Effect of different endometrial preparation protocols on pregnancy outcomes in frozen- embryo transfer cycles: a retrospective cohort study

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Research

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Abstract

Background

Owing to the crucial role the endometrium plays in embryo implantation, the four main endometrial preparation protocols have become important factors in the study of pregnancy outcomes in the FET cycles. Previous studies have shown that the best of these four protocols remains controversial for women undergoing FET.

Methods

A total of 10333 FET cycles from January 2018 to December 2018 were analyzed in this study. They were categorized into four groups according to endometrial preparation regimen: natural cycles (Group NC,n = 815), hormone replacement therapy cycles (Group HRT ,n = 6434), GnRH agonist artificial cycles (Group GAC,n = 1392) and ovarian stimulation cycles (Group OC, n = 1692). All patients were followed up for at least 1 year. Pregnancy outcomes were compared between the four groups and multiple logistic regression models were used to adjust for the effects of confounding factors.

Results

The ectopic pregnancy rate (P = 0.627) and miscarriage rate (P = 0.164) were not statistically significant between the four groups. Moreover, biochemical pregnancy rate, clinical pregnancy rate and live birth rate in the NC group were not statistically significant compared to the other three groups. After adjusting for covariates, multiple logistic regression analysis showed no statistical significance in pregnancy outcomes in the HRT, GAC and OC groups compared to the NC group.And the adjusted OR for live births was 0.988 (95 % CI0.847-1.152) for the HRT group, 0.955 (95 % CI0.795-1.146) for the GAC group,0.898 (95 % CI0.754-1.070) for the OC group.

Conclusions

Our study showed that natural cycles have similar pregnancy outcomes in terms of clinical pregnancy and live birth to the other three endometrial preparation options. As it has other advantages, the natural cycle protocol can therefore be the recommended option for endometrial preparation in the FET population.

Introduction

The frozen-thawed embryo transfer (FET) has increasingly been used in assisted reproductive technology (ART) compared to the fresh embryo transfer as a results of its higher live birth rate and lower risk of ovarian hyperstimulation syndrome (OHSS)(1–6).

Successful pregnancy is a result of dynamic crosstalk between a competent blastocyst and a receptive endometrium(7) .Synchronization of endometrial and embryonic development is an important factor which improves endometrial receptivity for a successful pregnancy(8–10). Owing to the crucial role the endometrium plays in embryo implantation, preparation of the endometrium involving endometrial thickness and morphology,

uterine blood flow and other factors related to receptivity (11), has become an important factor in the study of pregnancy outcomes in the FET cycles(12, 13).

There are four main endometrial preparation protocols for women undergoing FET cycles: natural cycle (NC),hormone replacement treatment cycle (HRT), GnRH agonist artificial cycle (GAC) and ovulation stimulation cycle (OC).Although a retrospective cohort study and other studies comparing pregnancy outcomes in four endometrial preparation groups showed that the natural cycle was associated with higher live birth rates(14–16), studies by Groenewoud et al. (17) and Mounce et al.(18) showed no statistically significant difference in live birth rates, or clinical pregnancy rates between the natural and hormone replacement cycle groups. Other studies have also shown that the best of these four protocols remains controversial for women undergoing FET(19, 20).

In the face of these controversial findings, our aim in this study therefore was to explore the optimal endometrial preparation regimen by comparing the pregnancy outcomes of the four protocols, taking into account a number of factors known to influence the pregnancy outcome of fresh embryo transfer.

Materials And Methods

Study Design and Patient Population

This was a retrospective cohort study comprising 10,333 cycles of frozen embryo transfers performed at Xinan Gynecological Hospital in Sichuan, China, from January 2018 to December 2018. All patients were followed up for at least 1 year, and the patients' clinical data were extracted from the electronic medical record system. Patients were excluded from the study if they met the following criteria: women who had a serious genetic, physical or mental illness that could affect their pregnancy; chromosomal abnormalities in either spouse; incomplete clinical and pregnancy data recording.

The study was approved by the Institutional Ethics Committee of Chongqing Medical University.

Endometrial Preparation

natural cycle (Group NC). On day 2 to 3 of the menstrual cycle, veinous blood was taken to assess hormonal levels. Follicular development and endometrial thickness were monitored by ultrasound, and triggered with intramuscular injections of HCG (Shanghai ,Lizhu) 6000 U (not all HCG injections are necessarily given). When the dominant follicle has been ovulated and the endometrium was ≥ 8 mm, oral dydrogesterone 10 mg/dose (Abbott, Holland) twice a day was started (some use 20mg bid). When the dominant follicle has been ovulated and the endometrium is < 8mm, oral dydrogesterone combination tablets 20 mg/dose (Abbott, Holland) twice a day was given for 4 days. Blastocysts were thawed and resuscitated for transfer, or on day 2 if the embryos were in the cleavage stage.

hormone replacement treatment cycle (Group HRT). Ultrasound and hormonal levels including HCG were monitored on the second to third day of menstruation. When both ultrasound and hormones showed basal ovarian status (i.e. E2 < 183.5 pmol/L, endometrial thickness < 5 mm, after elimination of pregnancy), estradiol (Abbott, Holland) 2 mg/time, was administered one to twice a day for 10–12 days. After 10 days of continuous used, endometrial thickness was followed up and monitored. When the endometrial thickness was ≥ 8mm, luteal conversion was initiated, i.e. intramuscular progesterone (Zhejiang Xianju) 60 mg once daily or vaginal administration of Certolone (Merck, Switzerland) 90 mg/d, or vaginal administration of Angel (CyndeaPharma,

France) 0.6 mg/d. Concurrently, estradiol administration was switched to complex packing estradiol tablets (Femoston, Abbott, Holland) 2–3 times daily. Thereafter, the frozen blastocysts were thawed for resuscitation transfer on day 6 of the luteal transition; for oocyte embryos, the frozen embryos were thawed for resuscitation transfer on day 4 of the luteal transition.

GnRH agonist artificial cycle (Group GAC). After ruling out pregnancy on the second to third day of menstruation, a gonadotropin-releasing hormone agonist (GnRH-a) (Dalfylline, Beaufort-Epsom, France; or Dabigat, Pfizer, Germany) 3.75 mg was administered once intramuscularly. After 28–30 days, patients were followed by blood sampling and ultrasound to determine whether pituitary downregulation criteria were met (i.e. E2 < 183.5 pmol/L, FSH < 5U/L, LH < 5U/L, endometrial thickness < 5mm). If the criteria for down-regulation was not met, a further delay for about 1 to 2 weeks was allowed until the criteria was met and the endometrium was then prepared using an artificial cycle protocol.

ovulation stimulation cycle (Group OC). Letrozole 2.5-5mg, or Tamoxifen 20-40mg, or Clomiphene 50mg was taken for 5 days on day 2–5 of menstruation. Monitored follicle development from day 10 of menstruation and decided whether to inject urinary sex hormones based on follicle development. When the follicle was greater than 18mm and the blood LH was 2–3 times the basal value, an intramuscular injection of 6,000–10,000 U of chlortetracycline HCG would be given. Post-ovulation medication was the same as in a natural cycle.

Embryo thawing, transfer and post-transfer corpus luteum support

Transfer of embryos under ultrasound guidance according to conventional vitrification and freezing methods. Oral estradiol was gradually reduced until discontinued at 8–9 weeks gestation. Intramuscular progesterone 60mg/d or vaginally administered progesterone (Certolone certolone 90mg/d or Angel 0.6mg/d) or oral progesterone (dydrogesterone) 30-40mg/d or oral complex packing estradiol tablets (Femoston, Abbott, Holland) 2 pieces/d was taken until 10–12 weeks gestation.

Pregnancy Confirmation

On 14 days after embryo transfer, pregnancy testing was done by measuring serum hCG level. Ultrasound was performed on day 28 after embryo transfer to determine the number of gestational sacs, and to monitor fetal heartbeats. All patients were closely followed up up to 1 year after embryo transfer.

Outcome parameters

The patients' baseline characteristics and clinical data were extracted from the medical record system: female age, female body mass index (BMI), male age, type of embryo transferred, endometrial thickness at one day before transfer, basal antral follicle count(AFC), basal anti-müllerian hormone(AMH) and basal follicle-stimulating hormone(FSH).

The primary outcomes were clinical pregnancy rates and live birth rates. Secondary outcomes were the incidence of biochemical pregnancy, miscarriage and ectopic pregnancy. Clinical pregnancy was defined as the presence of at least one gestational sac in the uterine cavity confirmed by vaginal ultrasound at 28 days of gestation, with an embryonic bud and primordial heartbeat. Live birth was defined as the birth of at least one live baby after 24 weeks of gestation. Biochemical pregnancy was defined as positive serum β-HCG (β-HCG ≥ 5 U/L) at 14 days after

transplantation. Ectopic pregnancy was defined as a gestational sac observed by ultrasound outside the uterus. Miscarriage was defined as clinical pregnancy loss by the 24th week of gestation.

Statistical analysis

Non-normally distributed continuous variables were statistically described using median (25th-75th percentile) and comparisons between groups were made using a non-parametric test (Kruskal-Wallis rank sum test). For categorical variables, they were described in terms of number of cases (percentages) and comparisons between groups were made using the Pearson chi-square test. When overall rates between groups were statistically significant, further multiple comparisons were made using the partitions of χ^2method, and p-values and corrected using the Boferroni method. Multiple logistic regression was used to analyse the pregnancy outcomes between the four endometrial preparation methods, adjusting for female age, female BMI, male age, type of embryo transferred, endometrial thickness at one day before transfer, basal AFC, basal FSH and basal AMH (Asassignments of classification variables in the model are shown in Supplemental table 1 and dummy variables are set in Supplemental table 2).

All statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS) version 25.0. P-value < 0.05 was considered to be statistically significant.

Results

A total of 10,333 FET cycles were included in our statistical analysis (Table 1). These FET cycles were divided into four groups: NC (n = 815), HRT (n = 6434), GAC (n = 1392) and OC (n = 1692) according to the endometrial preparation protocols. The results showed statistically significant differences in the general baseline characteristics of the four endometrial preparation groups ($p < 0.05$). The distribution of female age (< 35 or ≥ 35 years) was statistically significant between the four groups, with the HRT having the highest proportion of females aged < 35 years (73.8%). In terms of the body mass index (BMI), there was no statistical significance between the four groups in the proportion of people who were lean (BMI < 18.5 kg/m²) and obese (BMI ≥ 30.0 kg/m²). The results of the baseline characteristics also indicated that the HRT group had lower endometrial thickness at one day before transplantation (0.9cm) compared to the NC, GAC and OC groups. Moreover, basal AFC and basal AMH were highest in the HRT group [basal AFC:15.4(9.0–23.0), basal AMH:3.8(1.9–6.4)ng/mL] but lowest in GAC group [basal AFC:9.0(5.0–15.0)), basal AMH:2.0(0.9–3.9)ng/mL]. Also, the NC group had a higher basal FSH than the HRT group and OC group [NC = 7.4(6.3-9.0)miu/L; HRT = 7.0(5.9–8.4)miu/L; OC = 7.1(6.0-8.6)miu/L, with $p < 0.05$], but this difference was not statistically significant when computed against the GAC group.

Table 1
Baseline characteristics of the four endometrial preparation groups in FET cycles

	Group NC (n = 815)	Group HRT (n = 6434)	Group GAC (n = 1392)	Group OC (n = 1692)	P-value
Female age(years)					
< 35	502(61.6)[a]	4748(73.8)[b]	746(53.6)[c]	1141(67.4)[d]	< 0.001*
≥ 35	313(38.4)[a]	1686(26.2)[b]	646(46.4)[c]	551(32.6)[d]	
Female BMI(kg/m²)					0.002*
< 18.5	88(10.8)[a]	690(10.7)[a]	128(9.2)[a]	182(10.8)[a]	
18.5~	631(77.4)[a]	4652(72.3)[b]	1054(75.7)[ab]	1275(75.4)[ab]	
25.0~	89(10.9)[a]	988(15.4)[b]	188(13.5)[ab]	213(12.6)[a]	
≥ 30.0	7(0.9)[a]	104(1.6)[a]	22(1.6)[a]	22(1.3)[a]	
Male age(years)					< 0.001*
< 35	394(48.3)[a]	3864(60.1)[b]	602(43.2)[a]	926(54.7)[c]	
35~	232(28.5)[a]	1402(21.8)[b]	351(25.2)[a]	431(25.5)[a]	
40~	131(16.1)[ab]	771(12.0)[c]	276(19.8)[b]	215(12.7)[ac]	
≥ 45	58(7.1)[a]	397(6.2)[a]	163(11.7)[b]	120(7.1)[a]	
Type of embryo transferred					< 0.001*
Day3	271(33.3)[ab]	1914(29.7)[b]	622(44.7)[c]	641(37.9)[a]	
Day5	332(40.7)[a]	2964(46.1)[b]	476(34.2)[c]	692(40.9)[a]	
Day6	212(26.0)[a]	1556(24.2)[ab]	294(21.1)[b]	359(21.2)[b]	
Endometrial thickness (cm)	1.0(0.8–1.1)[a]	0.9(0.8–1.1)[b]	1.0(0.8–1.1)[a]	1.0(0.8–1.2)[c]	< 0.001**
Basal AFC	11.0(7.0–17.0)[a]	15.4(9.0–23.0)[b]	9.0(5.0–15.0)[c]	13.0(8.0–19.0)[d]	< 0.001**
Basal AMH(ng/ml)	2.5(1.5-4.0)[a]	3.8(1.9–6.4)[b]	2.0(0.9–3.9)[c]	2.9(1.7–5.3)[d]	< 0.001**

(Note:Data are number (%) or median (25th-75th percentile). *Comparisons were made by Pearson Chi-square test. **Comparisons were made by Kruskal-Wallis test.There was no statistically significant difference between groups with the same corner letters, and a significant difference between groups with different corner letters.NC, natural cycle; HRT, hormonal replacement cycle;GAC ,GnRH agonist artificial cycle;OC, ovarian stimulation cycle.FET, frozen embryo transfer. BMI, body mass index)

	Group NC (n = 815)	Group HRT (n = 6434)	Group GAC (n = 1392)	Group OC (n = 1692)	P-value
Basal FSH(miU/ml)	7.4(6.3-9.0)[a]	7.0(5.9–8.4)[b]	7.6(6.1–9.8)[a]	7.1(6.0-8.6)[b]	< 0.001**

(Note:Data are number (%) or median (25th-75th percentile). *Comparisons were made by Pearson Chi-square test. **Comparisons were made by Kruskal-Wallis test.There was no statistically significant difference between groups with the same corner letters, and a significant difference between groups with different corner letters.NC, natural cycle; HRT, hormonal replacement cycle;GAC ,GnRH agonist artificial cycle;OC, ovarian stimulation cycle.FET, frozen embryo transfer. BMI, body mass index)

The results of this study also show the pregnancy outcomes for the four different endometrial preparation protocols of FET cycles (Table 2). In relation to pregnancy complications among the four groups, there was no statistical significance between those who experienced ectopic pregnancy (P = 0.627) and miscarriage (P = 0.164). Biochemical pregnancy rate, clinical pregnancy rate and live birth rate in the NC group were also not statistically significant compared to the other three groups. However, the HRT group had a higher biochemical pregnancy rate (64.6%) than the GAC (57.7%) and OC (59.5%) groups with $p < 0.001$.Similar results were found for clinical pregnancy and live birth rates in the HRT group compared to the GAC and OC groups ($p < 0.001$) .But there were no statistically significant differences between Group OC and Group GAC in terms of biochemical pregnancy rates, clinical pregnancy rates, or live birth rates ($p > 0.001$).

Table 2
The pregnancy outcomes of the four endometrial preparation groups in FET cycles

	Group NC (n = 815)	Group HRT (n = 6434)	Group GAC (n = 1392)	Group OC (n = 1692)	P-value
Biochemical pregnancy					< 0.001*
yes	499(61.2)^{ab}	4155(64.6)^{b}	803(57.7)^{a}	1006(59.5)^{a}	
no	316(38.8)^{ab}	2279(35.4)^{b}	589(42.3)^{a}	686(40.5)^{a}	
Clinical pregnancy					< 0.001*
yes	436(53.5)^{ab}	3649(56.7)^{b}	676(48.6)^{a}	864(51.1)^{a}	
no	379(46.5)^{ab}	2785(43.3)^{b}	716(51.4)^{a}	828(48.9)^{a}	
Ectopic pregnancy					0.627*
yes	6(0.7)	54(0.8)	9(0.6)	18(1.1)	
no	809(99.3)	6380(99.2)	1383(99.4)	1674(98.9)	
Miscarriage					0.164*
yes	79(9.7)	614(9.5)	127(9.1)	132(7.8)	
no	736(90.3)	5820(90.5)	1265(90.9)	1560(92.2)	
Live birth					< 0.001*
yes	351(43.1)^{ab}	2986(46.4)^{b}	540(38.8)^{a}	714(42.2)^{a}	
no	464(56.9)^{ab}	3448(53.6)^{b}	852(61.2)^{a}	978(57.8)^{a}	

(Note:Data are number (%) .There was no statistically significant difference between groups with the same corner letters, and a significant difference between groups with different corner letters.

*Comparisons were made by Pearson Chi-square test. NC, natural cycle; HRT, hormonal replacement cycle;GAC ,GnRH agonist artificial cycle;OC, ovarian stimulation cycle.FET, frozen embryo transfer.)

Furthermore, the multiple logistics regression model was used to analyze pregnancy outcome among the four groups (Table 3). After adjusting for covariates in the baseline characteristics, the results showed no statistical significance in pregnancy outcomes (including biochemical pregnancy, clinical pregnancy, live birth and miscarriage) in the HRT, GAC and OC groups compared to the NC group. The adjusted odds ratio (OR) for clinical pregnancy compared to the NC group was 0.982 (95% CI 0.843–1.144) for the HRT group; 0.937 (95 % CI 0.783–1.122) for the GAC group; 0.852 (95% CI 0.716–1.013) for the OC group. The adjusted OR for live births was 0.988 (95 % CI0.847-1.152) for the HRT group, 0.955 (95 % CI0.795-1.146) for the GAC group, and 0.898 (95 % CI0.754-1.070) for the OC group.

Table 3
Multiple logistic regression analysis of pregnancy outcomes in four groups

	Biochemical pregnancy		Clinical pregnancy		Live birth		Miscarriage	
	aOR(95%CI)	P	aOR(95%CI)	P	aOR(95%CI)	P	aOR(95%CI)	P
Group NC	Referent		Referent		Referent		Referent	
Group HRT	0.993(0.849–1.161)	0.927	0.982(0.843–1.144)	0.815	0.988(0.847–1.152)	0.878	0.977(0.761–1.255)	0.858
Group GAC	1.001(0.833–1.202)	0.995	0.937(0.783–1.122)	0.479	0.955(0.795–1.146)	0.620	0.939(0.697–1.263)	0.677
Group OC	0.876(0.733–1.046)	0.143	0.852(0.716–1.013)	0.070	0.898(0.754–1.07)	0.229	0.815(0.607–1.093)	0.171

(Variables adjusted for in the model: female age, female BMI, male age, type of embryo transferred, endometrial thickness at transfer date, basal AFC, basal AMH, basal FSH. NC, natural cycle; HRT, hormonal replacement cycle;GAC ,GnRH agonist artificial cycle;OC, ovarian stimulation cycle.FET, frozen embryo transfer.aOR, adjusted odds ratio, CI,confidence interval)

Discussion

Endometrial receptivity is widely considered as an important player in the success of pregnancy and so optimum treatment of the endometrium has been a key focus of interest for decades due to its potential clinical importance(21). In this study, we showed that in the overall population, the HRT group had higher rates of positive biochemical pregnancy, positive clinical pregnancy and live births than the GAC and OC groups ($p < 0.001$), with no significant differences compared to the NC group. The findings in this study confirm previous studies that also showed similar pregnancy outcomes between the natural cycle group and other endometrial preparation regimen groups. A retrospective cohort study analysed 214 NC cycles and 276 HRT cycles, with similar live birth rates (NC = 33.6% HRT = 29.3%, P = 0.47) and clinical pregnancy rates (NC = 40.2% HRT = 36.6%, P = 0.35) in the two groups(22). In addition, a prospective randomized controlled trial comparing clinical data from the NC group (n = 59) and the OC group (n = 60) showed no significant differences between the two groups in terms of positive biochemical pregnancy rate (NC = 34.0% OC = 23.1%, P = 0.22), clinical pregnancy rate (OC: 13/53 = 24.5%; NC: 12/52 = 23.1%; P = 0.86) and live birth rate (OC = 24.5% and NC = 23.1%, P = 0.86) (23). In this study also, there were no significant differences in ectopic pregnancy rates and miscarriage rates between the four groups in our study. These findings are also consistent with a prospective RCT trial which did not find any difference in pregnancy outcome between the NC and GAC groups(24). Another study also corroborated that the NC and OC groups had similar clinical outcomes in frozen embryo transfer which is consistent with the results of our study(25). Although, we did not compute pregnancy outcome with age, a study showed that reduced pregnancy outcome has been seen to increase with increasing age of women, with the most occurring in women beyond 40 years of age. This implies that women below the age of 40 years tend to benefit from frozen embryo transfer(26).

After adjusting for confounding factors, there were no statistically significant differences in pregnancy outcomes in any of the three endometrial preparation groups compared to the NC group, which is consistent with the results of previous studies(22, 27).Similarly, a retrospective cohort study primarily compared live birth rates between 923 GnRH agonist artificial cycles and 105 natural cycles. After adjusting for female age, body mass index, diagnosis,

preimplantation genetic screening/diagnosis, year and number of embryo transfers in a logistic regression model, the results showed no difference in any pregnancy outcome, with live birth rates aOR1.0,95%CI0.6-1.5(28). Compared to the other three groups, the HRT group having the lowest endometrial thickness at one day before transplantation. Two retrospective cohort studies also showed that the endometrial thickness was less in the HRT group than in the NC group(29, 30).However, there was no statistical difference in the incidence of biochemical pregnancy, clinical pregnancy, miscarriage or live birth between the two groups(30), probably because endometrial thickness is not a decisive parameter for successful pregnancy (31). However, a study by Shaodi et al (2020) showed that to obtain optimal live birth rate, the endometrial thickness must remain within the range of 8.7-14.5mm as too thin or too thick endometrium would reduce the live birth live(32) .More studies are needed to address the effect of endometrial thickness on pregnancy outcome.

Patient specificity and acceptability need to be considered when deciding on the optimal endometrial preparation protocol for an individual. A study by Dancet and colleagues identified four treatment dimensions to be considered in the clinical advice given to patients during fertility treatment: burden, effectiveness, safety, and costs(33). Prato et al. also suggest that when two treatment options produce the same result, the less expensive option should be chosen(34). Natural cycles have a natural hormone-induced endometrial environment, avoid the use of exogenous hormones, avoid OHSS and are more conducive to embryo implantation, while being less costly and simple in terms of late luteal support, and are most acceptable to patients(35). Therefore, the natural cycle protocol could be the recommended option for endometrial preparation in the FET population. However, further research is needed in the future to determine the optimal endometrial preparation regimen in populations with different causes of infertility.

The strengths of this study include its relatively large sample size, limited exclusion criteria, and inclusion of women of all ages and infertility diagnoses. Furthermore, our study also took into consideration four endometrial preparation protocols commonly used in clinical practice and adjusted for other confounding factors using a multivariate logistic regression analysis model when exploring the effect of endometrial preparation protocols on pregnancy outcomes. However, the nature of the retrospective cohort study makes this study somewhat limited and more prospective cohort studies or RCT trial could be conducted in the future to explore pregnancy-related illnesses, fetal growth and development. Moreover, cost-effectiveness is an important factor to consider when developing a protocol for patients, and more research is needed in the future to investigate the optimal endometrial preparation protocol in the frozen-thawed embryo transfer population in relation to cost and different causes of infertility.

Conclusion

In conclusion, our study showed that natural cycles have similar pregnancy outcomes in terms of clinical pregnancy and live birth to the other three endometrial preparation options. Natural cycles have a natural hormone-induced endometrial environment, avoid the use of exogenous hormones, avoid OHSS, and are more conducive to embryo implantation.The natural cycles is also less costly and simple in terms of late luteal support. The natural cycle protocol can therefore be the recommended option for endometrial preparation in the FET population.

Abbreviations

FET, frozen-thawed embryo transfer; ART, assisted reproductive technology; OHSS, ovarian hyperstimulation syndrome; NC, natural cycle; HRT, hormone replacement treatment cycle; GAC, GnRH agonist artificial cycle; OC, ovulation stimulation cycle; AFC, antral follicle count; AMH, anti-müllerian hormone; FSH , follicle-stimulating hormone

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of Chongqing Medical University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZZH, GLH and XM are the coordinator of the project. QY and BXQ conceived and designed the study. LT and WQ revised the study and made comments. WQ, JY , FQ, LXY, MXQ, YY contributed to data collection. QY, BXQ, TXJ and ZZH analysed and interpreted the data. DYB revised the manuscript. All authors read and approved the final manuscript.

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References

1. Roque M, Haahr T, Geber S, Esteves S, Humaidan P. Fresh versus elective frozen embryo transfer in IVF/ICSI cycles: a systematic review and meta-analysis of reproductive outcomes. Hum Reprod Update. 2019;25(1):2–14.

2. Shi Y, Sun Y, Hao C, Zhang H, Wei D, Zhang Y, et al. Transfer of Fresh versus Frozen Embryos in Ovulatory Women. N Engl J Med2018 Jan 11;378(2):126–36.
3. Wei D, Liu J, Sun Y, Shi Y, Zhang B, Liu J, et al. Frozen versus fresh single blastocyst transfer in ovulatory women: a multicentre, randomised controlled trial. 2019;393(10178):1310–8.
4. Yu Y, Zhao S, Li Y, Niu Y, Wei D, Zhang S, et al. Live birth after a freeze-only strategy versus fresh embryo transfer in three randomized trials considering progesterone concentration. 2020;41(3):395–401.
5. Maheshwari A, Pandey S, Amalraj Raja E, Shetty A, Hamilton M, Bhattacharya SJHru. Is frozen embryo transfer better for mothers and babies? Can cumulative meta-analysis provide a definitive answer? 2018;24(1):35–58.
6. Zech J, Brandao A, Zech M, Lugger K, Neururer S, Ulmer H, et al. Elective frozen-thawed embryo transfer (FET) in women at risk for ovarian hyperstimulation syndrome. 2018;18(1):46–52.
7. Lamptey J, Li F, Adu-Gyamfi E, Chen X, Czika A, Otoo A, et al. Downregulation of fascin in the first trimester placental villi is associated with early recurrent miscarriage. 2021;403(1):112597.
8. Fazleabas AT, Strakova Z. Endometrial function: cell specific changes in the uterine environment. Molecular and cellular endocrinology2002 Jan 25;186(2):143–7.
9. Paulson RJF, sterility. Introduction: Endometrial receptivity: evaluation, induction and inhibition. 2019;111(4):609 – 10.
10. Mu Y, Li Q, Cheng J, Shen J, Jin X, Xie Z, et al. Integrated miRNA-seq analysis reveals the molecular mechanism underlying the effect of acupuncture on endometrial receptivity in patients undergoing fertilization. embryo transplantation. 2020;10(1):6.
11. Tao Y, Wang N. Adjuvant Vaginal Use of Sildenafil Citrate in a Hormone Replacement Cycle Improved Live Birth Rates Among 10,069 Women During First Frozen Embryo Transfers. Drug design, development and therapy2020;14:5289–97.
12. Mackens S, Santos-Ribeiro S, van de Vijver A, Racca A, Van Landuyt L, Tournaye H, et al. Frozen embryo transfer: a review on the optimal endometrial preparation timing. 2017;32(11):2234–42.
13. Madani T, Ramezanali F, Yahyaei A, Hasani F, Bagheri Lankarani N, Mohammadi Yeganeh L. Live birth rates after different endometrial preparation methods in frozen cleavage-stage embryo transfer cycles: a randomized controlled trial. Archives of gynecology and obstetrics2019 Apr;299(4):1185–91.
14. Guan Y, Fan H, Styer A, Xiao Z, Li Z, Zhang J, et al. A modified natural cycle results in higher live birth rate in vitrified-thawed embryo transfer for women with regular menstruation. 2016;62(5):335–42.
15. Li C, He Y, Xu J, Wang Y, Liu H, Duan C, et al. Perinatal outcomes of neonates born from different endometrial preparation protocols after frozen embryo transfer: a retrospective cohort study. 2021;21(1):341.
16. Liu X, Shi W, Shi J. Natural cycle frozen-thawed embryo transfer in young women with regular menstrual cycles increases the live-birth rates compared with hormone replacement treatment: a retrospective cohort study. Fertility and sterility2020 Apr;113(4):811–7.
17. Groenewoud E, Cohlen B, Al-Oraiby A, Brinkhuis E, Broekmans F, de Bruin J, et al. A randomized controlled, non-inferiority trial of modified natural versus artificial cycle for cryo-thawed embryo transfer. 2016;31(7):1483–92.
18. Mounce G, McVeigh E, Turner K, Child TJF. sterility. Randomized, controlled pilot trial of natural versus hormone replacement therapy cycles in frozen embryo replacement in vitro fertilization. 2015;104(4):915 – 20.e1.

19. Groenewoud E, Cantineau A, Kollen B, Macklon N, Cohlen BJHru. What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis. 2017;23(2):255–61.
20. Glujovsky D, Pesce R, Sueldo C, Quinteiro Retamar A, Hart R, Ciapponi AJTCdosr. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. 2020;10:CD006359.
21. Zhang T, Li Z, Ren X, Huang B, Zhu G, Yang W, et al. Endometrial thickness as a predictor of the reproductive outcomes in fresh and frozen embryo transfer cycles: A retrospective cohort study of 1512 IVF cycles with morphologically good-quality blastocyst. Medicine2018 Jan;97(4):e9689.
22. Sahin G, Acet F, Calimlioglu N, Meseri R, Tavmergen Goker E, Tavmergen EJJogo, et al. Live birth after frozen-thawed embryo transfer: which endometrial preparation protocol is better? 2020;49(8):101782.
23. Labrosse J, Lobersztajn A, Pietin-Vialle C, Villette C, Dessapt A, Jung C, et al. Comparison of stimulated versus modified natural cycles for endometrial preparation prior to frozen embryo transfer: a randomized controlled trial. 2020;40(4):518–24.
24. Greco E, Litwicka K, Arrivi C, Varricchio M, Caragia A, Greco A, et al. The endometrial preparation for frozen-thawed euploid blastocyst transfer: a prospective randomized trial comparing clinical results from natural modified cycle and exogenous hormone stimulation with GnRH agonist. 2016;33(7):873–84.
25. Li SJ, Zhang YJ, Chai XS, Nie MF, Zhou YY, Chen JL, et al. Letrozole ovulation induction: an effective option in endometrial preparation for frozen-thawed embryo transfer. Archives of gynecology and obstetrics2014 Mar;289(3):687–93.
26. Wang J, Yap Y, Matthews CJHr. Frozen-thawed embryo transfer: influence of clinical factors on implantation rate and risk of multiple conception. 2001;16(11):2316–9.
27. Ghobara T, Gelbaya T, Ayeleke RJTCdosr. Cycle regimens for frozen-thawed embryo transfer. 2017;7:CD003414.
28. Alur-Gupta S, Hopeman M, Berger D, Gracia C, Barnhart K, Coutifaris C, et al. Impact of method of endometrial preparation for frozen blastocyst transfer on pregnancy outcome: a retrospective cohort study. 2018;110(4):680–6.
29. Zong L, Liu P, Zhou L, Wei D, Ding L, Qin Y. Increased risk of maternal and neonatal complications in hormone replacement therapy cycles in frozen embryo transfer. Reproductive biology and endocrinology: RB&E2020 May 4;18(1):36.
30. Pang C, Guo L, Bi Y, Wang K, Lian F, Wu Z, et al. A comparison of pregnancy rate between natural cycle and hormone replacement cycle in patients who underwent frozen embryo transfer using 2 consecutive hormone replacement regiments: A STROBE-compliant retrospective study. 2020;99(37):e22163.
31. Kinay T, Tasci Y, Dilbaz S, Cinar O, Demir B. Haberal AJGetojotISoGE. The relationship between endometrial thickness and pregnancy rates in GnRH antagonist down-regulated ICSI cycles. 2010;26(11):833–7.
32. Shaodi Z, Qiuyuan L, Yisha Y, Cuilian ZJPo. The effect of endometrial thickness on pregnancy outcomes of frozen-thawed embryo transfer cycles which underwent hormone replacement therapy. 2020;15(9):e0239120.
33. Dancet E, Fleur Dancet E, D'Hooghe T, d'Hooghe T, van der Veen F, Bossuyt P, et al. "Patient-centered fertility treatment": what is required? 2014;101(4):924–6.
34. Dal Prato L, Borini AJF, sterility. Best protocol for frozen-thawed embryo transfer-cost benefit analysis needed. 2006;86(5):1554-5; author reply 5–6.

35. Peeraer K, Couck I, Debrock S, De Neubourg D, De Loecker P, Tomassetti C, et al. Frozen-thawed embryo transfer in a natural or mildly hormonally stimulated cycle in women with regular ovulatory cycles: a RCT. 2015;30(11):2552–62.

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