsoff and J.K. Choe

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of OB/GYN, Division of Reproductive Endocrinology & Infertility, Camden, NJ, U.S.A.

Summary

One of the options for a woman who is hyper-responding and runs the risk of ovarian hyperstimulation protocol is to proceed with oocyte retrieval but defer fresh embryo transfer (ET) and freeze all embryos. However, this option would not be so advantageous if subsequent pregnancy rates (PRs) for frozen ET are inadequate. A study of first frozen ETs from women with >25 follicles or a serum estradiol (E2) >5000pg/mL found quite adequate ongoing/delivered PRs of 40.5%, 32.4%, and 16.7% for women aged ≤ 35 , 36-39, and 40-42, respectively. These PRs compare quite favorably for PRs following fresh ET for these age groups. These data thus suggest that despite the production of so many eggs, the quality of them in general is as good as women making less follicles.

Introduction

Theoretically, the more oocytes produced the better the chance of conception following oocyte retrieval and embryo transfer (ET) because one has a larger cohort of embryos from which to select the best embryos to transfer. However, clinical experience with hyper-responders shows the opposite result, i.e., a lower pregnancy rate (PR) following fresh ET.

There are several theoretical reasons for the observed lower PRs. The risk of ovarian hyperstimulation causes some physicians to try coasting, i.e., skipping several days of gonadotropin injections and the lack of combined exposure to some follicle stimulating hormone (FSH) or maybe just some luteinizing hormone (LH) has detrimental effect to the quality of the follicle.

Another possible mechanism for lower PRs in this group may be the tendency for the physician to get nervous and stop the gonadotropins and give the human chorionic gonadotropin (hCG) injection before the follicles are sufficiently mature.

Sometimes to reduce the risk of ovarian hyperstimulation syndrome (OHSS) only 5000 IU of hCG is given instead of 10,000 IU and possibly this dosage is insufficient for adequate luteal phase function. Similarly, the use of gonadotropin releasing hormone (GnRH) agonists, e.g., leuprolide acetate can advance meiosis and decrease the risk of OHSS but may not provide adequate luteal function (1,2).

There is the possibility that when so many follicles are available there has not been adequate elimination by the body of the worst follicles making it difficult for the embryologist to choose the best ones for transfer.

Another possibility is that there is evidence that hyperstimulation may adversely effect embryo implantation and possibly excessive hormonal levels magnify this effect (3-5).

One option to decrease the severity of OHSS is women who hyper-respond is to defer fresh ET and freeze all embryos. It is well known that pregnancy magnifies the duration and intensity of OHSS because of the continuous secretion of hCG.

The present study evaluated PRs and implantation rates following frozen ET in women who hyper-respond and deferred fresh ET. The outcome could provide some further insight as to the mechanism why PRs following fresh ET in women who hyper-respond are lower.

Materials and Methods

A retrospective review was performed on all patients during a 6 year time period who had all embryos frozen and fresh ET deferred. The clinical and ongoing/delivered PRs and implantation rates following their first frozen ET was determined. The PRs and implantation rates were evaluated according to 3 different age groups: ≤ 35 years, 36-39, and 40-42. Fresh ET was deferred if there was more than 25 follicles >10 mm and/or a serum estradiol (E2) level >5000 pg/mL.

The 2 pronuclear embryos were frozen after 24 hours using a simplified freezing protocol with 1,2 propanediol as the cryoprotectant and were thawed with a one-step removal of the cryoprotectant (6). Assisted embryo hatching was performed prior to the transfer (7).

The policy was to thaw twice as many embryos as the couple desired to transfer and then transfer the best ones based on blastomere number, fragmentation index, and symmetry and re-freeze any other decent embryos still remaining.

In the COH cycle knowing that all embryos were to be frozen we did not change our normal policy of waiting until 2 lead follicles have attained an average 20mm diameter before giving the hCG injection.

The women were treated with graduated oral and/or vaginal estradiol until adequate follicular length of 14 days and then progesterone (P) 200mg twice daily vaginal suppositories plus 100mg IM P was added during the luteal phase. Embryo transfer exclusively used day 3 embryos. The embryos were transferred on the fourth or fifth day of P supplementation.

Results

The clinical and ongoing/delivered PRs and implantation rates according to the 3 age groups are seen in Table 1. As might be expected there was a much smaller percentage of women age 40-42 who deferred fresh transfer because of risk of OHSS (4.6%, 30/663).

The clinical and ongoing delivered PRs were significantly higher ($p < .05$) in the youngest group compared to the intermediate group and oldest group. Nevertheless the clinical PRs of 40.5%, 32.4%, and 20.0%,

Table 1 - Outcome of frozen ETs in hyper-responding women deferring fresh ET

	<35	36-39	40-42
# transfers	491	142	30
# ET	1603	544	129
Ave. # ET	3.3	3.8	4.3
# pregnancies	247	58	9
# clinical	218	51	6
% clinical	44.4	35.9	20.0
# ongoing/delivered	199	46	5
% ongoing/delivered	40.5	32.4	16.7
# implanted	342	85	11
% implanted	21.3	15.6	8.5
# miscarriages	29	7	1
% miscarriages/clinical preg	13.3	13.7	16.7
# chemical	24	7	3
# ectopic	5	0	0
# twins	72	19	1
# triplets	23	6	2
# quads	2	1	0

respectively for groups 1-3 compares favorably to the fresh and frozen ETs recorded with SART during that same time period.

Interestingly, the miscarriage rates were similar in each age group (13.3%, 13.7%, and 16.7%) and thus the difference in ongoing/delivered PRs (viable past 16 weeks) was mostly related to higher clinical PRs. In fact, women aged 36-39 are not even more prone to have a chemical pregnancy (beta-hCG >100mIU/mL) not proceed to a chemical pregnancy (chemical PR/transfer for group 1 - 24/491, 4.8% and for group 2, 7/142, 4.8%).

Discussion

The demonstration of comparable clinical and ongoing/delivered PRs and implantation rates in this group of hyper-responders who defer fresh ET in favor of frozen ET to women able to proceed with fresh ET suggests that the one theory that the majority of oocytes produced by these women are of lesser quality, and the defect is their failure to undergo atresia, is not correct. Since our policy is only to thaw twice as many embryos as desired for transfer, the good PRs were not based on finding a small number of good embryos out of a large cohort.

All other theories to explain lower PRs in this group following fresh ET are still plausible. The possibility exists that the good PRs following frozen ET only applies to freezing 2 pronuclear embryos with this particular technique. Other IVF centers using a different cryopreservation protocol and freezing at a later embryo stage need to evaluate their own data individually.

References

1. CHECK JH, VETTER BH, WEISS W. Comparison of hCG versus GnRH analog for releasing oocytes following ultra-low-dose gonadotropin stimulation. *Gynecological Endocrinology* 7(2):115-22, 1993
2. CHECK JH, NAZARI A, BARNEA ER, WEISS W, VETTER BH. The efficacy of short term gonadotrophin releasing hormone agonists versus human chorionic gonadotrophin to enable oocyte release in gonadotrophin stimulated cycles. *Hum Reprod* 8:568-71, 1993.
3. CHECK JH, O'SHAUGHNESSY A, LURIE D, FISHER C, ADELSON HG. Evaluation of the mechanism for higher pregnancy rates in donor oocyte recipients by comparison of fresh with frozen embryo transfer pregnancy rates in a shared oocyte programme. *Hum Reprod* 10:3022-7, 1995.
4. CHECK JH, CHOE JK, KATSOFF D, SUMMERS-CHASE D, WILSON C. Controlled ovarian hyperstimulation adversely affects implantation following in vitro fertilization-embryo transfer. *J Assist Reprod Genet* 16:416-20, 1999.
5. CHECK JH, CHOE JK, NAZARI A, SUMMERS-CHASE D. Ovarian hyperstimulation can reduce uterine receptivity. A case report. *Clin Exp Obst Gyn* 27:89-91, 2000.

6. BAKER AF, CHECK JH, HOURANI CL. Survival and pregnancy rates of pronuclear stage human embryos cryopreserved and thawed using a single step addition and removal of cryoprotectants. Hum Reprod Update 2 (CD-ROM), 1997.
7. CHECK JH, HOOVER L, NAZARI A, O'SHAUGHNESSY A, SUMMERS D. The effect of assisted hatching on pregnancy rates after frozen embryo transfer. Fertil Steril 65:254-7, 1996.





