Original Article

Comparison of fresh versus frozen embryo transfer in women with polycystic ovary syndrome

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Abstract

Introduction: Transfer of fresh embryos is a usual practice but in women at risk of ovarian hyperstimulation due to excess follicle development, elective cryopreservation of all embryos followed by transfer in subsequent cycle is preferred. Fresh cycles have supraphysiological steroid levels which may alter the endometrial receptivity and probably affect placentation adversely whereas frozen embryo transfer is performed to the uterus after a programmed physiologic cycle of hormone replacement to prepare the endometrium.

Objective: To find out whether frozen embryo transfer in subsequent cycle is better than that in fresh transfer in women with polycystic ovary syndrome (PCOS) when human chorionic gonadotropin (hCG) is used as a trigger in antagonist cycles.

Study Design, Size, Duration: It is a prospective cohort study. Infertile women <35 years with the PCOS diagnosed by Rotterdam criteria who were undergoing their first *in vitro*Please check whether the suggested full form for the acronyms *in vitro* fertilization (IVF) and assisted reproductive techniques (ART) provided in the article is correct. fertilization cycle from 1st January 2015 to 28th February 2016 were included. Cycles complicated by ovarian hyperstimulation syndrome were excluded.

Participants/Materials, Setting, Methods: Women ($N = 126$) with terminal estradiol levels below 2500 pg/ml were triggered with recombinant hCG, and based on the number of retrieved oocytes, they were divided into two groups: Group A <15 oocytes retrieved had fresh embryo transfer on day 3 and Group B where >15 oocytes were retrieved, but all embryos were frozen on day 3 and transferred in subsequent cycle. Primary outcomes were clinical pregnancy rates and live birth rates. Secondary outcomes were fertilization, implantation and miscarriage rates.

Results: Group A had 73 fresh transfer, and Group B had 53 frozen embryo transfer. Both groups were comparable regarding age, body mass index, basal follicular stimulating hormone, antimullerian hormone and antral follicle count. Categorical data were represented as frequency and percentages, differences in these measures between the groups were compared using chi-square tests, and quantitative data were analyzed by using student *t* test. Clinical pregnancy rates (Group A: 38.4% versus Group B: 41.5%, $P = 0.88$) and live birth rate (Group A: 26.0% versus Group B: 33.9%, $P = 0.25$) were slightly higher in Group B though not statistically significant. The miscarriage rate in both the groups was comparable (Group A: 15.1% and Group B: 15.1%, $P = 0.8$).

Keywords: Frozen embryo transfer (FET) in PCOS, fresh versus frozen embryo transfer, OHSS, terminal estradiol level

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Access this article online

Quick Response Code:

Website: www.fertilityscienceresearch.org

DOI: 10.4103/fsr.fsr_12_18

How to cite this article: Nayar KD, Gupta RA, Gupta M, Singh M, Kant G, Nayar D. Comparison of fresh versus frozen embryo transfer in women with polycystic ovary syndrome. Fertil Sci Res 2017;4:102-5.

INTRODUCTION

In vitro fertilization (IVF) is a commonly performed assisted reproductive technology procedure. There are concerns about the maternal and fetal safety of the procedure. Ovarian hyperstimulation syndrome (OHSS) is a life-threatening complication. Prevention of OHSS in high-risk populations has become a major goal in the research of controlled ovarian stimulation (COS) in IVF programs. Withholding human chorionic gonadotropin (hCG) and cycle cancellation is considered the safest option but carries adverse emotional and financial implications. Withholding treatment for several days (coasting) has been shown to diminish the incidence and severity of OHSS without compromising pregnancy rates.[1] The introduction of GnRH agonist trigger does prevent OHSS but compromises on pregnancy rates due to accelerated leuteolysis, which can be taken care of with dual trigger.[2,3]

Frozen embryo transfer is thought to give better results as compared to fresh transfer probably due to disturbed receptivity due to elevated steroidal levels in stimulated cycles.[4] In polycystic ovary syndrome (PCOS) females the endometrial receptivity is also disturbed due to reduced expression of $\alpha_v\beta_3$ integrin and glycodelin.[5] Observational studies have shown that rates of singleton pregnancy are higher after frozen embryo transfer than after fresh embryo transfer.[6] A meta-analysis of 11 observational studies showed that pregnancies from frozen embryo transfer were associated with lower risks of preterm birth, low birth weight and perinatal death than were pregnancies from fresh embryo transfer.[7] Subsequently, small, single-center, randomized studies comparing the two procedures have shown better ongoing pregnancy rates with frozen embryo transfer.[8] However, data are lacking from randomized trials to determine any differences between the two procedures in live birth rates and pregnancy complications.

PARTICIPANTS AND METHODS

Study design, size, duration

This study was performed at Akanksha IVF centre. Women with the PCOS who were undergoing their first IVF cycle from 1st January 2015 to 28th February 2016 were eligible.

To diagnose the PCOS, we used modified Rotterdam criteria,[9] which included menstrual abnormalities (irregular uterine bleeding, oligomenorrhea or amenorrhea) combined with either hyperandrogenism or polycystic ovaries. Hyperandrogenism was diagnosed on the basis of either hirsutism or hyperandrogenemia. Hirsutism was determined by means of a modified Ferriman–Gallwey score of more than 6 (on a scale of 0–36, with higher scores indicating increased hair growth) at the screening examination.[10] Hyperandrogenemia was defined as an elevated total testosterone level according to local laboratory criteria. Polycystic ovaries were defined as the presence of either an ovary containing 12 or more antral follicles measuring 2–9 mm in diameter or an increased ovarian volume ($>10\,cm^3$). Other causes of hyperandrogenism and ovulation dysfunction — including tumors, congenital adrenal hyperplasia, hyperprolactinemia and thyroid dysfunction were ruled out. All the patients received a standardized ovarian stimulation regimen, oocyte retrieval and fertilization, followed by a planned transfer of up to two day-3 embryos. In brief, recombinant follicle-stimulating hormone (Follisurge, Intas) at a daily dose of 150 IU for patients weighing 60 kg or less and 187.5 IU for those weighing more than 60 kg was started on day 2 or 3 of the menstrual cycle. These doses were adjusted according to the ovarian response, as monitored on ultrasonography and the measurement of serum sex steroids. Gonadotropin-releasing hormone antagonist (Cetrolix, Intas) at a daily dose of 250 μg was started on day 6 of gonadotropin. Serum estradiol levels were measured on the day of trigger, if less than 2500 pg/ml recombinant hCG (Ovitrelle, Merck Serono) at a dose of 250 μg (6500 IU), and GnRH agonist was administered to induce oocyte maturation when serum estradiol level was more than 2500 pg/ml. Only women with recombinant human chorionic gonadotropin trigger were included in the study. Oocyte retrieval was performed 34–36 h later. On the day of oocyte retrieval, based on the number of retrieved participants, they were divided into two groups: Group A <15 oocytes retrieved had fresh embryo transfer on day 3 and Group B where >15 oocytes were retrieved, all embryos were frozen on day 3, and transferred in subsequent cycle.

For patients who were assigned to the fresh-embryo group, micronized progesterone pessary at a daily dose of 400 mg twice a day vaginally was started for luteal-phase support, beginning on the day of oocyte retrieval until 10 weeks after conception. For patients who were assigned to the frozen-embryo group, no luteal-phase support was administered after oocyte retrieval, and day-3 embryos were cryopreserved for later transfer. Oral estradiol valerate (Progynova) was administered for endometrial preparation on day 2 or 3 of the subsequent menstrual cycle after oocyte retrieval. Micronized progesterone pessary at a daily dose of

400 mg twice a day vaginally was added when the endometrial thickness reached 7 mm or more. After 4 days of the progesterone regimen, two day-3 frozen embryos were thawed and transferred. The luteal-phase support with estradiol valerate and micronized progesterone pessary for endometrium preparation continued until 10 weeks after conception. Cycles complicated by OHSS were excluded.

Embryo culture, evaluation and selection for transfer

The oocytes were inseminated approximately 4–6 h after follicular aspiration by a conventional method or intracytoplasmic sperm injection, according to the sperm quality. Morphologic criteria were used for embryo scoring. On day 3, two high-quality embryos were picked out for fresh transfer or cryopreserved by means of vitrification in the group undergoing frozen embryo transfer. Biochemical pregnancy was defined as a human chorionic gonadotropin level of more than 10 mIU per milliliter, as measured at 14 days after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac in the uterine cavity at 35 days after embryo transfer, as detected on ultrasonography. Ongoing pregnancy was defined as the presence of a fetus with heart motion at 11–12 weeks of gestation. All pregnancy and neonatal outcomes were obtained through a review of medical records. Moderate and severe OHSSs were defined according to accepted criteria.

Study outcomes

Primary outcomes were clinical pregnancy rates and live birth rates. Secondary outcome were miscarriage rate and OHSS incidence.

Statistical analysis

Categorical data were represented as frequency and percentage; differences in these measures between the study groups were assessed by means of chi-square analysis, with the use of Fisher's exact test for expected frequencies of less than. Continuous data were expressed as means (±SD, standard deviation), with a Wilcoxon rank-sum test for between-group differences. The statistical analysis was performed using Statistical Package for the Social Sciences software (SPSS Inc., Chicago, IL, United States).

RESULTS

Study patients

The baseline characteristics of the patients were similar in the two study groups [Table 1].

Group A had 73 fresh transfer and Group B had 53 frozen embryo transfer. Both groups were comparable regarding age, body mass index (BMI), basal follicular stimulating hormone, antimullerian hormone (AMH) and antral follicle count. Categorical data were represented as frequency and percentages, differences in these measures between the groups were compared using chi-square tests and quantitative data by student *t* test. Clinical pregnancy rates (Group A: 38.4% versus Group B: 41.5%, $P = 0.88$), live birth rate (Group A: 26.0% versus Group B: 33.9%, $P = 0.25$) were slightly higher in Group B though not statistically significant. The respective miscarriage rates in both the groups were comparable (Group A: 15.1% and Group B: 15.1%, $P = 0.8$) [Table 2].

DISCUSSION

There is a continuous strive to improve pregnancy outcomes in IVF cycle. Also in women with PCOS IVF cycle is sometimes segmented to avoid the complication of OHSS. The introduction of GnRH agonist trigger followed by freeze all has almost

Table 1: Characteristics of the patients at baseline

	Group A (fresh ET)	Group B (frozen ET)	*P*-value
Age	32.2 ± 3.43	31.62 ± 3.69	
BMI	23.8 ± 3.8	23.9 ± 3.6	
Mean duration of infertility	5.2 ± 2.2	4.9 ± 3.2	NS
Mean antral follicle count	28.2 ± 7.8	29.1 ± 6.6	
Mean S. AMH (ng/ml)	5.7 ± 0.4	6.1 ± 0.9	

ET, endometrial thickenss; S. AMH, serum anti mullerian hormone.

Table 2: Outcomes of controlled ovarian hyperstimulation

	Group A (fresh ET)	Percentage	Group B (frozen ET)	Percentage	*P*-value
Mean dose of gonadotropin (IU)	1300		1350		0.78
Terminal estradiol (pg/ml)	2125.39		2258.49		0.67
Mean number of retrieved eggs	13.95		18.73		0.60
Pregnancy rate	30	41.09	26	49.05	0.37
Clinical pregnancy rate	28	38.35	22	41.50	0.88
Live birth rate	19	26.02	18	33.96	0.25
Miscarriage rate	11	15.06	8	15.09	0.8
OHSS	0		0		

ET, endometrial thickenss.

completely eliminated the risk of OHSS. It is seen that with hCG trigger and comparable steroid levels the yield of oocytes can be different. At an average estradiol of 2258.49 pg/ml 18.73 oocytes were retrieved in Group B. It is known that elevated estradiol levels affect the endometrial receptivity. More number of oocytes retrieved in PCOS women with average estradiol levels may affect the receptivity negatively more than when a lesser number of oocytes are retrieved. In absence of any definitive biochemical tests, the decision whether to go ahead with fresh transfer or freeze all is on the discretion of the consultant. Here in, we found out that with average estradiol levels (<2500 pg/ml) the number of retrieved oocytes guided to freeze all and transfer in subsequent cycle, yielding better pregnancy and live birth rates even in hCG-triggered cycles.

Wider implications of the findings

Performing frozen embryo transfer in PCOS women with average estradiol levels yet higher number of recovered oocytes is better than fresh transfer, implying adopting practice of routine elective freezing of embryos and transfer in subsequent cycle for better reproductive outcomes even in hCG-triggered cycles in PCOS women.

Limitations, reasons for caution

Due to the small sample size, the study lacks power, which is the main limitation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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