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Original Article

Does the "freeze-all" policy allow for a better outcome in assisted reproductive techniques than the use of fresh embryo transfers? – A retrospective study on cumulative live birth rates

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ABSTRACT

Objective: There are increasing concerns regarding the adverse effects associated with control ovarian hyperstimulation (COH) in both endometrial and uterine environments. With the "segmentation treatment policy" of assisted reproductive techniques (ART), endometrial problems may be obviated through embryo cryopreservation. However, it remains unclear if the "freeze-all policy" offers a better outcome when compared with fresh embryo transfer (ET). To clarify this, we compared the cumulative live birth rates (CLBRs) between these two patient populations.

Materials and methods: This is a retrospective study on 853 patients undergoing ovarian stimulation and ART (including IVF/ICSI) during the period from January 2012 to June 2014 in Taichung Veterans General Hospital, Taiwan, ROC. We followed up with these patients through to November 2016. Patients whose embryos were not completely transferred back were excluded. The study group ('freeze-all') included 84 patients whose cycles were performed initially without fresh ET, but were later given frozen-thawed ET. The control group ('fresh ET') had 625 patients whose cycles were performed with fresh ET, followed by frozen-thawed ET. Basic parameters and CLBRs were statistically compared between these two groups.

Results: The CLBRs in the study group were significantly higher than those in the control group (64.3% vs. 45.8%, $p = 0.001$). Subgroup analysis revealed that when the number of oocyte pick up (OPU) is between 4 and 15, the CLBRs in the study group were significantly better (58.3% vs. 40.9%, $p = 0.042$). For those with OPU <4 or OPU >15 the CLBRs were similar in these two groups (OPU < 4: study vs. control 23.1% vs. 18.8% respectively, $p = 0.713$; OPU>15: study vs. control 85.7% vs. 80.8% respectively, $p = 0.625$)

Conclusion: The Freeze-all policy improved the ART outcome for normal responders.

Introduction

Currently, fresh embryo transfer (ET) is a standard procedure in Assisted Reproductive Therapies. However, there are increasing concerns regarding the adverse effects of COH which could induce supra-physiologic hormonal levels, thus leading to decreased Endometrial Receptivity (ER), resulting in a poor outcome [1]. With improved embryo cryopreservation techniques, as high as a 95% survival rate of vitrified blastocysts could be achieved [2]. The transfer of frozen-thawed embryos does not seem to have any adverse effects on neonatal outcome [3,4]. These lines of evidence provide practical measures for the cryopreservation of embryos, and the transferring of them into a more physiological and receptive endometrium, when compared with a fresh cycle, as COH may decrease the ER [5]. Furthermore, there are risks of developing severe ovarian hyperstimulation syndrome (OHSS) in cycles with fresh ET, where there has been an incidence rate of 1–14% [6]. With this strategy, it is possible to prevent OHSS using antagonist protocols with a GnRH agonist trigger, along with the subsequent elective cryopreservation of all embryos [7]. As such, the freeze-all

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policy seems to be an ideal alternative for fresh ET. With the use of the freeze-all policy, all the embryos in a fresh in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle were cryopreserved, with the frozen-thawed embryos then transferred in later cycles. However, it remains unclear who will really benefit from the freeze-all policy. There are studies which indicate that elective FET may improve pregnancy rates [8,9]. But so far as to our knowledge, there is still a lack of studies reporting the cumulative live birth rates. Here, we performed a retrospective study to compare the cumulative live birth rates between patients using fresh ET, and patients using the freeze-all policy.

Materials and methods

Study participants

All enrolled patients (n = 853) underwent COH and IVF/ICSI in the Center for Reproductive Medicine in the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology and Women's Health, Taichung Veterans General Hospital, Taichung, Taiwan, between January 2012 and June 2014. These patients were then followed up until November 2016. We excluded those cycles in which no oocyte was retrievable or embryos transferable (n = 52), with donated oocyte (n = 1), planned for PGS/PGD (n = 7) or with oocytes collected before the study period (n = 2). Cycles with all embryos frozen totaled 123, and those with fresh ET were 668. After excluding patients whose embryos were not yet completely transferred, the study group (freeze-all policy) was composed of 84 cycles, and the control group (fresh ET) 625 cycles. The details of the patient groups are shown in Figs. 1 and 2. Patients were further divided according to their age and the number of OPU (OPU<4, OPU 4–15 and OPU >15). The control group had a total of 625 patients, where the group with OPU <4, had 96 patients (38 aged<38 years old and 58 aged ≥ 38). In the group of OPU 4–15 there were a total of 399 patients (261 aged<38 years old and 138 aged ≥ 38). In the group of OPU >15 there were a total of 130 patients (121 aged<38 years old and 9 aged ≥ 38). In the study group, there were a total of 84 patients. Thirteen patients had <4 oocytes retrieved (2 aged < 38, and 11 aged ≥ 38). Thirty-six patients had 4–15 oocytes retrieved (23 aged < 38, and 13 aged ≥ 38). Thirty-five patients had >15 oocytes retrieved (31 aged < 38, and 4 aged ≥ 38).

The procedures of IVF

Superovulation was induced through the use of one of the following two methods [1]: long agonist protocol, including a luteal phase pituitary down-regulation with a Gonadotropin-releasing Hormone (GnRH) agonist (Leuprolide; Ipsen Biotech) for > 10 days, followed by follicular stimulation with a recombinant FSH (Gonal-F; Merck Serono; or Puregon; Organon) ± highly purified hMG (Menopur, Ferring Pharmaceuticals) as appropriate for the condition of each individual patient [2]. GnRH antagonist protocol (Cetrotide, Merck Serono) with follicular stimulation with a recombinant FSH and hMG. Ovulation triggering was induced by injecting the recombinant hCG (Ovidrel, Merck Serono) or GnRH agonist (in antagonist patients with a predictive high risk of OHSS). Ultrasound-guided transvaginal oocyte retrieval was carried out 35–36 h post-triggering. Oocytes were either inseminated (IVF) or underwent intracytoplasmic sperm injection approximately 4 h after collection, and fertilization was confirmed 16–18 h afterwards. Embryos were cultured in Vitrolife G-series medium (Vitrolife AB, Goteborg, Sweden). For the control group, D2 or D3 cleavage stage embryos or D5 blastocysts were transferred in the fresh cycle. The number of embryos transferred was usually 1–4, in accordance with the Taiwanese Society of Reproductive Medicine guidelines (2012), and depended on the condition of each individual patient. Blastocysts were classified according to the criteria of Gardner and Schoolcraft [10]. The surplus embryos were cryopreserved through vitrification by CryoTop (before July 2013) or CryoTech (after July 2013), in a method proposed by Kuwayama [11,12]. In the study group, embryos were cryopreserved by vitrification either at the 2 Pronuclear stage (2PN), cleavage embryo stage (day 2–3) or blastocyst stage (day 5–6). The endometrial preparations in the following frozen ET cycles were programmed by either hormone replacement cycles or modified natural cycles, depending on the

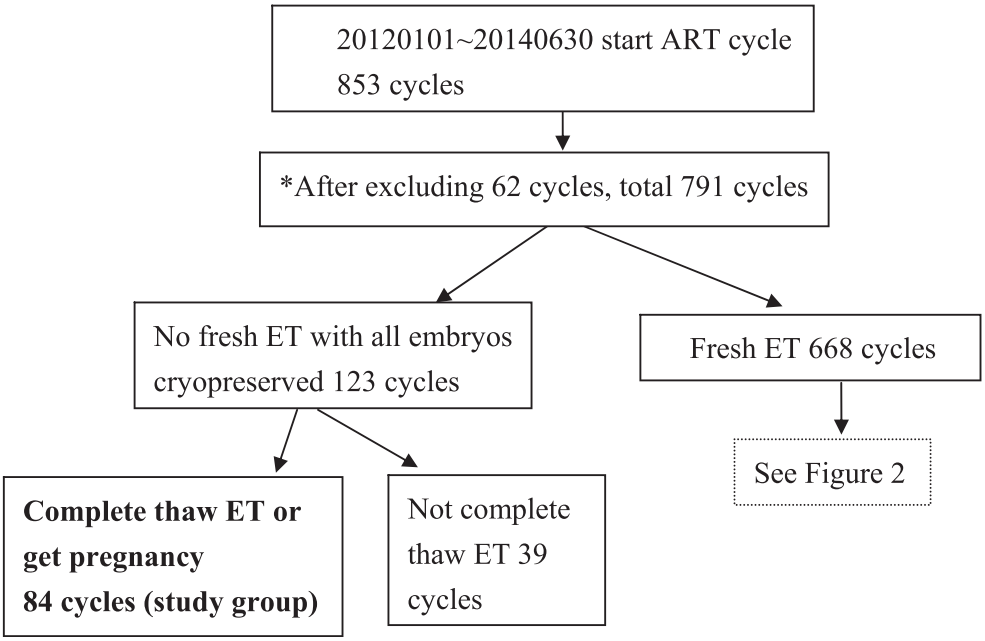

Fig. 1. Depicts the allocation of the study group (n = 84). *The excluded cycles include 52 cycles with no oocyte retrieved, one for oocytes donor, seven for PGD and two cycles with combined embryo derived from that present and previous cycles before the study period.

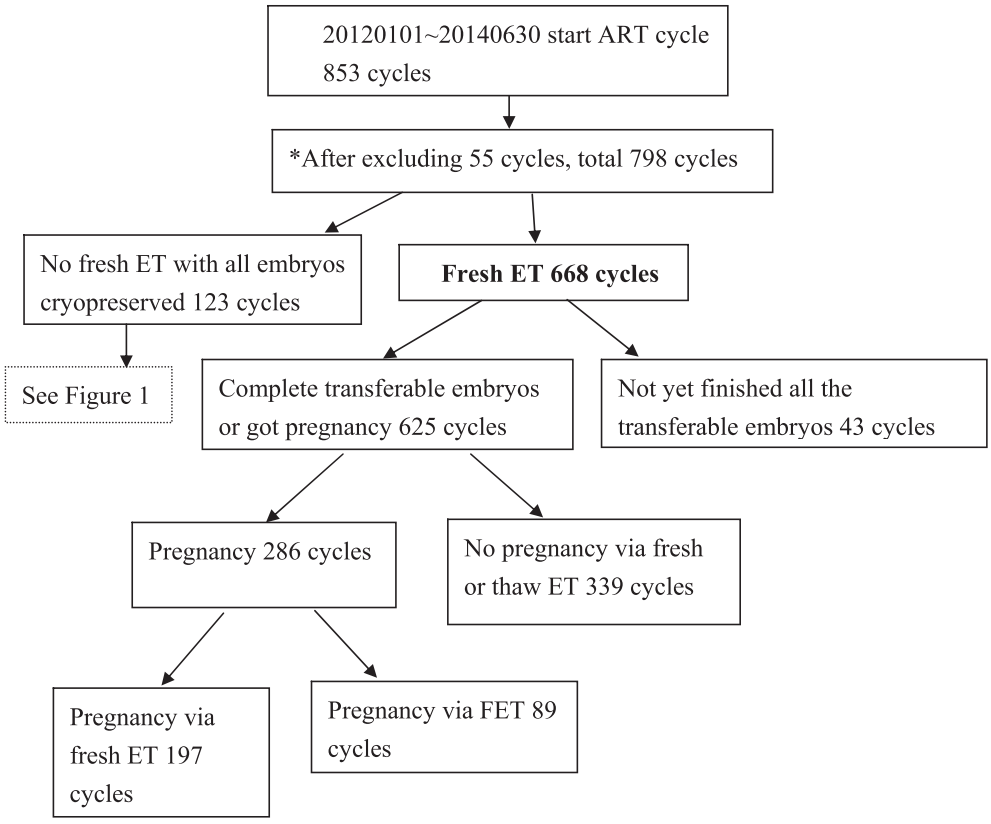

Fig. 2. Depicts the allocation of the control group (n = 625, 286 + 339).

conditions of the individual patients. In the hormonal preparation cycle, oral estradiol (Estrade, SYNMOSA) was administered at 8 mg/day from day 3 through day 7 of the menstrual cycle, and at 12 mg/day from day 8 onward until the completion of the treatment cycle. After more than 10 days, a transvaginal ultrasound examination was performed to confirm that no dominant follicle had emerged and to also measure endometrial thickness. When the endometrium thickness reached ≥8 mm, progesterone at 50 mg daily (PROGESTERONE injection ASTAR) was begun and embryo thawing and transfer was planned. During the modified nature cycle, Letrozole (Femara, Teva's) was given for ensuring ovulation induction, and ovulation timing was confirmed through the use of transvaginal ultrasound scan. Oral estradiol and micronized progestereone (Utrogestan, Besins) for luteal supplementation were then given after ovulation. The frozen-thawed ET was then scheduled on day 2, 3 or 5 (for D5~D6 blastocyst) accordingly, depending on the stage of embryo cryopreservation.

Outcome measures

We followed up patients through to November 2016. Only women who had already become pregnant or had completed the replacement of all available frozen embryos were included for analysis. A live birth was defined as the delivery of a live infant after at least 24 weeks of gestation. The CLBRs obtained with fresh or vitrified embryos from the same oocyte retrieval cycle were then determined.

Statistical analysis

The data was presented as the mean ± Standard Deviation (SD), or as a percentage. Group comparison was performed in SPSS (Version 18) using Mann–Whitney and Pearson's Chi square tests. Differences were considered significant at $p < 0.05$.

Results

In the study group, the clinical reasons for not adopting the fresh ET included the following: a high serum progesterone (P4) level (P4>1.5 ng/mL) on the day of triggering ovulation (n = 44), a high risk of OHSS (n = 10), adenomyosis or endometriosis with a high serum CA-125 level (n = 16), and personal considerations such as a need to accumulate embryos or inconvenient timing (n = 14). The overall CLBRs in the study group were significantly higher than those in the control group: 64.3% (54/84) vs. 45.8% (286/625), $p < 0.05$. However, the control group was generally in a poorer condition at the start of the study, having being given more medication for the COH, possessing fewer oocytes and having fewer mature oocytes retrieved (Table 1). The outcome between the study and control groups in the subgroup analysis is shown in Fig. 3 (Table 2).

In the group with OPU 4–15, the clinical characteristics were comparable between the study and control groups except for Estradiol (E2) and Progesterone (P4) levels on trigger ovulation day and the previous infertility year. The CLBR was significantly higher in the freeze-all group (study vs. control group 58.3% (21/36) vs. 40.9% (163/399), $p = 0.042$) (Table 1). When further dividing patients based on their ages, either for patients ≥38 years-old or <38 years-old, the CLBR was higher in the freeze-all group (for patients ≥ 38 years-old, study vs. control 46.2% (6/13) vs. 23.2% (32/138), $p = 0.068$; for patients < 38 years-old, study vs. control 65.2% (15/23) vs. 50.2% (131/261), $p = 0.167$).

In the group of OPU <4, the clinical characteristics were comparable between the study and control groups. The CLBR was similar in these two groups (study vs. control 23.1% (3/13) vs. 18.8%

Table 1
Patients and treatment cycle characteristics in comparison of the study (freeze-all) group and control (with fresh ET) group.

	Study (n = 84)	Control (n = 625)	P-value
Female age	35.0 ± 4.7	35.6 ± 4.4	.342
Infertility year	4.0 ± 3.0	3.9 ± 3.1	.94
BMI index	21.2 ± 3.6	21.9 ± 3.3	.401
AMH	4.3 ± 3.9	2.7 ± 2.5	.01[a]
E2, day of HCG	4495 ± 3959	2238 ± 1887	.000[a]
P4, day of HCG	1.7 ± 1.9	.9 ± .54	.000[a]
Retrieved oocytes	15.5 ± 11.3	10.4 ± 7.3	.000[a]
Mature oocyte	12.3 + 9.3	8.1 + 5.9	.000[a]
Stimulation protocol			
Antagonist	50 (59.5%)	386 (61.7%)	.69
Agonist	34 (40.5%)	239 (38.3%)	
CLBR	64.3% (54/84)	45.8% (286/625)	.042[a]

Table 1 shows the control group was in a relatively poorer starting status, while the CLBR is better in the freeze-all group.
[a] With statistical significance.

Table 2
Comparison of the study (freeze-all) group and control (with fresh ET) group in patients with normal response (OPU 4–15).

	Study (n = 36)	Control (n = 399)	P-value
Female age	35.8 ± 4.1	35.7 ± 4.3	.824
Infertility year	3.3 ± 2.9	4.0 ± 3.1	.049[a]
BMI index	20.8 ± 4.1	21.8 ± 3.0	.629
AMH	2.6 ± 1.9	2.3 ± 1.7	.385
E2, day of HCG	2655 ± 1845	1992 ± 1372	.020[a]
P4, day of HCG	1.5 ± 1.0	.9 ± .56	.001[a]
Retrieved oocytes	9.5 ± 3.7	8.6 ± 3.4	.133
Mature oocyte	7.6 + 3.3	6.7 + 3.2	.151
Stimulation protocol			
Antagonist	26 (72.2%)	252 (63.1%)	.278
Agonist	10 (27.8%)	147 (36.8%)	
CLBR	58.3% (21/36)	40.9% (163/399)	.042[a]

Table 2 shows that the clinical characteristics are compatible between these two groups, and the CLBR is better in the freeze-all group.
[a] With statistical significance.

(18/96)) (Table 3). When focusing on women age ≥38 years-old and OPU <4, the CLBRs in these two groups were also similar (study group vs. control group 9.1% (1/11) vs. 10.3% (6/58)).

In the group with OPU >15, the E2 and P4 on trigger ovulation day, the number of OPU and AMH were higher in the control group, but the CLBRs were similar between these two groups (study vs. control 85.7% (30/37) vs. 80.8% (105/130), p = 0.625) (Table 4). Subgroup analysis also showed the same result in patients age <38 years-old and ≥38 years-old.

Table 3
Comparison of the study (freeze-all) group and control (with fresh ET) group in patients with poor response (OPU<4).

	Study (n = 13)	Control (n = 96)	P-value
Female age	39.5 ± 3.5	38.7 ± 3.9	.343
Infertility year	5.9 ± 3.6	4.4 ± 3.5	.135
BMI index	22.0 ± 3.0	21.7 ± 3.1	.512
AMH	1.3 ± 1.6	.9 ± 1.3	.403
Previous ART cycles	1.8 ± 1.6	2.2 ± 2.8	.755
E2, day of HCG	1241 ± 2526	556 ± 365	.640
P4, day of HCG	1.3 ± 1.33	.6 ± .30	.241
Retrieved oocytes	2.2 ± .73	2.2 ± .63	.979
Mature oocytes	1.9 + .76	1.7 + .83	.499
Stimulation protocol			
Antagonist	12 (92.3%)	92 (95.8%)	.477
Agonist	1 (7.7%)	4 (4.2%)	
CLBR	23.1% (3/13)	18.8% (18/96)	.713

Table 3 shows that the clinical characteristics and responses are comparable between these two groups, and the CLBRs were the same in the two groups.

Table 4
Comparison of the study (freeze-all) group and control (with fresh ET) group in patients with high response (OPU>15).

	Study (n = 35)	Control (n = 130)	P-value
Female age	32.5 ± 4.1	32.8 ± 3.2	.795
Infertility year	4.1 ± 2.8	3.4 ± 2.5	.174
BMI index	21.4 ± 3.2	22.4 ± 3.9	.155
AMH	7.5 + 4.3	5.5 + 3.3	.020[a]
E2, day of HCG	7882 ± 3697	4273 ± 2217	.000[a]
P4, day of HCG	2.05 ± 2.6	1.18 ± .49	.000[a]
oocytes retrieved	26.5 ± 8.3	21.7 ± 5.58	.001[a]
Mature oocytes	20.9 + 7.4	16.9 + 5.2	.000[a]
Stimulation protocol			
Antagonist	12 (34.3%)	42 (32.3%)	.825
Agonist	23 (65.7%)	88 (67.7%)	
CLBR	85.7% (30/35)	80.8% (105/130)	.625

Table 4 shows that the cumulative live birth rate was not worse in the control group.
[a] With statistical significance.

Discussion

To the best of our knowledge, this is the first retrospective study comparing the ART outcome of the freeze-all policy and fresh ET with "cumulative" live birth rates. Our results showed that the overall CLBRs were significantly higher in the freeze-all group (64.3% vs. 45.8%, p < 0.05). However, the starting status of the fresh ET group was relatively poorer. To correct for this bias, we performed a subgroup analysis by dividing patients according to their number of OPU. Because we had chosen patients with a high P4

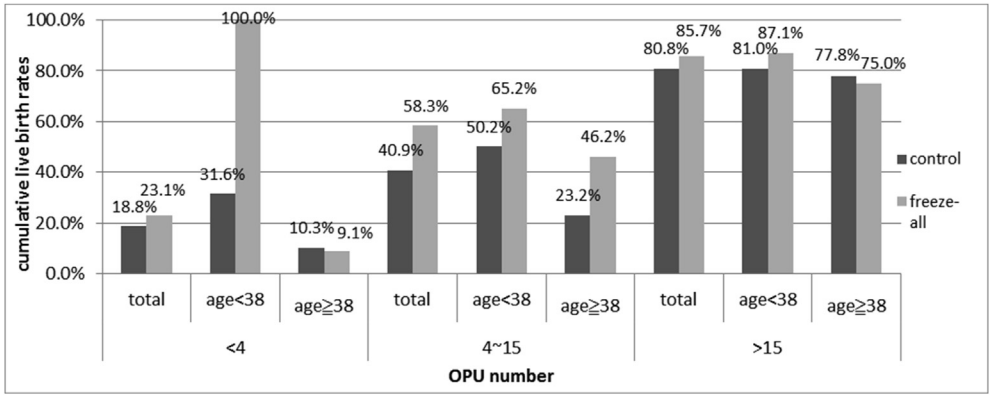

Fig. 3. Cumulative live birth rates of the study and control groups by different responsive groups and subdivided by age. Cumulative live birth rates were significantly higher in freeze-all group in the normal responders (OPU 4–15). And the CLBRs were similar in high (OPU>15) and low (OPU<4) responders.

level (P4 > 1.5) not to receive fresh ET, the P4 level is significantly higher in the study group within all the subgroups.

In the group of OPU 4–15, the CLBR was significantly higher in the freeze-all group. The difference may possibly be due to the suboptimal endometrial receptivity occurring in the fresh ET cycles. Recently, one prospective study comparing the IVF outcome between fresh ET and FET groups (when fresh ET was only performed under a P4 level <1.5 ng/ml), showed a higher ongoing pregnancy rate with the freeze-all policy [13]. They concluded that endometrial receptivity may have been impaired by COH even when the P4 level <1.5 ng/ml, leading to a better outcome in the freeze-all group. Our findings are consistent with this. Additionally, a systematic review and meta-analysis of three randomized controlled trials which included 633 women, showed that FET resulted in significantly higher rates in both ongoing pregnancy and clinical pregnancy than did fresh ET [1]. Furthermore, the end-point of our study is the cumulative live birth rate which was less frequently reported, though this rate is more reassuring.

In the group with OPU >15, as with the high responders, the CLBRs per oocyte retrieved were similar in these two groups. This may be explained by a previous study that the P4 threshold could possibly be modified according to the ovarian response, rising from 1.5 ng/mL in low responders to 2.25 ng/mL in high responders [14]. Additionally, there were only 4 patients whose P level was above 2.25 ng/ml in the group with OPU >15. Therefore, we could not detect the poor influence on endometrial receptivity, or that the influence was overcome by the embryo quality itself in the high responders. These results coincide with previous reports [15,16]. Therefore, if the patient has enough oocytes and no contraindication for fresh ET, fresh ET would still be a reasonable choice to shorten the waiting time while lowering the total cost of treatment. However, there still exists an increased risk of OHSS.

In the group with OPU <4, the CLBRs were similar in these two group regardless of age. This may be because the ovarian response is low and thus the influence of endometrium is small. Therefore, for poor responders, defined as OPU <4 and aged ≥38 years-old in our study, if patients do not plan to receive preimplantation genetic diagnosis, there is no need to cryopreserve their embryo for the purpose of embryo accumulation. Fresh ET should be the priority for saving both time and money while achieving a successful outcome.

Because this is a retrospective study there were some selection biases, including different stages of embryo transfer. However, due to our primary result being CLBR, the bias may be omitted. A recent Cochrane review points out that although there is a benefit towards favoring blastocyst transfer in fresh cycles, it remains unclear whether the day of transfer impacts on cumulative live birth and pregnancy rates [17]. Another recent study also concluded that cumulative live birth rates after Day 3 and Day 5 transfers were similar in young patients [18]. Another bias may also be due to different methods of cryopreservation. Therefore we analyzed our data and discovered that live birth rates via FET using different methods of cryopreservation were not different (cryotrop vs. cryotech, 34.6% vs. 37.4%, p = 0.664). As for different methods of endometrium preparation for FET, our own unpublished data also showed that either Hormonal Replacement Treatment (HRT) or a modified nature cycle provided a comparable pregnancy outcome (live birth rate in HRT and modified nature cycle were 42.9% and 42.7% respectively). Moreover, according to the recent systemic review and meta-analysis, there is no superiority of any endometrial preparation for FET [19]. Thus, we feel comfortable putting together all the FET cycles with different endometrial preparation regimens.

Several histological, transcriptomic and proteomic studies of endometrium have demonstrated dramatic differences between the normal cycling endometrium and the COH endometrium. Findings indicate that endometrial receptivity is disturbed in IVF cycles which underwent COH, hence impairing the outcome. Histological studies showed a complete failure for implantation when the endometrial development was ≥3 days (as assessed by highly experienced pathologists using Noyes' criteria) [20,21]. One recent study on developmental advancement showed that it's not only the absence of receptivity, but also the lack of developmental synchrony among different compartments of the endometrium, that could be a result of the assisted reproduction protocols [22].

The freeze-all policy not only provided a better environment for the embryo, it may have also improved the birth outcome. Recently, several lines of evidence show that the freeze-all policy leads to lower rates of perinatal morbidity/mortality, a smaller gestational age, lower birth weight, more antepartum hemorrhage and fewer birth defects [7,23,24]. Moreover, the COH associated supraphysiologic serum E2 levels in fresh ET cycles could be due to an altered placentation, leading to both an increased risk of preeclampsia and a fetus of smaller gestation age, when compared to the FET cycles [25–27]. The freeze-all policy also allows patients to receive Preimplantation Genetic Screening (PGS). Another study showed that older women have the opportunity for an elective single-embryo transfer, with live birth rate results as high as those reported for younger, good-prognosis infertility patients. This is due to using selective FET with euploid vitrified blastocysts, following a trophectoderm biopsy and comprehensive chromosome screening [28]. Reports in favor of the freeze-all policy are growing in number, including our own present study.

In conclusion, the IVF outcome is improved when using the freeze-all policy in normal responders. For hyper-responders and those with enough embryos, fresh ET still remains a legitimate choice, since the cumulative pregnancy rate in the fresh ET group is shown to be the same as in the freeze-all group. For poor responders, fresh ET should be the first priority when looking to save time and money. Further randomized control trials are urgently needed to conclude our findings, along with determining more specifically who in the patient population the freeze-all policy would be the most beneficial for.

Disclosure of Interests

None.

Details of ethics approval

Institutional Review Board, TCVGH, No. CE16055B.

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