International Journal of Biomedicine 13(4) (2023) 250-254
http://dx.doi.org/10.21103/Article13(4)_OA3

ORIGINAL ARTICLE

Obstetrics and Gynecology

INTERNATIONAL JOURNAL OF BIOMEDICINE

Outcomes of Frozen-Thawed Embryo Transfer in Overweight and Obese Infertile Women

Yang Zhang

Medical Centre for Human Reproduction, Beijing CHAO-YANG Hospital, Capital Medical University Beijing, China

Abstract

***Background*:** This study aimed to retrospectively analyze the effects of different endometrial preparation protocols on live birth rate (LBR) of overweight/obese patients in frozen-thawed embryo transfer (FET) cycles.

***Methods and Results*:** The study population comprised women who received IVF treatment between June 2013 and December 2020 in the Reproductive Medical Centre. We collected 529 patients with BMI ≥24 kg/m^2 according to the inclusion criteria. The patients were divided into four groups according to the different endometrial preparation protocols in the freeze-thaw cycle: modified natural cycle group (135 cases), stimulated cycle group (124 cases), artificial cycle group (85 cases), and artificial cycle with down-regulation group (185 cases). There was no statistical difference in LBR, clinical pregnancy rate, miscarriage rate, or ectopic pregnancy rate among different endometrial preparation protocols. Multivariate logistic regression analysis showed that only the duration of infertility was related to the LBR (P=0.048).

Conclusion: For overweight and obese people who want to receive FET, different endometrial preparation protocols may not affect the LBR.**(International Journal of Biomedicine. 2023;13(4):250-254.)**

Keywords: frozen-thawed embryo transfer • live birth rate • overweight • obesity

For citation: Zhang Y. Outcomes of Frozen-Thawed Embryo Transfer in Overweight and Obese Infertile Women. International Journal of Biomedicine. 2023;13(4):250-254. doi:10.21103/Article13(4)_OA3

Abbreviations

AC, artificial cycle; **AFC**, antral follicular count; **CET**, cryopreserved embryo transfer; **FET**, frozen-thawed embryo transfer; **GnRH**, gonadotrophin-releasing hormone; **hCG**, human chorionic gonadotropin; **hMG**, human menopausal gonadotropin; **IVF**, in vitro fertilization; **ICSI**, intracytoplasmic sperm injection; **LH**, luteinizing hormone; **LBR**, live birth rate; **MC**, menstrual cycle; **OPU**, ovum pick up.

Introduction

With the development of the economy and the improvement of living standards, obesity has become a world health problem and is a major public health issue in China. Overweight and obesity have increased rapidly in the past four decades.[1,2] The overweight rate and obesity rate of women of childbearing age in China have reached 25.4% and 9.2%, respectively.[3] Obesity affects female reproduction in that obese women show lower levels of gonadotropin hormones, reduced fecundity, higher miscarriage rates, and poorer outcomes of in vitro fertilization.[4] There is also an association between maternal overweight/obesity and gestational diabetes, hypertensive disorders, intrauterine fetal death, stillbirth, and neonatal mortality.[5] Overweight/obese patients have difficulty in losing weight.

Endometrial preparation protocols in the frozen-thawed embryo transfer (FET) cycle can be divided into natural cycle, modified natural cycle, ovulation stimulation cycle, and artificial protocol with or without pretreatment of GnRH-agonist. There is no conclusion on which is better for endometrial cycle preparation.[6] A study by Gu et al.[7] shows that compared with hormone replacement therapy, the natural

***Correspondence**: Yang Zhang, Medical Centre for Human Reproduction, Beijing CHAO-YANG Hospital, Capital Medical University, Beijing, China. E-mail: zhangyang@coga.org.cn*

cycle FET of young women with normal menstrual cycle (MC) has improved the live birth rate (LBR).

Our study posed the question, which endometrial preparation protocol is more suitable for obese patients? For this article, we retrospectively analyzed the LBR of different FET protocols for overweight/obese patients.

Methods

Study Design and Population

In our retrospective study, the study population comprised women who received IVF treatment between January 2013 and December 2020 in the Reproductive Medical Centre, Beijing CHAO-YANG Hospital, Capital Medical University, Beijing. All the patients received follow-up observation for at least one year, and study data were extracted from the medical record. The study was approved by the ethics committee of the hospital (LGH-2022-No-4). Because of the retrospective character of the study, informed consent was waived.

Patients were considered eligible if they met the following criteria: women who had previous IVF/ICSI cycles with embryo cryopreservation, BMI ≥24 kg/m^2, age of 20–42, regular MCs (25–35 days), first cycle of FET between June 2013 and December 2020, and at least one high-quality embryo was transferred. The exclusion criteria were endometriosis, history of recurrent pregnancy loss, uterine pathology, problems of the immune system and abnormal coagulation mechanism, rescued ICSI for routine IVF fertilization failure, TESA-ICSI due to male factor, or cycles that were canceled due to failure of embryo thaw survival.

Endometrial Preparation Protocols

Modified natural cycle protocol: The patients underwent transvaginal ultrasound on Days 8 to 10 of the MC. Follicular growth was monitored through transvaginal ultrasound, and luteinizing hormone (LH) was measured in urine or serum. When the leading follicle had reached a mean diameter of >17mm, urine test paper was positive, or serum LH level was 20 IU/L, 250 ug recombinant hCG was administered to trigger ovulation. The day of ovulation was confirmed by transvaginal ultrasound. From the day of ovulation, dydrogesterone 20 mg daily was initiated. The FET was scheduled on Day 3 (cleavage stage) or Day 5 (blastocyst stage).

Stimulated cycle: Patients were administered letrozole (Jiangsu Hengrui) 2.5 mg/d on Days 3 to 5 of the MC for five consecutive days or hMG 37.5 IU to 7 5IU on Days 3 to 5 of the MC for five consecutive days. Follicular development was monitored using ultrasonography. When the diameter of dominant follicles was ≥18 mm, and endometrial thickness ≥7 mm, 250 ug recombinant hCG was administered to trigger ovulation, and dydrogesterone 20 mg daily was initiated. Embryos were transferred 3 to 5 days later.

Artificial cycle (AC) and down-regulated AC: Endometrial preparation was initiated with oral estradiol valerate (Progynova; Bayer Schering Pharma AG) at a daily dose of 6-8 mg from Day 2 to 3 of the MC with or without down-regulation of GnRH agonist. The serum estradiol, LH, and progesterone levels were measured, and a transvaginal ultrasound was performed 10 to 12 days later. Provided the endometrial thickness reached 7mm or more, and the serum progesterone level was <1.5 ng/ml, 60 mg of intramuscular progesterone was initiated. Embryos were transferred 4 or 6 days later.

Luteal phase support and pregnancy confirmation: From the day of embryo transfer, luteal phase support was continued. The pregnancy testing was performed by measuring serum β-hCG 14 days after embryo transfer. If the β-hCG level was >15 IU/L, biochemical pregnancy was diagnosed, and luteal support was continued. All the patients were followed until one year after embryo transfer.

Observation Indicators

Main outcome measure: LBR. Secondary outcome measures: clinical pregnancy rate, miscarriage rate, ectopic pregnancy. Clinical pregnancy was defined as a pregnancy diagnosed by ultrasonographic visualization of the gestational sac, fetal bud, and fetal heart at four weeks after transfer. Ectopic pregnancy was defined as a gestational sac observed by ultrasound outside the uterine cavity. Miscarriage was defined as a spontaneous loss of a clinical pregnancy before 28 completed weeks of gestational age. Live birth was defined as the delivery of at least one live-born baby beyond 28 weeks of gestation. The birth rate was defined as live deliveries (at least one live birth) per woman after embryo transfer.

Statistical analysis was performed using the statistical software package SPSS version 21.0 (SPSS Inc, Armonk, NY: IBM Corp). The normality of distribution of continuous variables was tested by the Kolmogorov-Smirnov test with the Lilliefors correction and Shapiro-Wilk test. For the descriptive analysis, results are presented as mean (M) and standard deviation (SD). For data with normal distribution, inter-group comparisons were performed using Student's t-test. Multiple comparisons were performed with one-way ANOVA or a non-parametric Kruskal-Wallis test. Group comparisons with respect to categorical variables were performed using the chi-square test. Binary logistic regression analysis was used to assess the association between the type of endometrial preparation and LBR. A multiple logistic regression analysis was conducted to calculate the unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (CI). A probability value of P<0.05 was considered statistically significant.

Results

We collected 529 patients with BMI ≥24 kg/m^2 according to the inclusion criteria from 1/1/2013 to 12/31/2020. The patients were divided into four groups according to the different endometrial preparation protocols in the freeze-thaw cycle: modified natural cycle group (135 cases), stimulated cycle group (124 cases), artificial cycle group (85 cases), and artificial cycle with down-regulation group (185 cases). There were statistical differences among the four groups in the AFC and endometrial pattern (Tables 1 and 2). There was no statistical difference in LBR, clinical pregnancy rate, miscarriage rate, or ectopic pregnancy rate among different endometrial preparation protocols.

The endometrial preparation plan is divided into two groups according to whether there is corpus luteum. The

modified natural cycle group and stimulated cycle group are groups with luteal, and the artificial cycle group with or without down-regulation are groups without luteal. There was no statistical difference in clinical pregnancy rate, LBR, miscarriage rate, or ectopic pregnancy rate between the groups with or without corpus luteum.

Table 1.

Characteristics of the patients at baseline.

Group	MNC	SC	AC	AC with GnRHa	*P*
Number	135	124	82	185	
Age at OPU	32.39(6)	33.11(6)	32.36(5)	32.48(5)	0.74
Age at embryo transfer	32.65(7)	33.53(6)	32.89(5)	33.13(5)	0.84
BMI, kg/m^2	25.53(2.88)	26.2(2.91)	25.71(3.08)	26.35(3.42)	0.14
Primary infertility, %	66(48.9)	60(48.4)	46(56.1)	111(60.0)	0.12
Duration of infertility (years)	3.00(3)	3.36(2)	2.00(3)	3.00(3)	0.51
Infertility cause					0.71
Tubal factors	62(45.9)	60(48.4)	42(51.2)	100(54.1)	
Male factor	23(17.0)	46(15.3)	4(4.9)	21 (11.4)	
Other factors	32(23.7)	25(20.2)	29(35.4)	44 (23.8)	
Mixed factors	18(13.3)	20(16.1)	7(18.5)	20 (10.8)	
bFSH	6.49(2)	6.12(2)	5.78(2)	5.96 (2)	0.18
AFC	13(7)[a]	15(8)	17(11)[a]	14 (11)[a]	0.024
Protocol of COH (n, %)					0.21
Antagonist	81(75.7)	66(53.2)	54(65.9)	94 (50.8)	
Agonist	38(28.1)	45(36.3)	20(24.4)	71 (38.4)	
Others	16(11.9)	13(10.5)	9(9.8)	20 (10.8)	
Fertilization type (n, %)					0.11
IVF	96(71.1)	88(71.0)	63(76.8)	134 (72.4)	
ICSI	22(16.3)	9(7.3)	10(12.2)	26 (14.1)	
IVF/ICSI	17(12.6)	27(21.8)	9(11.0)	25 (13.5)	

MNC - modified natural cycle, SC - stimulated cycle, AC -artificial cycle; [a] The difference between groups is statistically significant.

Univariate logistic regression analysis showed that age at OPU, age at CET, and duration of infertility were correlated with LBR (P<0.05) (Table 3). There was no correlation between the LBR and the endometrial preparation protocol, BMI, ovarian hyperstimulation protocol, fertilization method, endometrial thickness and morphology, the number of transferred embryos, or high-quality embryos in the freeze-thaw cycle. Multivariate logistic regression analysis showed that only the duration of infertility was related to the LBR (P=0.048), correcting age at OPU, age at CET, AFC, endometrial pattern, and endometrial preparation plan. According to the stratified analysis of BMI, there was no correlation between the LBR and the endometrial preparation protocol.

Table 2.

Outcomes of different endometrial preparation protocol.

Group	MNC	SC	AC	AC with GnRHa	*P*
Number	135	124	82	185	
Endometrial thickness	10(2.5)	10(2.9)	9(2.5)	10(2.6)	0.12
Endometrial pattern					0.011
A	69(51.1)[b]	60(48.4)[b]	49(59.8)[b]	121(65.4)	
others	66(48.9)[b]	64(51.6)[b]	33(40.2)[b]	64(34.6)	
Type of embryo transferred					0.25
D3	123(91.1)	105(84.7)	64(78.0)	160(86.5)	
Blastosphere	10(7.4)	17(13.7)	16(19.5)	23(12.4)	
Both	2 (1.5)	2(1.6)	2(1.6)	2(1.1)	
No. of embryos transferred (n, %)					0.34
1	10(7.4)	13(10.5)	11(13.4)	14(7.6)	
2	125(92.6)	111(89.5)	71(86.6)	171(92.4)	
No. of good quality embryos transferred (n,%)					0.39
1	85(63)	80(64.5)	55(61.1)	106(57)	
2	50(37)	44 (35.5)	27(32.9)	79(42)	
Clinical pregnancy rate, %	53.3	62.1	56.1	58.4	0.54
Live birth rate, %	40.7	45.2	48.8	45.4	0.69
Miscarriage rate, %	11.9	14.5	6.1	11.9	0.32
Ectopic pregnancy rate, %	0	0.8	0	1.1	0.53

MNC - modified natural cycle, SC - stimulated cycle, AC -artificial cycle; [b] There was no statistical difference between groups b1, 2, and 3, but there was a statistical difference compared to the four groups.

Table 3.

Univariate analysis for LBR.

Covariate	OR	(95% CI)	*P*
Age at OPU	0.948	0.908-0.989	0.015
Age at embryo transfer	0.950	0.910-0.992	0.019
BMI (kg/m^2)	0.960	0.897-1.027	0.233
Infertility type			
Primary infertility	Reference		
Secondary infertility	0.656	0.463-0.928	0.017
Duration of infertility (years)	0.918	0.856-0.985	0.017
Infertility cause			
Tubal factors	Reference		
Male factor	1.070	0.991-2.917	0.054
Other factors	1.043	0.682-1.595	0.846
Mixed factors	1.257	0.729-2.167	0.411
bFSH	0.972	0.897-1.054	0.499
AFC	1.032	1.000-1.047	0.054

Table 3 (Continued).

Univariate analysis for LBR.

Covariate	OR	(95% CI)	*P*
Protocol of COH (n, %)			
Antagonist	Reference		
Agonist	1.221	0.837-1.78	0.301
Others	0.788	0.426-1.46	0.449
Fertilization type (n, %)			
IVF	Reference		
ICSI	0.82	0.484-1.391	0.462
IVF/ICSI	1.042	0.639-1.698	0.870
Endometrial thickness	1.056	0.971-1.149	0.200
Endometrial pattern			
A	Reference		
others	0.957	0.676-1.354	0.802
Type of embryo transferred			
D3	Reference		
Blastosphere	1.375	0.820-2.307	0.227
Both	1.294	0.32-5.24	0.718
No. of embryos transferred (n, %)			
1	Reference		
2	1.529	0.824-2.837	0.178
No. of good quality embryos transferred (n, %)			
1	Reference		
2	1.055	0.741-1.503	0.766

Discussion

This paper reviewed and analyzed the effect of different freeze-thaw cycles on the LBR in overweight and obese women. The results showed no statistical difference in the LBR between different endometrial preparation protocols. The factors affecting the LBR were age at OPU, age at CET, and duration of infertility. These results will have some clinical implications for the transfer of frozen embryos to overweight and obese individuals.

The pre-pregnancy overweight/obese population is associated with adverse perinatal pregnancy outcomes, such as pregnancy diabetes, pre-eclampsia, induced labor, cesarean section, preterm birth, and macrosomia. Pre-pregnancy overweight and obesity are associated with obesity in children and adolescents. A meta-analysis showed that even 5% to 7% weight loss may improve metabolic health and pregnancy outcomes.[8] Obese patients have difficulty in losing weight and easily rebound. And even if weight loss is successful, obesity still impacts physical health. There is no report in the literature on what the best endometrial preparation protocol for overweight and obese patients is. Our results provide a clinical basis for guiding the embryo development of such populations.

In the past few years, the use of FET has increased exponentially. It is very important to optimize the endometrial preparation protocol before FET to improve the pregnancy outcome. There are five kinds of freeze-thaw cycle endometrial preparation protocols. Natural cycle protocol is the closest to the physiological situation. Estrogen produced by follicular development promotes the growth of endometrium. After waiting for the follicle to mature naturally and ovulation, the embryo is transferred according to the embryo development date. The modified natural cycle is to give hCG triggers to promote ovulation when the follicles mature. The stimulation cycle or ovulation induction cycle is the use of letrozole, or combined with gonadotropin, to induce the development of single or multiple follicles, and hCG triggers ovulation when the follicles mature. In the natural cycle, modified natural cycle, and stimulation cycle, the luteal support of the embryo depends on the luteal function formed in the cycle, and progesterone supplemented externally is small. These protocols use fewer drugs, and the time should be determined according to the follicular growth. Patients have more visits, and the cycle cancelation rate is high.

In the AC, the growth of the endometrium entirely depends on exogenous estrogen. After the endometrium reaches a certain thickness, exogenous progesterone is added to transform the endometrium, and the corpus luteum support is continued until the placenta is formed after embryo transfer. The AC with down-regulation is pretreated with GnRH-agonist. Whether the AC is pretreated with GnRH-agonist or not, there is no luteal formation. The artificial protocol is relatively reliable and convenient for work arrangements.

Many scholars have studied and compared the advantages and disadvantages of different endometrial preparation protocols. Some patients with ovulation disorders are not suitable for natural cycles or modified natural cycle protocols. If it is difficult to induce ovulation, only AC schemes can be used. AC may increase the risk of eclampsia during pregnancy.[7] According to a recent meta-analysis, GnRH-agonist pretreatment in FET can improve implantation, clinical pregnancy, and LBR, especially in patients with repeated implantation failure. GnRH-agonist pretreatment seems to improve the results of FET, although its premature delivery rate is higher.[9] The latest large European register study evaluated early pregnancy complications and LBR per pregnancy after FET between three different cycle regimens. The miscarriage rate was highest in the AC, compared with the stimulation or natural cycles.[10] The latest review showed no strong evidence to support the use of one preparation method over the other regarding pregnancy outcomes.[6]

The results of the analysis suggest that the factors related to the LBR are age and duration of infertility; that is, young patients and shorter duration of infertility are more likely to obtain live birth. Many studies have shown that maternal age was associated with poor pregnancy outcomes, such as miscarriage, preterm birth, stillbirth, low birth weight, neonatal death, and perinatal neonatal death.[11] As age increases, the number and quality of eggs decrease. Age also has an impact on the endometrium[12] and a crucial impact on assisted reproductive survival.[12-14] The longer the duration of

infertility, the more severe it is and the more difficult it is to achieve a live birth. For overweight and obese patients, the FET protocol does not affect the biochemical pregnancy rate, clinical pregnancy rate, or LBR.[15]

Limitations of the Study

The number of cases was limited. The analysis results may be more reliable if combined with data from multiple centers. This article was a retrospective study. The research results need to be further confirmed by designing randomized controlled studies. The outcome data of clinical complications in our research data are incomplete. Unfortunately, we could not analyze whether different endometrial preparation protocols increase pregnancy complications.

Conclusion

For overweight and obese people who want to receive FET, different endometrial preparation protocols may not affect the LBR. Age and duration of infertility were related to LBR. Weight loss is recommended before accepting FET. Further research needs to be confirmed by a prospective randomized controlled study.

Competing Interests

The author declared that there are no competing interests.

References

1. Pan XF, Wang L, Pan A. Epidemiology and determinants of obesity in China. Lancet Diabetes Endocrinol. 2021 Jun;9(6):373-392. doi: 10.1016/S2213-8587(21)00045-0. Erratum in: Lancet Diabetes Endocrinol. 2021 Jul;9(7):e2. PMID: 34022156.
2. Zhang L, Wang Z, Wang X, Chen Z, Shao L, Tian Y, Zheng C, Li S, Zhu M, Gao R; China Hypertension Survey investigators. Prevalence of overweight and obesity in China: Results from a cross-sectional study of 441 thousand adults, 2012-2015. Obes Res Clin Pract. 2020 Mar-Apr;14(2):119-126. doi: 10.1016/j.orcp.2020.02.005. Epub 2020 Mar 2. PMID: 32139330.
3. Fang HY, Zhao LY, Ju LH. 2018. Prevalence of malnutrition and overweight and obesity among childbearing women aged 15-49 years in China. Chin J Public Health. 34: 1229–32.
4. Yong W, Wang J, Leng Y, Li L, Wang H. Role of Obesity in Female Reproduction. Int J Med Sci. 2023 Jan 31;20(3):366-375. doi: 10.7150/ijms.80189. PMID: 36860674; PMCID: PMC9969507.
5. Grünebaum A, Dudenhausen JW. Prevention of risks of overweight and obesity in pregnant women. J Perinat Med. 2022 Aug 29;51(1):83-86. doi: 10.1515/jpm-2022-0313. PMID: 36018720.
6. Roelens C, Blockeel C. Impact of different endometrial preparation protocols before frozen embryo transfer on pregnancy outcomes: a review. Fertil Steril. 2022 Nov;118(5):820-827. doi: 10.1016/j.fertnstert.2022.09.003. PMID: 36273850.
7. Gu F, Wu Y, Tan M, Hu R, Chen Y, Li X, Lin B, Duan Y, Zhou C, Li P, Ma W, Xu Y. Programmed frozen embryo transfer cycle increased risk of hypertensive disorders of pregnancy: a multicenter cohort study in ovulatory women. Am J Obstet Gynecol MFM. 2023 Jan;5(1):100752. doi: 10.1016/j.ajogmf.2022.100752. Epub 2022 Sep 15. PMID: 36115572.
8. Armstrong MJ, Mottershead TA, Ronksley PE, Sigal RJ, Campbell TS, Hemmelgarn BR. Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials. Obes Rev. 2011 Sep;12(9):709-23. doi: 10.1111/j.1467-789X.2011.00892.x. Epub 2011 Jun 21. PMID: 21692966.
9. Li X, Lin J, Zhang L, Liu Y. Effects of gonadotropin-releasing hormone agonist pretreatment on frozen embryo transfer outcomes in artificial cycles: a meta-analysis. Arch Gynecol Obstet. 2023 Sep;308(3):675-683. doi: 10.1007/s00404-022-06823-7. Epub 2022 Oct 20. PMID: 36266549.
10. Pape J, Levy J, von Wolff M. Early pregnancy complications after frozen-thawed embryo transfer in different cycle regimens: A retrospective cohort study. Eur J Obstet Gynecol Reprod Biol. 2022 Dec;279:102-106. doi: 10.1016/j.ejogrb.2022.10.015. Epub 2022 Oct 21. PMID: 36308939.
11. González-Plaza E, Bellart J, Martínez-Verdú MÁ, Arranz Á, Luján-Barroso L, Seguranyes G. Pre-pregnancy overweight and obesity prevalence and relation to maternal and perinatal outcomes. Enferm Clin (Engl Ed). 2021 Jun 19:S1130-8621(21)00081-4. English, Spanish. doi: 10.1016/j.enfcli.2021.04.004. Epub ahead of print. PMID: 34158216.
12. Devesa-Peiro A, Sebastian-Leon P, Parraga-Leo A, Pellicer A, Diaz-Gimeno P. Breaking the ageing paradigm in endometrium: endometrial gene expression related to cilia and ageing hallmarks in women over 35 years. Hum Reprod. 2022 Apr 1;37(4):762-776. doi: 10.1093/humrep/deac010. PMID: 35085395.
13. Zhang C, Yan L, Qiao J. Effect of advanced parental age on pregnancy outcome and offspring health. J Assist Reprod Genet. 2022 Sep;39(9):1969-1986. doi: 10.1007/s10815-022-02533-w. Epub 2022 Aug 4. PMID: 35925538; PMCID: PMC9474958.
14. Dew JE, Don RA, Hughes GJ, Johnson TC, Steigrad SJ. The influence of advanced age on the outcome of assisted reproduction. J Assist Reprod Genet. 1998 Apr;15(4):210-4. doi: 10.1023/a:1023004503697. PMID: 9565851; PMCID: PMC3454935.
15. Zhang L, Cai H, Li W, Tian L, Shi J. Duration of infertility and assisted reproductive outcomes in non-male factor infertility: can use of ICSI turn the tide? BMC Womens Health. 2022 Nov 28;22(1):480. doi: 10.1186/s12905-022-02062-9. PMID: 36443809; PMCID: PMC9706853.