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Original Research Article

Obstetric and perinatal outcomes in pregnancies occurring as a result of Fresh and Thawed frozen embryo transfer

Nishita Shah*, K. Jayakrishnan

Department of Obstetrics and Gynecology, KJK Hospital, Fertility Research and Gynec Center, Trivandrum, Kerala, India

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***Correspondence:**
Dr. Nishita Shah,
E-mail: nkdesai.89@gmail.com

ABSTRACT

Background: In vitro fertilization is a known independent risk factor for adverse perinatal outcomes. To explore obstetric and perinatal outcomes in pregnancies occurring as a result of fresh and thawed frozen embryo transfer.
Methods: Retrospective observational study with 208 patients. A period of 2 years from October 2015 to October 2017. Tertiary care Fertility, Laparoscopy and research centre. All pregnancies conceived by IVF (n= 208) between the study period were included. The patients were grouped by fresh (n= 108) versus frozen (n= 100) embryo transfer. Patients conceived with donor embryo transfer were excluded. Primary outcomes were missed abortions, ectopic pregnancy, live births. Incidence singleton pregnancies and multiple gestations, preterm delivery, birth weight, an obstetric complication includes gestational hypertension, preeclampsia, gestational DM, placenta previa.
Results: A total 208 patient analyzed who conceived with IVF treatments, among them 108 patients were in Fresh ET group and 100 were in Frozen ET group. The incidence of Ectopic Pregnancy was more in fresh ET as compared to Frozen ET (14.8%, 02% respectively, p value <0.05) whereas that of missed abortions were more in Frozen ET (22% versus 11.1%, p value 0.03). There were no significant differences in obstetric and perinatal outcomes in both groups.
Conclusions: In this study of IVF pregnancies, adverse obstetric and neonatal outcomes did not differ between fresh and frozen embryo transfers. Literature tells that there may be an increased risk of preeclampsia and large for gestational age babies in pregnancies conceiving after frozen embryo transfer. So freeze all policy should be applied to only indicated cases and not to all because both the groups having similar outcomes.

Keywords: Ectopic pregnancy, Fresh and frozen ET, Missed Miscarriage, Obstetric and perinatal outcomes

INTRODUCTION

Since the birth of Louise Brown in 1978, more than 6 million babies have been born as a result of IVF and intra cytoplasmic sperm injection (ICSI). Today, nearly one in six couples faces fertility issues, as they fail to achieve a clinical pregnancy even after regular copulation.[1,2] Consequently, couples are turning to assisted reproductive technology (ART) to become pregnant, which will hopefully result in the birth of a healthy baby. Conventionally, the aim has been to transfer the best-quality embryo or embryos in a fresh treatment cycle; any spare embryos are frozen for subsequent use. In 1983, the first frozen-thawed embryo was transferred by Trounson, which resulted in a successful pregnancy.[3] Since then, continuous advancements in cryopreservation techniques have been made and at present, the quality and potential for frozen-thawed embryo implantation is comparable to those of fresh embryos.[4,5]

With refinement of technology in recent years, the numbers of thawed frozen embryo transfers have increased, as have pregnancy rates associated with them.[6,7]

Although fresh embryo transfer is still the norm in most in vitro fertilization (IVF) treatments, as it involves a shorter process that leads to pregnancy, this method is related to increased hormone levels due to controlled ovarian stimulation (COS). The supra-physiologic hormonal levels observed during COS results in a suboptimal uterine environment that may negatively impact embryo implantation and placentation, eventually culminating to untoward obstetrical and perinatal outcomes.[8,9] Conversely, FET cultivates better environmental conditions within the uterus during embryo transfer, leading to improved endometrial receptivity.[10,11] This better uterine environment may be related with better placentation during a FET cycle, leading to improved obstetric outcomes when compared to fresh transfer cycles.[12,13]

The knowledge concerning the differences in obstetrical and neonatal outcome between cryopreserved and fresh embryos is increasing. Literature suggests that the health of neonates born after FET is similar or even more favorable compared to the health of children born after fresh embryo transfer.[14,15]

Recent studies showed that neonates born after FET have decreased risks of preterm birth, LBW and being small for gestational age (SGA, below 10th percentile) compared to fresh ET.[12,14-17] An increased risk of high birth weight and being large for gestational age (LGA, above 90th percentile) was reported as well.[14-18] A higher risk of congenital malformations for infants born after cryopreservation compared to fresh ET is also described.[19,20]

Recently published meta-analysis comparing obstetric outcomes in pregnancies after fresh and FET did not report major obstetric outcomes such as pregnancy-induced hypertension (PIH), pre-eclampsia, placenta previa, and placenta accreta.[12,21] So we have done a retrospective observational study to evaluate obstetric and perinatal outcomes in pregnancies occurring as a result of fresh and thawed frozen embryo transfer.

METHODS

It is a retrospective observational study carried out at Tertiary care Fertility, Laparoscopy and research centre, between periods of 2 years from October 2015 to October 2017. Total 208 patients were included in the study.

Inclusion criteria

- All pregnancies conceived by IVF (n=208) between the study period were included. The patients were grouped by fresh (n=108) versus frozen (n=100) embryo transfer.

Exclusion criteria

- Patients conceived with donor embryo, donor sperm and ovum donation were excluded from the study.

Missed miscarriage, ectopic pregnancy, live births were considered as primary outcomes and incidence singleton pregnancies and multiple gestations, preterm delivery, birth weight, obstetric complications includes gestational hypertension, preeclampsia, gestational DM, placenta previa were taken as secondary outcomes in the study.

Statistical analysis

For statistical analysis collected data was entered in MS Excel file. Descriptive statistics like frequency, percentage, mean, SD were calculated for summarizing data. Pearson’s Chi-Square test was applied to check association between two categorical data. Logistic regression was run to estimate Fresh and Frozen Embryo Transfer. Throughout the result, significance level was set at 5%.

RESULTS

Minimum age of the patients undergoing treatment was 22 years and maximum was 47 years with the mean age of 32 years.

Table 1 details the baseline characteristics between the two groups. Minimum age of the patients undergoing treatment was 22 year and maximum was 47 years with the mean age of 32 year. There was a statistically significant difference in the two groups in terms of women who underwent previous IVF treatment.

The proportion of women who had undergone previous treatment was significantly higher in the thawed frozen embryo transfer group (70% versus 33.3%). This is not surprising: thawed frozen embryos are generally transferred either after fresh embryo transfer is unsuccessful or for when a couple wishes to have a second baby using their pool of frozen embryos. Freeze all policy will be applied to only those patient who are at risk of OHSS, raised progesterone on the trigger day and endometrium less than 7 mm according to the protocol of our institution.

61.1% 0f patient in fresh ET and 68% of patient in frozen ET were below 34 years of age. 72.2% cases of fresh ET and 75% cases on Frozen ET have primary infertility. 5 patients in fresh group and 3 patients in a frozen group had a previous live birth. In most of the cases in both the group two embryo were transferred. Average duration of infertility in fresh transfer group is 6.4 years and frozen group is 6.3 years. Most common indication of infertility treatment in fresh ET group was Male factor infertility while in Frozen group was PCOD.

Table 1: Comparison of baseline characteristics.

		Fresh embryo transfer (n=108)	Frozen embryo transfer (n=100)	p-value
Age group	<=34	66 (61.1%)	68 (68%)	0.779
	35-37	27 (25%)	19 (19%)	
	38-39	9 (8.3%)	7 (7%)	
	40-42	5 (4.6%)	4 (4%)	
	>42	1 (0.9%)	2 (2%)	
Previous IVF	Yes	36 (33.3%)	70 (70%)	<0.001
	No	72 (66.7%)	30 (30%)	
Type of infertility	Primary	78 (72.2%)	75 (75%)	0.753
	Secondary	30 (27.8%)	25 (25%)	
Previous live birth	Yes	5 (4.6%)	3 (3%)	0.723
	No	103 (95.4%)	97 (97%)	
No of embryos transferred	1	2 (1.9%)	4 (4%)	0.160
	2	92 (85.2%)	90 (90%)	
	>=3	14 (13%)	6 (6%)	
Duration of infertility	0-4	33 (30.6%)	40 (40%)	0.478
	5-9	50 (46.3%)	39 (39%)	
	10-14	23 (21.3%)	18 (18%)	
	15-20	2 (1.9%)	3 (3%)	
Indications	Tubal	6 (5.6%)	6 (6%)	0.017
	Male Factor	30 (28%)	26 (26%)	
	Unexplained	19 (17.8%)	12 (12%)	
	Endometriosis	15 (14%)	7 (7%)	
	PCOD	23 (21.5%)	32 (32%)	
	Low AMH	14 (13.1%)	9 (9%)	
	Others	0 (0%)	8 (8%)	

Table 2: Live birth rate.

		Group		Total (N= 208)	P- value
		Fresh embryo transfer (N= 100)	Frozen embryo transfer (N= 108)		
Live Birth	Yes	67	67	134	0.455
		62.0%	67.0%	64.4%	
	No	41	33	74	
		38.0%	33.0%	35.6%	

Table 3: Ectopic pregnancy.

		Group		Total			
		Fresh embryo transfer	Frozen embryo transfer				
Ectopic pregnancy	Yes	16	2	18			
		14.8%	2.0%	8.7%	Pearson CHI-Square Test Value	df	P- value
	No	92	98	190	10.787	1	0.001
		85.2%	98.0%	91.3%			
Total		**108**	**100**	**208**			
		100.0%	**100.0%**	**100.0%**			

In recent years, a freeze-all strategy has been suggested as a way to further improve IVF outcomes. By adopting this strategy, the potential deleterious effects of controlled ovarian stimulation (COS) on the endometrium could be avoided, and better results would be obtained. Live birth in fresh group was 62% and in frozen group was 67%. Table 2 suggesting that there is no significant difference in the live birth rate in both the groups (P-value 0.45).

Table 3 showing ectopic pregnancy was found significantly more in fresh ET group as compared to Frozen ET. (14.8% versus 2%, p-value 0.001). It was observed that the subfertility requiring ART treatment is one of the independent risk factors for ectopic pregnancy. Among pregnancies following ART treatment, the reproductive health characteristics of women including tubal factor subfertility, endometriosis, previous pelvic inflammatory disease and previous ectopic pregnancy history have been identified as the most prominent risk factors for ectopic pregnancy.

Table 4: Missed miscarriage.

	Fresh embryo transfer (n=108)	Frozen embryo transfer (n=100)	p-value	RR
Missed miscarriage	12 (11.1%)	22 (22%)	0.034	0.640

Table 5: Obstetric outcomes of fresh and frozen ET.

	Fresh embryo transfer (n=108)	Frozen embryo transfer (n=100)	p-value	RR
PIH	12 (11.1%)	14 (14%)	0.529	0.565
Preeclampsia	4 (3.7%)	6 (6%)	0.439	0.762
GDM	21 (19.4%)	18 (18%)	0.790	1.046
Placenta previa	4 (3.4%)	0 (0%)	0.052	1.962
PPROM	8 (7.4%)	8 (8%)	0.873	0.960

Table 6: Neonatal outcomes.

		Fresh embryo transfer (n=67)	Frozen embryo transfer (n=67)	p-value	Un standardized OR	Accuracy in prediction
BW	Normal	42 (62.7%)	37 (55.2%)	0.380	1	53.7%
	LBW	25 (37.3%)	30 (44.8%)		1.362	
Gestational age (wk)	Normal	48 (71.6%)	46 (68.7%)	0.475	1	55%
	Preterm	16 (23.9%)	20 (29.9%)		1.304	
	Very preterm	3 (4.5%)	1 (1.5%)		0.348	

Table 4 indicate that rate of missed miscarriage is found to be more in frozen ET group. 12 cases in the fresh ET and 22 cases in the frozen ET group were ended in Missed Miscarriage which was statistically significant.

Table 5 showing obstetric complications in both the groups. Gestational hypertension was found in 14% of the cases in frozen ET while only in 11% in fresh ET. Preeclampsia also found more in frozen ET as compared to fresh ET though statistically not significant. GDM found in 21 cases as compared to 18 cases in both groups respectively.

Preterm delivery was defined as the delivery before 37 completed weeks of gestation. There was no statistical difference in the risk of preterm delivery in pregnancies occurring as a consequence of thawed frozen embryo transfer in comparison with those following fresh embryo transfers as shown in table 6. (29.9% versus 23.9%, p-value 0.47). Low birth weight is considered when birth weight is less than 2.5kg. While comparing two groups there was no statistical difference found. (37.3% in fresh ET versus 44.8% in frozen ET, p- value 0.38). Mean birth weight in fresh ET is 2.51kg and in frozen ET is 2.33kg.

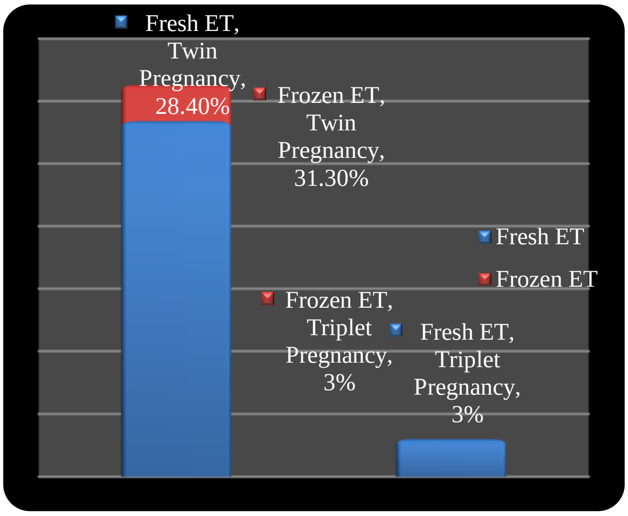

Figure 1: Multiple pregnancy.

Figure 1 showing the incidence of multiple pregnancy in both the group. Frozen ET group has slightly raised proportion of twin gestation though not statistically significant (31.30% versus 28.40%, p-value 0.93). 20 babies in the fresh and 25 in the frozen group required NICU admission after delivery seen in Figure 2.

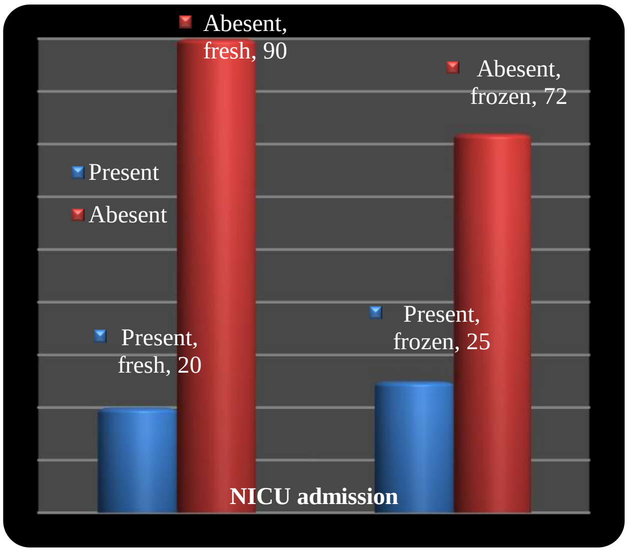

Figure 3: NICU admission.

DISCUSSION

In this study, we have done a retrospective analysis of the effect of FET and fresh embryo transfer on the risks of developing major obstetric and neonatal complications in pregnancies following the use of ART.

The main outcome of the study is there is no significant difference in live birth rate in both the group. Incidence of ectopic pregnancy found significant in fresh ET group and missed miscarriage found in frozen group.

A retrospective cohort study of 13426 cycles comparing live birth rate after fresh or frozen-thawed embryo transfers in relation to maternal age conclude that in every age-group, frozen cleavage-stage embryo transfers had lower LBR than that of fresh cleavage-stage embryo transfers.[22]

Another study comparing fresh and frozen embryo cycles showing that fresh embryo transfer cycles were associated with improved clinical pregnancy and live birth rates compared to previously frozen embryo transfer cycles. The miscarriage rate and the multiple pregnancy rates were similar in both groups.[23]

A single-center, randomized, controlled trial, assigned 782 infertile women without the polycystic ovary syndrome into fresh and frozen embryo transfer group conclude that the transfer of frozen embryos did not result in significantly higher rates of ongoing pregnancy or live birth than the transfer of fresh embryos.[3] this results are similar to our study.[24]

Retrospective historical cohort study conducted to evaluate whether the uterine environment is associated with the risk of ectopic implantation by comparing outcomes of fresh and frozen-thawed embryo transfers found that Embryo transfers in frozen cycle, were associated with lower rates of Ectopic pregnancy compared with fresh autologous cycles, suggesting that a difference in the tubal-uterine environment contributes to abnormal implantation after IVF.[25]

The increased risk of Ectopic pregnancy after fresh embryo transfers with autologous oocytes may be related to the effect of supraphysiologic hormonal levels on uterine contractility or endometrial receptivity.[26-31] Another possible mechanism may be related to multifollicular ovulation and the oocyte retrieval procedure itself, which could contribute to both uterine contractility and release of implantation mediators adjacent to the fallopian tube.[32,33] The role of inflammation in ectopic pregnancy is also well known, and could help explain our findings of Increased odds of EP in fresh ET group.

There is no significant difference in obstetric complications in both the groups in our study.

A systematic review and meta-analysis on Obstetric outcomes after fresh versus frozen-thawed embryo Transfers searched 654 papers and showing that when comparing pregnancies that arose from FET or fresh embryo transfer, there was an increase in the risk of obstetric complications in pregnancies resulting from FET when compared to those emerging from fresh embryo transfers in PIH (aOR 1.82; 95% CI 1.24-2.68), pre-eclampsia (aOR 1.32, 95% CI 1.07, 1.63), and placenta accreta (aOR 3.51, 95% CI 2.04-6.05).[34]

A retrospective cohort study compared the frequency of preeclampsia diagnosis for cryopreserved-warmed versus fresh ET in 15,937 births from ART found that Among pregnancies conceived with autologous eggs resulting in singletons, preeclampsia was greater after cryopreserved-warmed versus fresh ET (7.51% versus 4.29%, adjusted odds ratio = 2.17 [95% CI 1.67-2.82]) and among twin pregnancies, the frequency of preeclampsia with severe features (9.26% versus 5.70%) and preeclampsia with preterm delivery (14.81% versus 11.74%) was higher after cryopreserved versus fresh transfers.[35] In our study also gestational hypertension and preeclampsia were found more in Frozen ET group though statistically not significant.

Low levels of E2 in early primate pregnancy allow for migration of extravillous trophoblasts into uterine spiral arteries with artery remodelling; elevation of E2 later in pregnancy prevents further remodelling. If E2 is elevated prematurely, extravillous trophoblast invasion of spiral arteries is suppressed. It is possible that prematurely cryopreserved-warmed transfers may contribute to more frequent preeclampsia in ART pregnancies compared with spontaneous conceptions.[35]

In our study there is no significant difference in the neonatal outcomes when comparing both groups. But recent studies found that there is a higher risk of large for gestational age babies after FET. A recent retrospective cohort study to explore obstetric and perinatal outcomes in singleton pregnancies in fresh and Frozen ET group conclude that the findings of low birth and very low birth weight after thawed frozen embryo transfer are consistent with the literature but they highlight the possibility of high birth weight in this babies.[36] In our study we didn't found any significant difference in the birth weight in both the groups.

CONCLUSION

In this study of IVF pregnancies, adverse obstetric and neonatal outcomes did not differ between fresh and frozen embryo transfers. Literature tells that there may be an increased risk of preeclampsia and large for gestational age babies in pregnancies conceiving after frozen embryo transfer. So freeze all policy should be applied to only indicated cases and not to all because both the groups having similar outcomes.

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