ORIGINAL

Is a freeze-all strategy necessary for all embryo transfers : Fresh embryo transfer without progesterone elevation results in an equivalent pregnancy rate to cryopreserved embryo transfer

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Abstract : Objectives : It has been suggested that the clinical outcomes of frozen-thawed embryo transfer (ET) are superior to those of fresh embryo transfer. We examined whether a freeze-all strategy is necessary for all embryo transfers, and, if not, to evaluate the conditions in which the pregnancy rates of fresh embryo transfer and frozen-thawed ET did not differ. Methods : Patients who underwent blastocyst transfer at Tokushima University Hospital between 2008 and 2019 were enrolled. The clinical outcomes and clinical characteristics of 1,022 patients that underwent fresh embryo transfer and 1,728 patients that underwent frozen-thawed ET were examined retrospectively. We considered the factors that influenced the pregnancy outcomes of fresh embryo transfer. Results : The frozen-thawed ET group exhibited significantly higher pregnancy, live-birth, and miscarriage rates than the fresh embryo transfer group. In the fresh embryo transfer group, a high progesterone level on the day of the human chorionic gonadotropin (hCG) trigger and lower grade embryos were risk factors for a low pregnancy rate. However, in the cases in which the progesterone level was <1.0 ng/mL the pregnancy rate was equal to that of frozen-thawed ET. Conclusions : A freeze-all strategy is not necessary for embryo transfers, but should be employed in cases involving pre-ovulatory progesterone elevation. J. Med. Invest. 69 : 224-229, August, 2022

Keywords **:** *freeze-all, fresh embryo transfer, progesterone level*

INTRODUCTION

Since the first successful in vitro fertilization-embryo transfer (IVF-ET) in 1978, fresh ET ; i.e., performing ET in the cycle in which the oocyte is retrieved, has been the main IVF-ET method (1). However, due to the development of cryopreservation technology embryos can now be safely frozen and preserved for later use. Multiple studies have reported that the uterine environment is unfavorable for embryo implantation in cycles in which oocytes are retrieved and that the clinical outcomes of frozen-thawed embryo transfer (ET) are better than those of fresh ET (2-5). Thus, a freeze-all strategy, in which all high-quality embryos are frozen in the cycle in which oocyte retrieval is performed and are transferred in subsequent cycles, may be recommended, especially under conditions involving supraphysiological hormonal levels.

In Japan, about 85% of children born using assisted reproductive technology (ART) in 2019 were conceived through FET, and about 48% were conceived using a freeze-all strategy (6). One of the reasons why the freeze-all strategy is becoming more common in Japan is that this strategy can prevent or reduce the risk of ovarian hyperstimulation syndrome (OHSS). Another reason is that mild stimulation using clomiphene citrate is more common in Japan, which can result in the formation of thin endometria (7). In addition, as mentioned above, it has been reported that the clinical outcomes of frozen-thawed ET may be better, e.g., the pregnancy rate per frozen-thawed ET is 35.4%, whereas that per fresh ET is 21.0% (6). Although these findings may lead to the idea that a freeze-all strategy should be employed for all ET, it should be noted that fresh ET also has several advantages. For example, fresh ET can reduce costs associated with cryopreservation and subsequent frozen-thawed ET as well as the time between oocyte collection and ET. In addition, some previous studies and meta-analyses have shown that the cumulative live birth rate in fresh ET did not differ from that in frozen-thawed ET after the freezing of all embryos (8-10). Thus, it is important to determine whether there are certain conditions in which the pregnancy rate of fresh ET is equal to that of frozen-thawed ET by unifying the stimulation, freezing, and ET conditions.

Therefore, we compared the clinical outcomes of fresh ET and frozen-thawed ET to examine whether a freeze-all strategy is necessary in all cases. Furthermore, we examined the factors that affect the pregnancy rate in fresh ET and evaluated the conditions in which the pregnancy rate of fresh ET was equal to that of frozen-thawed ET.

MATERIALS AND METHODS

This was a retrospective cohort study that included patients that underwent IVF at Tokushima University Hospital between January 2008 to December 2019. In total, 1,022 cases involving fresh ET and 1,728 cases involving frozen-thawed ET after 2,173 cycles of oocyte retrieval were evaluated. Cases in which cleavage-stage ET was performed were excluded. Firstly, clinical outcomes were compared between fresh ET and frozen-thawed ET. Primary outcome was pregnancy rate. Secondly, baseline and

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clinical characteristics were compared between the pregnant and non-pregnant groups in the fresh ET group. Thirdly, the clinical conditions that favor fresh ET were evaluated, focusing on endometrial thickness, embryo quality, and the progesterone level on the day of the human chorionic gonadotropin (hCG) trigger.

This study was approved by the institutional clinical research review board of Tokushima University (No.3861) and the information is disclosed in an information disclosure document in Tokushima University Hospital HP.

Procedures

The participants were treated with one of the following controlled ovarian stimulation protocols : the gonadotropin-releasing hormone (GnRH) antagonist protocol, the GnRH agonist long protocol, or mild stimulation with clomiphene citrate in combination with or without low-dose gonadotropins. In the GnRH antagonist and GnRH agonist long protocols, the participants received daily injections of recombinant follicle-stimulating hormone and/or human menopausal gonadotropin. The initial gonadotropin dose was based on the patient's age, body mass index, basal FSH and anti-Müllerian hormone levels, and antral follicle count, and the dose was adjusted during stimulation in accordance with the number of follicles and follicular growth. When at least three follicles had reached ≥18 mm or in mean diameter, 5000-10000 IU hCG was administered to induce the final maturation of oocytes. The oocytes were retrieved at 34-36 h after the injection of hCG. Embryos were cultured using sequential media until the blastocyst stage. Although our first-choice ET method was fresh ET ; i.e., 5-6 day-cultured blastocysts were transferred in the same cycle as when the oocyte was retrieved, a freeze-all strategy was selected for patients that were at high risk of OHSS (moderate to severe OHSS) and frozen-thawed ET was performed in the next cycle. Luteal-phase support was started from the day of oocyte retrieval with vaginal progesterone or the intramuscular administration of hCG. All or extra embryos were frozen using vitrification-based methods. Frozen-thawed ET was performed in a hormone replacement (HRT) cycle or natural cycle. When it was performed in an HRT cycle, the patients received oral estradiol (E2) or E2 patches, and the daily administration of chlormadinone acetate or intramuscular progesterone was started on day 6 prior to thawing and the ET. If pregnancy was achieved, the administration of E2 and progestin was continued until 9-10 weeks' gestation. In the natural cycle protocol, hCG was administered as an ovulation trigger, and luteal phase support was started after ovulation. Frozen-thawed ET was carried on day 5 after suspected ovulation. We defined clinical pregnancy as the detection of a gestational sac in the uterine cavity by ultrasound, and good-quality embryos were defined as a Gardner classification of 3AB or higher.

Statistical analysis

Statistical analyses were performed using the χ^2test or the multivariate Wilcoxon's test using the BellCurve Excel software ver7.08. Comparisons between the two groups were carried out using the Student's t-test or one-way analysis of variance. The normality of continuous variables was examined by Shapiro-Wilk test. The multivariate analysis was performed for the explanation variables which determined in advance with reference to previous reports.

Data are expressed as the mean and standard deviation (SD). *P*-values of <0.05 were considered to indicate a significant difference.

RESULTS

In total, 1,022 fresh ET and 1,728 frozen-thawed ET were included in this study, and the subjects' clinical outcomes and baseline and clinical characteristics were examined retrospectively. A freeze-all strategy was employed in 15% (326/2173) of oocyte retrieval procedures, and age, causes of infertility, endometrial thickness, and the percentage of good quality embryos were comparable in the fresh ET and frozen-thawed ET groups (Table 1). In total, 82.9% (847/1022) of patients in the fresh ET group and 90.6% (1566/1728) of those in the frozen-thawed ET group underwent a single ET ; i.e., one blastocyst was transferred to the uterus. The number of transferred embryos was greater in the fresh ET group (1.18 ± 0.02) than in the frozen-thawed ET group (1.10 ± 0.01). On the day of the ET, the uterine endometrium was thicker in the fresh ET group (11.0 ± 2.8 mm) than in the frozen-thawed ET group (9.8 ± 2.4 mm). The clinical outcomes of the fresh ET and frozen-thawed ET groups are shown in Table 2. The clinical pregnancy rate per transfer was lower in the fresh ET group (34.1%) than in the frozen-thawed ET group (42.1%) (Table 2). Similarly, the ongoing pregnancy rate per transfer (at 12 weeks' gestation) was lower in the fresh ET group (26.7%) than in the frozen-thawed ET group (30.8%). Furthermore, the live birth rate per transfer was lower in the fresh ET group (26.3%) than in the frozen-thawed ET group (30.7%). On the other hand, the miscarriage rate per pregnancy was lower in the fresh ET group (20.1%) than in the frozen-thawed ET group (26.2%).

The clinical characteristics of the pregnant and non-pregnant

Table 1. Baseline and cycle characteristics of the fresh embryo transfer and frozen-thawed embryo transfer groups

	Fresh ET (n = 1,022)	Frozen-thawed ET (n = 1,728)	*P*-value
Age (years)	36.2 ± 4.2	36.2 ± 4.4	0.193
Cause of infertility			0.176
Tubal factors	206 (20.3%)	328 (24.7%)	
Endometriosis	46 (4.5%)	56 (4.2%)	
Male factors	286 (28.1%)	307 (23.2%)	
Unexplained	388 (38.2%)	566 (42.7%)	
Combination of above	90 (8.9%)	65 (4.9%)	
Number of embryos for transfer	1.18 ± 0.02	1.10 ± 0.01	< 0.01
Endometrial thickness on the day of ET (mm)	11.0 ± 2.8	9.8 ± 2.4	< 0.01
Good quality embryos (%)	73.0	75.6	0.365

ET ; embryo transfer

patients in the fresh ET group are shown in Table 3. The total administered gonadotropin dose was smaller in the pregnant group (2691 ± 917 IU) than in the non-pregnant group (3070 ± 1105 IU), and the progesterone level on the day of the hCG trigger was lower in the pregnant group (0.74 ± 0.03 ng/mL) than in the non-pregnant group (0.79 ± 0.03 ng/mL) (Table 3). On the day of the ET, the endometrium was thicker in the pregnant group (11.3 ± 2.8 mm) than in the non-pregnant group (10.8 ± 3.2 mm), and the percentage of good quality embryos was higher in the pregnant group (88.1%) than in the non-pregnant group (65.1%).

According to the multivariate analysis as an explanation variable in quality embryos, endometrial thickness and progesterone level on the day of hCG, the progesterone level on the day of the hCG trigger (OR = 1.34 95%CI : 1.03-2.15, p = 0.037) and quality of embryos (OR = 3.96 95%CI : 2.77-5.67, p<0.01) were independent factors. Focusing on the relationship between progesterone levels and the pregnancy rate in the fresh ET group, the cut-off level of progesterone levels using the ROC curve was 0.9 ng/mL. And the cases involving low progesterone levels (<1.0 ng/mL) showed a higher pregnancy rate than those with high progesterone levels (≥1.0 ng/mL) (Figure 1). Furthermore, when the pregnancy rates of the fresh ET and frozen-thawed ET groups were compared in each age category, the pregnancy rates were lower in the fresh ET group than in the frozen-thawed ET group in the cases involving patients aged <30 years and 36-38 years. On the other hand, no such differences were observed among the patients aged over 39 years (Figure 2A). Furthermore, the pregnancy rate did not differ between the frozen-thawed ET group and the fresh ET cases involving low progesterone levels (<1.0 ng/mL), even among the patients aged <38 years (Figure 2B).

Table 2. Clinical outcomes of the fresh embryo transfer and frozen-thawed embryo transfer groups

	Fresh ET (n = 1,022)	Frozen-thawed ET (n = 1,728)	*P*-value
Clinical pregnancies / ET	349 (34.1%)	728 (42.1%)	< 0.01
Ongoing pregnancies / ET	273 (26.7%)	533 (30.8%)	0.022
Live births / ET	269 (26.3%)	531 (30.7%)	0.015
Miscarriages / pregnancy	70 (20.1%)	191 (26.2%)	0.032

ET : embryo transfer

Table 3. Baseline and cycle characteristics of the pregnant and non-pregnant patients in the fresh embryo transfer group

	Pregnant group (n = 352)	Non-pregnant group (n = 670)	*P*-value
Age (y)	35.2 ± 4.0	36.8 ± 4.3	0.132
Baseline FSH level (IU/L)	7.4 ± 6.9	7.2 ± 3.7	0.436
Causes of infertility			0.05
Tubal factors	69 (19.8%)	137 (20.5%)	
Endometriosis	22 (6.3%)	24 (3.6%)	
Male factors	100 (28.7%)	186 (27.9%)	
Unexplained	127 (36.4%)	261 (39.1%)	
Combination of above	31 (8.9%)	59 (8.8%)	
COS protocol			0.786
GnRH agonist	290 (82.4%)	464 (69.3%)	
GnRH antagonist	59 (16.8%)	199 (29.7%)	
Mild (CC*, natural)	3 (0.8%)	7 (1.4%)	
Days of ovarian stimulation	11.2 ± 1.5	11.5 ± 1.9	0.056
Total dose of gonadotropin (IU)	2691 ± 917	3070 ± 1105	< 0.01
Estradiol level on the day of hCG trigger (pg/mL)	2483 ± 1799	2473 ± 1970	0.088
Progesterone level on the day of hCG trigger (ng/mL)	0.74 ± 0.03	0.79 ± 0.03	< 0.01
Number of oocytes retrieved	11.0 ± 6.1	10.4 ± 6.2	0.707
Number of bipronuclear oocytes	6.8 ± 4.2	6.2 ± 4.1	0.875
Number of transferred embryos	1.2 ± 0.4	1.2 ± 0.4	0.996
Endometrial thickness on the day of ET (mm)	11.3 ± 2.8	10.8 ± 3.2	< 0.01
Supernumerary blastocysts	2.1 ± 2.3	1.5 ± 2.2	0.228
Good quality embryos (%)	88.1	65.1	< 0.01

CC : clomiphene citrate
COS : controlled ovarian stimulation
ET : embryo transfer
FSH : follicle-stimulating hormone
hCG : human chorionic gonadotropin

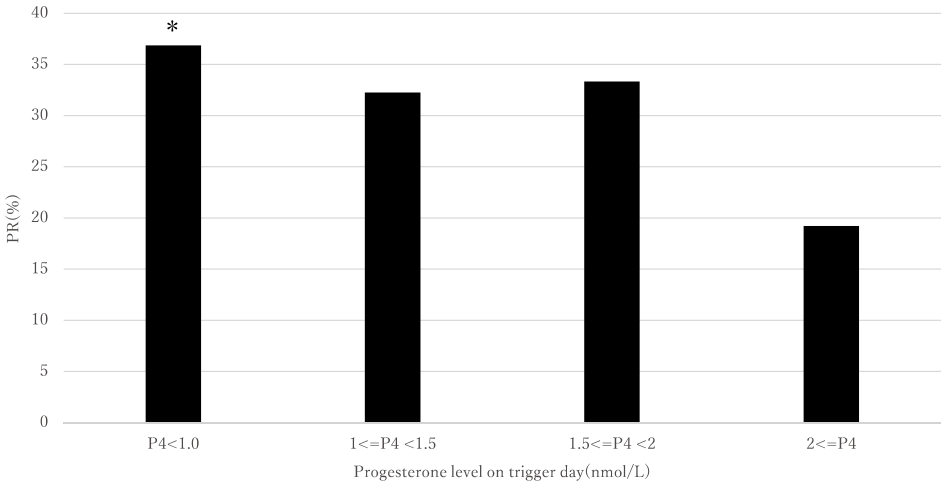

Figure 1. Pregnancy rate according to the progesterone level on the day of the hCG trigger
* : P <0.05 vs. others, PR : pregnancy rate per embryo transfer

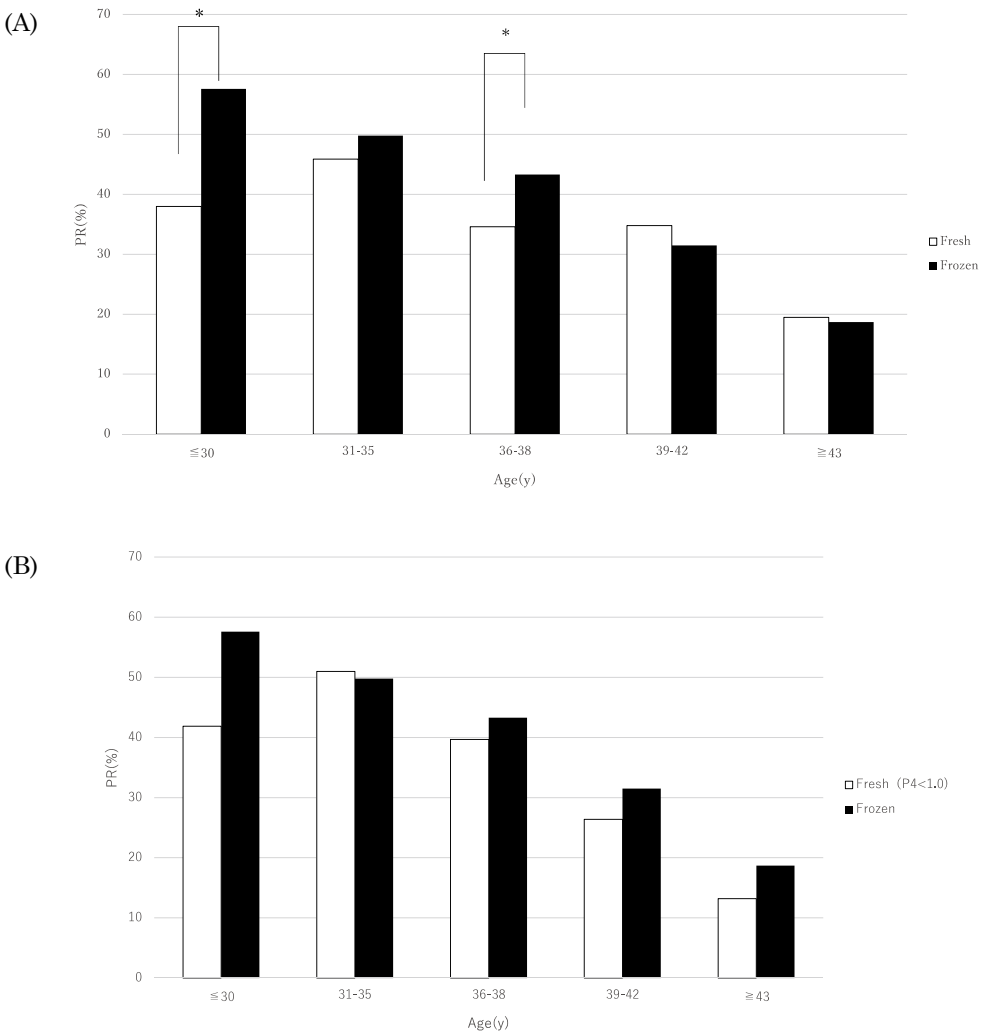

Figure 2. (A) Pregnancy rates of the fresh embryo transfer and frozen-thawed embryo transfer groups according to age category
(B) Pregnancy rates in the frozen-thawed embryo transfer group and the patients with low progesterone levels (<1.0 ng/mL) that underwent fresh embryo transfer according to age category
* : P <0.05 fresh ET vs. FET, PR : pregnancy rate per embryo transfer, ET : embryo transfer, P4 : progesterone

DISCUSSION

A freeze-all strategy has been recommended for patients that are at high risk of OHSS ; i.e., those in which large numbers of follicles are growing, to avoid serious adverse effects, whereas such benefits may not be evident in patients in which small numbers of follicles are growing. However, because some previous studies reported that FET produced higher clinical pregnancy rates than fresh ET (2-5), a freeze-all strategy is often employed in cases involving patients that are at low risk of OHSS to improve the clinical outcomes of ART. Actually, some ART clinics and hospitals employ a freeze-all strategy for all cases.

It has been suggested that the receptivity of the uterine endometrium may be impaired when the endometrium is exposed to a high concentration of steroids resulting from the development of multiple follicles. Previous studies have pointed out that the changes in the hormonal environment that accompany ovarian hyperstimulation affect the periodic changes and gene transcription of the uterine endometrium, and reduce the receptivity of the endometrium to embryos (11-12). Thus, it is now considered that a freeze-all strategy would improve pregnancy rates in these cases.

Recently, systematic reviews and meta-analyses have shown that the probability of a live birth is higher after a first frozen ET followed by a freeze-all cycle than after a first fresh ET in high responders (patients in whom large numbers of follicles grow easily and often have higher progesterone levels on the day of hCG trigger), but not normal responders (13-16). On the other hand, some randomized controlled trials and meta-analyses have indicated that the live birth rate does not differ between fresh ET and frozen-thawed ET (8-10). We speculate that differences in the ovarian stimulation and cryopreservation methods and in the stages at which the embryos were transferred may have caused these discrepancies. One of the strengths of this study was that the stage at which the embryos were transferred (the blastocyst stage) and the freezing method (vitrification method) were unified across all cases. As a result, it was found that the clinical pregnancy rate, ongoing pregnancy rate, and live birth rate were significantly higher in the frozen-thawed ET group than in the fresh ET group. These tendencies were evident in patients younger than 38 years old, whereas no such differences were observed in those aged over 39 years. Similar results have been reported in a previous study (17).

We also found that the progesterone level on the day of the hCG trigger affects the pregnancy rate in patients that undergo fresh ET. In addition, we showed that pregnancy rate of the patients with progesterone levels of <1.0 ng/mL that underwent fresh ET was equal to that seen in the frozen-thawed ET group. However, as noted above some meta-analyses have suggested that premature progesterone elevation has negative effects on implantation (18-20), but it has also been reported that such adverse effects of progesterone on clinical outcomes do not occur in subsequent frozen-thawed ET or the donor/recipient cycles (19). These findings suggest that the premature elevation of the progesterone level does not influence the quality of embryos. It has been hypothesized that premature progesterone elevation may occur readily in younger patients that exhibit excessive ovarian responses to gonadotropins. Our finding that the pregnancy rate of the fresh ET group was lower than that of the frozen-thawed ET group among younger patients (≤38 years) may be consistent with this hypothesis. On the other hand, our finding that the pregnancy rate in patients with lower progesterone levels (<1.0 ng/mL) that underwent fresh ET was equal to that seen in the frozen-thawed ET group indicated that fresh ET can be employed in cases that fulfil certain criteria.

It has been suggested that compared fresh ET with frozen-thawed ET may increase the risk of some perinatal events, such as the birth of large-for-gestational-age infants, hypertensive disorders of pregnancy, and excessive bleeding after delivery (21-22). Thus, a freeze-all strategy should be employed in selected cases in which this method can improve clinical outcomes. It is not a prospective study, there is limitation and it may take potential bias in the process to choose fresh or freeze all cycles. The cases of high ovarian reserve often were selected to freeze all cycles, and such cases may not be included in the fresh embryo transfer group. And confounding factors such as BMI, parity, gravidity and duration of infertility were not included in this study. A further prospective study is required to confirm our hypotheses.

In conclusion, out findings suggest that a freeze-all strategy should be employed for patients that are at high risk of premature progesterone elevation or OHSS. On the other hand, for other patients fresh ET should be chosen in order to reduce costs and the time to pregnancy.

CONFLICT OF INTEREST

No conflicts of interest exist.

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