Original Article

Fresh Versus Frozen Embryo Transfer in Women with Repeated Implantation Failure

Saeideh Dashti[1], Sahereh Arabian[2], Robab Davar[1]

[1]Research and Clinical Center for Infertility, Yazd Reproductive Sciences Institute, Shahid Sadoughi, University of Medical Sciences, Yazd, Iran, [2]Abnormal Uterine Bleeding Research Center, Semnan University of Medical Sciences, Semnan, Iran

Abstract

Background: To compare the outcomes of fresh embryo transfer (ET) versus frozen ET (FET) in women with recurrent implantation failure (RIF).

Materials and Methods: This retrospective cohort study was performed at Yazd Reproductive Sciences Institute. A total of 498 cycles, including 418 FET cycles and 80 fresh cycles, from women with RIF were reviewed between February 2020 and February 2023. The chemical and clinical pregnancy rates and live birth rate were compared.

Results: FET cycles demonstrated significantly higher rates of both chemical (29.7% vs 13.8%, $P = 0.002$) and clinical pregnancy (20.6% vs 10.0%, $P = 0.027$) compared to fresh ET cycles. The live birth rate in the frozen transfer group was higher compared to the fresh transfer group, but the difference was not statistically significant (8.7% vs 4.9%, P value = 0.127).

Conclusions: Our findings showed that FET cycles may be associated with improved pregnancy rates in women with RIF.

Keywords: Embryo transfer, implantation, pregnancy rate

Address for correspondence: Dr. Robab Davar, Research and Clinical Center for Infertility, Yazd Reproductive Sciences Institute, Bouali Ave., Safaeyeh - 8916877391, Yazd, Iran.
E-mail: r_davar@yahoo.com
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Introduction

Despite progress in laboratory techniques and therapeutic strategies within assisted reproductive technology (ART), a significant number of individuals continue to encounter with infertility. Implantation is the first step for successful pregnancy achieved by communication between embryo and endometrium. So far, various definitions have been provided for implantation failure. There is no consensus on accepted definition of recurrent implantation failure (RIF). Some studies considered RIF when more than two or three transfers with good-quality embryos failed to achieve pregnancy. [1,2]

RIF is a concerning clinical issue that impacts approximately 10% of ART cycles.[3-5] Some reasons considered to be responsible for this phenomenon include poor embryonic quality, insufficient endometrial receptivity, or both.[6-8] The process of embryo implantation, which is influenced by ovarian hormones, needs a viable embryo, a receptive endometrium, and reciprocal interactions between the embryo and endometrium.[5,9] Supraphysiological hormone levels during the follicular stage of controlled ovarian stimulation may lead to decreased endometrial receptivity and an altered uterine environment, resulting in a decreased implantation rate in fresh embryo transfer (ET) cycles and a decreased likelihood of pregnancy.[10] In an effort to create a more physiologically suitable environment for ET and enhance implantation, numerous studies have proposed a frozen-all policy that embryos are cryopreserved to be transferred in

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the subsequent frozen-thawed cycle. Frozen-thawed embryo transfer may improve implantation.[11,12] To date, there are a few published data regarding the outcome of frozen ET (FET) in patients with RIF; therefore, in hopes of establishing a new approach for RIF management, we conducted this study to compare outcomes of fresh ET versus FET in women suffering recurrent implantation failure.

Materials and Methods

We conducted a retrospective study on women with RIF at the Yazd Reproductive Sciences Institute between February 2020 and February 2023. The data of 498 ET cycles in 430 infertile women aged 18-45 years with a history of at least two implantation failures were extracted from medical records. The inclusion criteria were women aged 18–45 years with a history of at least two implantation failures. Exclusion criteria included ovarian stimulation using the agonist protocol, endometrial preparation using a natural or stimulated cycle, the presence of uterine anomalies, and severe male factor infertility. Outcomes were compared between fresh and frozen cycles.

Ovarian stimulation and FET cycle protocol

For ovarian stimulation, all women underwent antagonist protocol. The gonadotropin dose was adjusted according to the women's age, antral follicular count, and AMH levels.[13] Endometrial preparation for FET was done by oral estradiol valerate 6 mg starting on the second day of cycle. When the endometrial thickness reached at least 7.5 mm, progesterone administration began as vaginal progesterone 400 mg twice a day. [2,14]

Statistical analysis

The statistical package for the social science version 26 for Windows (SPSS Inc, Chicago, IL, USA) was applied for data analysis. For continuous variables, Student's t-test was used to compare differences between groups assuming normal distribution. Alternatively, the Mann–Whitney U test was used if normality was not assumed. Categorical variables were analyzed using the Chi-square test for larger sample sizes or the Fisher's exact test for smaller sample sizes or sparse data. Logistic regression was used for adjusting confounding variables considering chemical pregnancy rates. Data were presented as mean ± SD for continuous variables and frequency (%) for categorical variables. A significance level of $P < 0.05$ was used in this study.

Results

A total of 498 embryo transfer cycles in 430 women were analyzed, of which 418 were FET cycles, and the remaining 80 cycles were fresh ET cycles. Baseline characteristics of the two groups, including body mass index (BMI), infertility type, and infertility duration, were comparable, as shown in Table 1 (P value > 0.05). Women in the FET group were significantly younger than those in the fresh group (32.79 vs 36.04, P value = 0.000). Cycle characteristics are shown in Table 2. Pregnancy outcomes revealed significantly higher chemical (29.7% vs 13.8%, P value = 0.002) and clinical (20.6% vs 10.0%, P value = 0.027) pregnancy rates in the FET group compared to the fresh group. The live birth rate in the frozen transfer group was higher compared to the fresh transfer group, but the difference was not statistically significant (8.7% vs 4.9%, P value = 0.127) [Table 3].

Based on logistic regression analysis, the likelihood of chemical pregnancy was increased by 2.33 times using FET compared to fresh ET. Multivariable logistic regression analysis indicated that after adjusting for age, AMH, and endometrial thickness, FET significantly increases the likelihood of chemical or clinical pregnancy compared to fresh ET [Table 4].

Discussion

The present study aimed to compare ART outcomes between fresh ET and FET in women with recurrent implantation failure. The findings demonstrated a significantly higher rate of both chemical and clinical pregnancy in the FET group compared to the fresh ET group. This observation aligns with previous studies suggesting that FET might be a beneficial strategy for patients with RIF.[7,15-17]

The improved outcomes in the FET group could be attributed to several factors. One potential explanation is the creation of a more favorable uterine environment by delaying ET. The controlled ovarian hyperstimulation (COH) process used in fresh cycles can lead to supraphysiological hormone levels, potentially impairing endometrial receptivity.[6,18] By allowing the endometrium to recover in a natural cycle before performing FET, a more receptive uterine environment may be achieved, enhancing implantation chances.[19-21]

Another possibility is the selection bias inherent in the FET group. Women undergoing FET often have a longer history of infertility and multiple failed implantation attempts.[22,23] This implies a more rigorous selection process for embryos as only the good-quality embryos are typically cryopreserved.[24] Consequently, the FET group may have a higher proportion of high-quality embryos, contributing to the observed increased pregnancy rates.

Furthermore, the significant differences in age and AMH levels between the two groups warrant consideration. Younger age and higher AMH levels are generally associated with better reproductive outcomes. The FET group in our study exhibited both these favorable factors, which could have influenced the results. To address these biases, further adjusted analyses controlling for age and AMH are performed.

Our study suggests a potential benefit of FET for women with RIF. The retrospective design and inherent selection bias restrict the ability to establish a causal relationship between FET and improved outcomes. In conclusion, our findings indicate that FET may be a promising approach for women with RIF. The limitation of this study is its retrospective design. A prospective study with a larger sample size is recommended.

Table 1: Baseline characteristics of study groups

Variable		Fresh cycle *n*=80	FET cycle *n*=418	*P*
Female Age, years*		36.04±4.23	32.79±5.20	0.000**
BMI* kg/m^2		26.44±4.58	25.90±3.73	0.255**
Type of Infertility (%)	Primary	54 (67.5%)	295 (70.6%)	0.582*****
	Secondary	26 (32.5%)	123 (29.4%)	
Duration of Infertility, years*		7.03±4.37	7.42±4.22	0.454**
		6.00 (7)	7.00 (6)	
AMH***		3.05±2.36	5.90±4.50	0.000****
		2.65 (2.93)	4.50 (4.53)	

*Data presented as Mean±SD. **Independent Samples *t*-Tests. ***Data presented as Mean±SD and Median (Interquartile Range). ****Mann–Whitney Test. *****Chi-Square Tests

Table 2: Cycle characteristics of study groups

Variable	Fresh cycle *n*=80	FET cycle *n*=418	*P*
Endometrial Thickness (mm)*	8.74±1.84	8.97±1.41	0.006**
	8.00 (1.1)	8.70 (1.7)	
No. of Transferred Embryos*	1.78±0.42	1.89±0.31	0.005**
	2.00 (0)	2.00 (0)	
No. of Implantation Failures*	3.60±1.05	3.58±0.97	0.839**
	3.00 (1)	3.00 (1)	

*Data presented as Mean±SD and Median (Interquartile Range). **Mann–Whitney Test

Table 3: ART Outcomes of study groups

Variable	Fresh cycle *n*=80	FET cycle *n*=418	*P*
Chemical pregnancy rate y (%)	11 (13.8%)	128 (29.7%)	0.002*
Clinical Pregnancy rate (%)	8 (10.0%)	86 (20.6%)	0.027*
Live birth rate per transfer (%)	7 (4.9%)	69 (8.7%)	0.127*

*Chi-square test

Table 4: Determining the odds ratio of chemical pregnancy for frozen versus fresh cycles based on baseline characteristics

Variable	OR	95% CI	*P*
freeze/fresh	2.33	1.08_5.02	0.031
freeze/fresh	2.10	0.964_4.612	0.062
Age	0.970	0.928_1.014	0.178
freeze/fresh	2.149	0.982_4.702	0.055
AMH	1.028	0.978_1.080	0.276
freeze/fresh	2.311	1.072_4.984	0.033
Endometrial thickness	1.047	0.901_1.216	0.547
freeze/fresh	1.976	0.893_4.374	0.093
Age	0.973	0.929_1.018	0.228
AMH	1.022	0.972_1.075	0.397
Endometrial thickness	1.047	0.901_1.217	0.550

Potential directions for future research

Randomized controlled trials are needed to confirm these findings. Additionally, pregnancy complications and long-term outcomes should be analyzed in future studies. Furthermore, investigation of different endometrial preparation protocols on FET outcomes are recommended.

Conclusion

In conclusion, FET may be beneficial in patients with RIF.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran (IR.SSU.RSI. REC.1400.008).

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Conflicts of interest

There are no conflicts of interest.

References

1. Cimadomo D, Fernandez LS, Soscia D, Fabozzi G, Benini F, Cesana A, *et al.* Inter-centre reliability in embryo grading across several IVF clinics is limited: Implications for embryo selection. Reprod BioMed Online 2022;44:39-48.
2. Dashti S, Mirzaei M, Eftekhar M, Mangoli E. Is there any difference between the obstetric and perinatal complications of pregnancy in patients with and without repeated implantation failure in fresh and frozen-thawed embryo transfer cycles? Middle East Fertil Soc J 2022;27:6.
3. Shohayeb A, El-Khayat W. Does a single endometrial biopsy regimen (S-EBR) improve ICSI outcome in patients with repeated implantation failure? A randomised controlled trial. Eur J Obstet Gynecol Reprod Biol 2012;164:176-9.
4. Stern JE, Brown MB, Luke B, Wantman E, Lederman A, Hornstein MD, *et al.* Cycle 1 as predictor of assisted reproductive technology treatment outcome over multiple cycles: An analysis of linked cycles from the society for assisted reproductive technology clinic outcomes reporting system online database. Fertil Steril 2011;95:600-5.
5. Busnelli A, Reschini M, Cardellicchio L, Vegetti W, Somigliana E, Vercellini P. How common is real repeated implantation failure? An indirect estimate of the prevalence. Reprod Biomed Online 2020;40:91-7.
6. Margalioth EJ, Ben-Chetrit A, Gal M, Eldar-Geva T. Investigation and treatment of repeated implantation failure following IVF-ET. Hum Reprod 2006;21:3036-43.
7. Cha J, Sun X, Dey SK. Mechanisms of implantation: Strategies for successful pregnancy. Nat Med 2012;18:1754-67.
8. Bashiri A, Halper KI, Orvieto R. Recurrent Implantation Failure-update overview on etiology, diagnosis, treatment and future directions. Reprod Biol Endocrinol 2018;16:121.
9. Craciunas L, Gallos I, Chu J, Bourne T, Quenby S, Brosens JJ, *et al.* Conventional and modern markers of endometrial receptivity: A systematic review and meta-analysis. Hum Reprod Update 2019;25:202-23.

10. Roque M, Lattes K, Serra S, Solà I, Geber S, Carreras R, *et al.* Fresh embryo transfer versus frozen embryo transfer in *in vitro* fertilization cycles: A systematic review and meta-analysis. Fert Steril 2013;99:156-62.
11. Roque M, Valle M, Guimarães F, Sampaio M, Geber S. Freeze-all policy: Fresh vs. frozen-thawed embryo transfer. Fert Steril 2015;103:1190-3.
12. Pontré JC, Ryan JP, Tan A, Hart RJ. The interval transfer of a frozen-thawed embryo is more successful than a fresh embryo transfer for women undergoing IVF with recurrent implantation failure after cleavage stage embryo biopsy. Aust N Z J Obstet Gynaecol 2019;59:134-9.
13. Dashti S, Pejman A, Tabibnejad N, Mortezanasab M. The effect of transferring a poor-quality embryo together with a good-quality embryo on the singleton birth weight: A retrospective cohort study. Int J Reprod BioMed 2022;20:79-90.
14. Glujovsky D, Pesce R, Sueldo C, Retamar AMQ, Hart RJ, Ciapponi A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. Cochrane Database Syst Rev 2020;10:CD006359.
15. Bosch E, De Vos M, Humaidan P. The future of cryopreservation in assisted reproductive technologies. Front Endocrinol 2020;11:67.
16. Jia Y, Ai Z, Zhu X, Che Z, Pratikshya A, Tang S, *et al.* Analysis of predictors of clinical pregnancy and live birth in patients with RIF treated with IVF-ET technology: A cohort study based on a propensity score approach. Front Med 2024;11:1348733.
17. Wang S, Liu L, Ma M, Wang H, Han Y, Guo X, *et al.* Preimplantation genetic testing for aneuploidy helps to achieve a live birth with fewer transfer cycles for the blastocyst FET patients with unexplained recurrent implantation failure. Arch Gynecol Obstet 2023;308:599-610.
18. Racca A, Drakopoulos P, Neves AR, Polyzos NP. Current therapeutic options for controlled ovarian stimulation in assisted reproductive technology. Drugs 2020;80:973-94.
19. Neykova K, Tosto V, Giardina I, Tsibizova V, Vakrilov G. Endometrial receptivity and pregnancy outcome. J Matern Fetal Neonatal Med 2022;35:2591-605.
20. Governing L, Luongo FP, Haxhiu A, Piomboni P, Luddi A. Main actors behind the endometrial receptivity and successful implantation. Tissue Cell 2021;73:101656.
21. Polanski LT, Baumgarten M. Endometrial receptivity testing and therapy in assisted reproductive treatment. Semin Reprod Med 2021;39:27-33.
22. Song J-Y, Dong F-Y, Li L, Zhang X-X, Wang A-J, Zhang Y, *et al.* Immediate versus delayed frozen embryo transfer in women following a failed IVF-ET attempt: A multicenter randomized controlled trial. Reprod Biol Endocrinol 2021;19:131.
23. Franasiak JM, Alecsandru D, Forman EJ, Gemmell LC, Goldberg JM, Llarena N, *et al.* A review of the pathophysiology of recurrent implantation failure. Fert Steril 2021;116:1436-48.
24. Ji H, Zhou Y, Cao S, Zhang J, Ling X, Zhao C, *et al.* Effect of embryo developmental stage, morphological grading, and ploidy status on live birth rate in frozen cycles of single blastocyst transfer. Reprod Sci 2021;28:1079-91.