J Assist Reprod Genet (2017) 34:179–185
DOI 10.1007/s10815-016-0834-x

ASSISTED REPRODUCTION TECHNOLOGIES

Freeze-all cycle for all normal responders?

Matheus Roque[1,2] · **Marcello Valle**[1] · **Fernando Guimarães**[1] · **Marcos Sampaio**[3] · **Selmo Geber**[2,3]

Received: 22 July 2016 / Accepted: 23 October 2016 / Published online: 5 November 2016

Abstract
Purpose The purpose of this study is to evaluate the freeze-all strategy in subgroups of normal responders, to assess whether this strategy is beneficial regardless of ovarian response, and to evaluate the possibility of implementing an individualized embryo transfer (iET) based on ovarian response.
Methods This was an observational, cohort study performed in a private IVF center. A total of 938 IVF cycles were included in this study. The patients were submitted to controlled ovarian stimulation (COS) with a gonadotropin-releasing hormone (GnRH) antagonist protocol and a cleavage-stage day 3 embryo transfer. We performed a comparison of outcomes between the fresh embryo transfer ($n = 523$) and the freeze-all cycles ($n = 415$). The analysis was performed in two subgroups of patients based on the number of retrieved oocytes: Group 1 (4–9 oocytes) and Group 2 (10–15 oocytes).
Result(s) In Group 1 (4–9 retrieved oocytes), the implantation rates (IR) were 17.9 and 20.5% ($P = 0.259$) in the fresh and freeze-all group, respectively; the ongoing pregnancy rates (OPR) were 31 and 33% ($P = 0.577$) in the fresh and freeze-all group, respectively. In Group 2 (10–15 oocytes), the IR were 22.1 and 30.1% ($P = 0.028$) and the OPR were 34 and 47% ($P = 0.021$) in the fresh and freeze-all groups, respectively.
Conclusion(s) Although the freeze-all policy may be related to better in vitro fertilization (IVF) outcomes in normal responders, these potential advantages decrease with worsening ovarian response. Patients with poorer ovarian response do not benefit from the freeze-all strategy.

Keywords Freeze-all policy · Elective frozen-thawed embryo transfer · Delayed frozen-thawed embryo transfer · Embryo cryopreservation · IVF/ICSI

Capsule Although the freeze-all policy may be related to better IVF outcomes in normal responders, these potential advantages decrease with worsening ovarian response. Patients with poorer ovarian response do not benefit from the freeze-all strategy. The implementation of an individualized embryo transfer (iET) would ultimately benefit patients with respect to IVF outcomes.

✉ Matheus Roque
matheusroque@hotmail.com

[1] ORIGEN-Center for Reproductive Medicine, Avenida Rodolfo de Amoedo, 140-Barra da Tijuca, Rio de Janeiro, Brazil

[2] Universidade Federal de Minas Gerais, Avenida Alfredo Balena, 190, Belo Horizonte, Brazil

[3] ORIGEN-Center for Reproductive Medicine, Av do Contorno, 7747-Lourdes, Belo Horizonte, Brazil

Introduction

Although fresh embryo transfer is still a routine practice in in vitro fertilization (IVF) cycles, elective frozen-thawed embryo transfer (FET)—otherwise known as the freeze-all policy—has emerged as an alternative for selected IVF treatments. In the last decade, cryopreservation techniques have improved, which means that the quality and potential for implantation of frozen embryos are similar to those for fresh embryos [1–3]. Moreover, many questions have arisen regarding the adverse effects associated with controlled ovarian stimulation (COS) on the endometrium, as well as its consequences on endometrial receptivity [3]. The implementation of the freeze-all policy has been used to avoid deleterious effects of hyperstimulation, as embryo transfer may be performed in a more physiologic uterine environment in a later cycle [4]. With this strategy, it is possible to segment the IVF cycle, where cryopreservation of the entire cohort of embryos is performed and selected embryos are transferred in a further natural cycle—or following endometrial priming with hormonal replacement [5, 6].

COS is performed to improve cumulative pregnancy rates during assisted reproductive technologies (ART) as it leads to the development and maturation of many follicles and oocytes [7]. However, this stimulation is related to supraphysiologic hormonal levels that are associated with modifications in the peri-implantation endometrium [8, 9], biochemical and morphologic endometrial alterations, and endometrial advancement [10, 11]. Since IVF success depends not only on embryo quality, but also on endometrial receptivity and on embryo–endometrium interactions [12], these modifications might jeopardize IVF outcomes following fresh embryo transfer and not after FET [13, 14].

The freeze-all strategy is being used for those patients at increased risk of ovarian hyperstimulation syndrome (OHSS), owing to the concept of an OHSS-free clinic [15]. However, it is still uncertain whether this strategy might be beneficial for all patients that are submitted to ART treatments [6, 16]. A recent meta-analysis showed an increase in ongoing pregnancy rates (OPR) when the freeze-all strategy was performed when compared to fresh embryo transfer [14]; however, there were only three studies included in this meta-analysis [13, 17, 18]. Furthermore, one of the included studies [17] was retracted due to methodological flaws. A recent published study evaluated the freeze-all policy in IVF cycles with pre-implantation screening (PGS) and also demonstrated benefit in performing elective cryopreservation of all embryos [19]. A recently published randomized clinical trial (RCT) [20] evaluated 1508 infertile women with the polycystic ovary syndrome who were submitted to a first IVF cycle. The patients in the freeze-all group had a higher frequency of live birth after the first transfer when comparing to fresh embryo transfer (49.3 vs. 42.0%, $P = 0.004$). These results were mainly due to a lower frequency of pregnancy loss in the freeze-all group (RR = 0.67; 95% CI 0.54–0.83; $P < 0.001$). However, the few available studies evaluating the freeze-all policy [13, 18–22] were performed in patients with both a good prognosis and a good ovarian response (normal and high responders) and these investigations did not take into account whether different ovarian responses (number of retrieved oocytes) in normal responders would have different implantation rates when evaluating the effectiveness of this strategy.

The objectives of this study were to evaluate the freeze-all strategy in subgroups of normal responders, to assess whether this strategy is beneficial regardless of ovarian response, and to evaluate the possibility of implementing an individualized embryo transfer (iET) based on ovarian response.

Materials and methods

We conducted a prospective, observational, cohort study between January 2012 and December 2015. An institutional review board approved this study, and informed consent was obtained from all patients.

Patient selection

The patients that were enrolled in this study fulfilled the following inclusion criteria: 1) cleavage-stage day 3 embryo transfers; 2) gonadotropin-releasing hormone (GnRH) antagonist cycles; 3) embryo transfers performed with top/good-quality embryos (Grades 1–6–10 cells, no fragmentation and equal blastomere size; Grade 2—allowing up to 20% fragmentation); and 4) females aged 20–45 years old. The exclusion criteria were as follows: 1) poor-responder patients [23]; 2) previous recurrent pregnancy loss; 3) implantation failure (≥3 previous embryo transfers without a pregnancy); 4) severe male factor infertility (oligospermia <1 million/mL and azoospermia); 5) uterine pathology; 6) patients with an estradiol (E_2) level >3,000 pg/mL on the trigger day; 7) patients with >15 retrieved oocytes; 8) those on oocyte donor cycles; and 9) those on cycles with embryo biopsy. Fresh embryo transfer was performed only if the progesterone level (P_4) was ≤1.5 ng/mL on the trigger day. The freeze-all strategy was implemented in cases when the P_4 was >1.5 ng/mL and/or the endometrial thickness was <7 mm on the trigger day, or if the patient decided previously to the treatment to undergo cryopreservation of their entire cohort of embryos.

Controlled ovarian stimulation and oocyte retrieval

COS was performed with recombinant follicle-stimulating hormone (FSH) (Gonal-F®; Merck Serono) or recombinant FSH + recombinant luteinizing hormone (LH) (Pergoveris®; Merck Serono), with starting doses ranging from 150 to 450 IU/day (based on the patient's age and ovarian reserve tests), in a step-down GnRH antagonist protocol. A GnRH antagonist (Cetrotide®; Merck Serono) was introduced when a leading follicle achieved 14 mm. Final oocyte maturation was induced with 250 μg of recombinant human chorionic gonadotropin (hCG) (Ovidrel®; Merck Serono) and/or 0.2 mg of triptorelin (Gonapeptyl daily; Ferring Pharmaceuticals, Saint Prex, Switzerland) when at least two follicles reached a diameter of 18 mm. All patients submitted to fresh embryo transfer received hCG for final oocyte maturation. During COS, hormone measurements (LH, E_2, and P_4) were performed on three different days of stimulation, with the last one performed on the trigger day. Serum P_4 levels were measured using a chemiluminescent immunoassay for quantitative determination of the hormone (Diagnostics Biochem Canada Inc., Dorchester, ON, Canada) with a sensitivity of 0.1 ng/mL.

Oocyte retrieval was performed 35–36 h after the trigger, guided by transvaginal ultrasound with a Wallace 17-gauge oocyte recovery set (Smiths Medical International Ltd, Kent, UK), followed by intracytoplasmic sperm injection (ICSI) [24]. On the third day following oocyte retrieval, embryo quality was evaluated and embryo transfer was performed

(the fresh group) or the entire cohort was cryopreserved (the freeze-all group). Patients submitted to a fresh embryo transfer received vaginal micronized progesterone in gel formulation (Crinone® 8%; Merck Serono) for a single daily administration [25] starting on the day of oocyte retrieval. Progesterone was used for at least 13 days, when a pregnancy test was performed, and until 9 weeks if pregnancy was confirmed.

Cryopreservation/thawing and endometrial priming

In the freeze-all group, good-quality embryos were cryopreserved on day 3 by vitrification using an open system as previously described [26, 27]. Briefly, the vitrification procedure was performed by embryo exposure to the equilibrium solution, followed by a 30-s exposure to the vitrification solution. After that, they were placed on top of a polypropylene strip with a minimum amount (<0.1 μL) of vitrification solution and then immediately vertically immersed into liquid nitrogen. The strip with the vitrified embryo was then inserted into the plastic sheaths and transferred to a liquid nitrogen tank.

For thawing, immediately after removing the strip from the protecting plastic sheath, the thin part of the strip was totally immersed into thawing solution at 37°C for 1 min. The embryo was then transferred to a dilution solution for 3 min at room temperature and then washed in a buffer solution twice for 5 min each. After thawing, a survival assessment was carried out using morphological criterion. Embryos with more than 50% of the cells intact were considered viable.

The endometrial priming for FET cycle started on the second day of the menstrual cycle with 6 mg/day of estradiol valerate that was orally administered. After 12 days of estradiol replacement, an ultrasound and hormone level measurements were performed. If the endometrium was ≥7 mm and the P_4 level was ≤1.5 ng/mL, the FET was scheduled and replacement with vaginal micronized progesterone was started 3 days prior to the embryo transfer. Estradiol valerate and progesterone were continued up until the ninth week of pregnancy.

Outcomes and groups of normal responders

The main outcome measure was the ongoing pregnancy rate (OPR), which was shown to be comparable to that for live births, as a measure of efficacy [28]; the implantation rate (IR), pregnancy rate (PR), and clinical pregnancy rate (CPR) were the secondary outcome measures. The IR was calculated as the ratio of the number of observed embryo heartbeats to the number of transferred embryos. HCG levels that were measured 11 days following embryo transfer were used to define pregnancies. Clinical pregnancy was defined by the observation of an intrauterine embryo heartbeat by 7–8 week gestation. Ongoing pregnancy was defined as a pregnancy that completed at least 12 weeks of gestation. Normal responders were divided into one of two groups according to the number of retrieved oocytes: Group 1 (4–9 oocytes)—suboptimal responders and Group 2 (10–15 oocytes)—normal responders, based on a new suggested stratification [29, 30]. Age, basal FSH level, antral follicle count (AFC), the number of retrieved and mature (MII) oocytes, the number of 2PN, the number of transferred embryos, and cycle type (freeze-all vs. fresh) were included in the analysis.

Statistical analysis

The data are presented as the mean ± standard deviation (SD), or as a percentage. A comparison of the quantitative variables was performed using Student's *t* test for independent samples. For a comparison of the categorical data, the chi-squared test or Fisher's exact test was performed. The results were considered significant when $P < 0.05$. The relative risk (RR) with its SD and 95% confidence intervals (CI), as well as the number needed to treat (NNT), was calculated for OPR. A multiple logistic regression analysis was performed to evaluate those variables that might be independently associated with OPR. Age, basal FSH level, antral follicle count, number of retrieved oocytes and mature eggs, number of transferred embryos, and cycle type (freeze-all vs. fresh) were included in the analysis. Sample size calculation was performed using an ongoing pregnancy rate as the base outcome. Based on the improvements of a previous study evaluating the freeze-all strategy in normal responders [13], accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, it was necessary for at least 107 patients in each group to obtain statistically significant results.

Results

During the study period, 938 IVF cycles fulfilled the inclusion criteria. The women's characteristics are shown in Table 1. There were no statistically significant differences between the fresh and freeze-all patients in Group 1 and Group 2 when evaluating age, ovarian reserve tests, days of stimulation, total gonadotropin consumption, and ovarian response. We only performed the analysis of the first embryo transfer in fresh and freeze-all cycles.

In Group 1, the mean E_2 levels on the trigger day were 1470.57 ± 617.74 pg/mL in the fresh group and 1573.76 ± 1045.65 pg/mL in the freeze-all group ($P = 0.186$). The mean P_4 levels on the trigger day were 0.69 ± 0.31 ng/mL in the fresh group and 0.79 ± 0.51 ng/mL in the freeze-all group ($P = 0.020$). In Group 2, the mean E_2 levels on the trigger day were 1950.58 ± 534.94 pg/mL in the fresh group and 2367.37 ± 1016.91 pg/mL in the freeze-all group ($P = 0.001$). The mean P_4 levels on the trigger day were 0.95 ± 0.31 ng/mL in the fresh group and 1.23 ± 0.55 ng/mL in the freeze-all group ($P = 0.001$). In Group 1 (4–9 oocytes), a total of 882 embryos

Table 1 Clinical characteristics of the patients who were submitted to freeze-all cycles and fresh embryo transfer cycles

	Group 1 (4–9 oocytes)			Group 2 (10–15 oocytes)		
	Fresh	Freeze-all	*P*	Fresh	Freeze-all	*P*
No. of cycles	380	243		143	172	
Age, years ± SD	36.17 ± 4.51	35.57 ± 4.34	0.100	33.76 ± 4.79	33.89 ± 3.99	0.797
FSH levels	8.46 ± 2.59	8.35 ± 4.99	0.769	7.34 ± 1.71	7.28 ± 1.67	0.814
AFC	8.84 ± 6.50	9.09 ± 3.67	0.608	12.75 ± 3.02	13.14 ± 3.44	0.304
Days of stimulation	10.36 ± 1.35	10.39 ± 1.24	0.808	10.34 ± 1.15	10.22 ± 1.24	0.379
Total Gonadot ± SD (IU)	2429.88 ± 704.97	2423.64 ± 661.64	0.913	2071.12 ± 555.63	2045.99 ± 527.61	0.682
E_2 trigger (pg/mL)	1470.57 ± 617.74	1573.76 ± 1045.65	0.186	1950.58 ± 534.94	2367.37 ± 1016.91	0.001
P_4 trigger (ng/mL)	0.69 ± 0.31	0.79 ± 0.51	0.020	0.95 ± 0.31	1.23 ± 0.55	0.001
Retrieved oocytes ± SD	6.27 ± 1.62	6.40 ± 1.63	0.327	11.91 ± 1.63	12.22 ± 1.89	0.124
Mature oocytes ± SD	4.53 ± 1.60	4.49 ± 1.67	0.793	7.94 ± 2.22	8.04 ± 2.44	0.696
Fertilization rate, %	81%	79.6%	0.374	80.6%	81.9%	0.439

*Values are expressed as the mean ± SD

AFC antral follicle count, E_2 estradiol levels, *FSH* follicle-stimulating hormone, P_4 progesterone levels

were transferred in the fresh group and 548 embryos on the freeze-all group. There were no statistical differences in the percentage of Grade 1 and Grade 2 embryos between fresh and freeze-all groups. In Group 1 (4–9 oocytes), there were 31% (273/882) of grade 1 embryos in the fresh group and 30% (164/548) in the freeze-all group ($P = 0.21$). In Group 2 (10–15 oocytes), there were 34% (110/322) of grade 1 embryos in the fresh group and 32% (123/385) in the freeze-all group ($P = 0.14$). The post-thaw survival rate was 94.7% in Group 1 and 94.1% in Group 2.

The IVF outcomes in each group are presented in Table 2. There was no statistically significant difference when comparing the fresh and freeze-all cycles in Group 1 (4–9 oocytes) as shown in Fig. 1. Performing the freeze-all cycle was not independently associated with OPR in this subgroup of patients. The multiple logistic regression performed in this subgroup showed an adjusted odds ratio (aOR) of 1.09 (95% CI: 0.76–1.56). We observed an improvement in the IVF outcomes in Group 2 (10–15 oocytes) for those patients who had freeze-all cycles. Multiple logistic regression performed in this subgroup showed that the freeze-all strategy was independently associated with OPR, with an aOR of 1.87 (95% CI: 1.14–3.08). In Group 1, the RR for the OPR was 1.07 (95% CI: 0.85–1.35) and the NNT was 47. In Group 2, the RR for the OPR was 1.37 (95% CI: 1.04–1.81) and the NNT was 8.

Discussion

To our knowledge, this is the largest published study comparing the freeze-all policy to fresh embryo transfers in normal responder patients. Moreover, this is the first study to evaluate elective FET in subgroups of normal responders based on the number of retrieved oocytes. The results of this study suggest that the potential advantage of performing the freeze-all policy decreases in association with a reduction in ovarian response, suggesting that the implementation of an iET based on an ovarian response would be beneficial for IVF patients.

Embryo cryopreservation has become a routine procedure in most IVF centers, and it is associated with good outcomes

Table 2 IVF outcomes in the freeze-all cycles and fresh embryo transfer cycles

	Group 1 (4–9 oocytes)			Group 2 (10–15 oocytes)		
	Fresh	Freeze-all	*P*	Fresh	Freeze-all	*P*
No. of cycles	380	243		143	172	
nET ± SD	2.32 ± 0.77	2.26 ± 0.68	0.261	2.25 ± 0.69	2.24 ± 0.57	0.853
IR, %	17.9%	20.5%	0.259	22.1%	30.1%	0.028
PR, *n* (%)	39%	44%	0.235	43%	56%	0.021
CPR, *n* (%)	35%	39%	0.334	38%	52%	0.018
OPR, *n* (%)	31%	33%	0.577	34%	47%	0.021

**nET* number of embryos transferred, *IR* implantation rate, *PR* pregnancy rate, *CPR* clinical pregnancy rate, *OPR* ongoing pregnancy rate

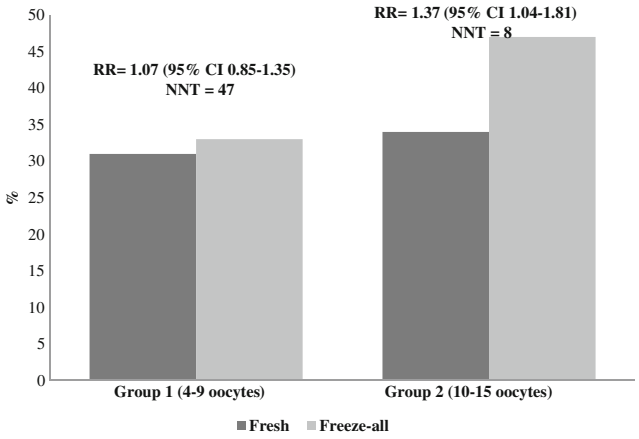

Fig. 1 Ongoing pregnancy rates with its relative risk (RR) and the number needed to treat (NNT) in fresh vs. freeze-all cycles

when FET is performed [1, 31]. Therefore, the freeze-all policy can serve as an alternative to fresh embryo transfer to avoid the deleterious effects of COS in embryo–endometrium synchrony [13, 18]. With this strategy, the entire cohort of embryos is cryopreserved and delayed FET is performed in an endometrium that is possibly more receptive [32]. Our results showed good embryo survival rates (over 94% in both groups), which is in accordance with the findings of previous studies [1, 33]. While in our study, the cryopreservation and thawing procedures were performed on day 3; it is still unclear which developmental embryo stage yielded better results when performing the freeze-all cycle [34, 35].

Recent studies suggest that a stricter segmentation based on ovarian response could be related to a better prediction of IVF outcomes [29, 30]. The authors of those studies considered the following categories of responders: poor (1–3 retrieved oocytes), suboptimal (4–9 oocytes), normal (10–15 oocytes), and high (>15 oocytes). In the study by Drakopoulos et al. [30], the authors correlated these groups with the live birth rates and cumulative live birth rate, following a fresh embryo transfer. There are also new data suggesting that a novel patient stratification approach using low-prognosis patients may help improve the management of IVF patients [36]; however, these proposed stratification methods take into account only the number of retrieved oocytes and ovarian reserve tests as outcome predictors. They did not consider the potential adverse effect that ovarian stimulation has over the endometrium. In the present study, we used the stratification method proposed by Polyzos and Sunkara [29] and we found that the benefit of performing the freeze-all policy, particularly as it pertained to implantation potential, was only observed in the group of patients with the higher ovarian response (10–15 oocytes). This group of patients benefited from the freeze-all strategy. In suboptimal response group (4–9 oocytes), regardless of the strategy (fresh embryo transfer vs. freeze-all) used, the IVF outcomes were the same.

With the stratification of normal responders into one of two groups, we avoided potential differences in patients' prognosis when comparing the fresh and freeze-all groups. The patients' baseline characteristics are presented in Table 1, and they showed that the study and control groups in this study were similar when evaluating ovarian reserve tests and ovarian responses. However, the ovarian response may be associated with endometrium modifications that could influence implantation and pregnancy outcomes. Previous studies showed that COS may lead to an endometrial advancement following endometrial histology evaluation on the day of oocyte retrieval using the Noyes criteria. When this advancement was over 3 days, no pregnancies were achieved [37, 38]. In the first study, all of the patients with endometrial advancement over 3 days were present in the group that had a $P_4 \geq 1.1$ ng/mL on the trigger day. The mean number of retrieved oocytes in this group of patients was 15.8. In the group of patients with $P_4 \leq 0.9$ ng/mL, the advancement was 3 days or less, suggesting that there was no interference that resulted from ovarian stimulation over the endometrium in this group of patients. In our study, the patients in Group 2 who were submitted to freeze-all cycle showed higher levels of estradiol and progesterone on the trigger day when compared to the patients in Group 1. In 2005, Horcajadas et al. [10] evaluated the consequences of COS via the endometrial gene expression profile. The researchers performed endometrial biopsies in oocyte donors during a stimulated cycle (day hCG +7) and compared these findings to endometrial samples of the same patients in a natural cycle (LH +7), while evaluating the gene expression profile. They found that over 200 genes related to implantation were over- or underexpressed in patients submitted to COS. The patients included in this study were oocyte donors that were submitted to a protocol that enabled the retrieval of 13–18 oocytes; these patients had a mean estradiol level of 2200 pg/mL. Furthermore, the findings of Labarta et al. [39] are also related to patients with a higher ovarian response (with a mean number of retrieved oocytes >20 and mean estradiol levels of >2200 pg/mL). Thus, it seems that altered endometrial receptivity related to COS cannot be extrapolated to all patterns of ovarian response.

All published studies on the freeze-all policy showed that although this strategy would lead to improvements in IVF outcomes of at least 30% in CPR and OPR when compared to fresh embryo transfers [13, 18–22], there is also a large number of patients that become pregnant even after fresh embryo transfer. To date, there is no effective non-invasive clinical tool that can be used to evaluate endometrial receptivity. This tool would help to select those patients without alterations in endometrial receptivity that should maintain the fresh embryo transfer, and it would also help select those patients that would really benefit from the freeze-all strategy. The results of our study have demonstrated that the freeze-all policy would not benefit all normal responders; rather, the findings suggest that an iET strategy

based on the number of retrieved oocytes would benefit some patients (normal responders—10–15 retrieved oocytes) if performing the freeze-all strategy. The iET can also avoid unnecessarily submitting suboptimal responders to this strategy, which would lead to an unnecessary increase in treatment costs and delays in the embryo transfer.

Previous studies have evaluated live birth rates in a fresh cycle, as well as cumulative live birth rates, correlating these outcomes to ovarian response [30, 40]. The authors of these studies observed that when stratifying patients by the number of retrieved oocytes, the live birth rate following a fresh embryo transfer fails to increase when over 10–11 oocytes are retrieved. Moreover, the live birth rate decreases when >15 oocytes are retrieved. Thus, if we could increase the outcomes in the first embryo transfer of the normal and high responders, we would also improve the cumulative live birth rate among our IVF patients. We hypothesize that if a freeze-all cycle was performed in this group of patients, the first embryo transfer would lead to better outcomes, improving the cumulative live birth rate. It would be interesting if more studies would evaluate iET and compare the IVF outcomes from fresh and freeze-all cycles.

This was an observational study, and it was subject to bias, mainly associated with patient selection. One of the inclusion criteria that determined whether the patients would be submitted to the freeze-all strategy was based on each patient's decision to do so following a discussion with his or her medical assistant. However, when stratifying patients into Group 1 (4–9 oocytes) and Group 2 (10–15 oocytes), there were no differences between the fresh and freeze-all groups. Moreover, this study did not evaluate the cumulative pregnancy rates.

Although this study was not an RCT, it evaluated a large number of patients that were submitted to the freeze-all policy. Furthermore, it also introduced a new idea of an iET, where the stratification of normal responders may be important with respect to endometrial receptivity. Although there are many concerns about the obstetric and perinatal outcomes when comparing pregnancies from fresh and FET, we did not compare these outcomes as they were not the objective of our study. There are some registered randomized controlled trials (RCT) aiming to evaluate the freeze-all policy (NCT00823121, NCT02148393, NCT02471573, NTR3187, ACTRN 12612000422820, HTA 13/115/82), and we will probably have more robust evidence to determine whether or not elective FET is favored once these studies are concluded. There are also concerns about the cost effectiveness of the freeze-all strategy; to our knowledge, there is only one study evaluating this issue [41]. In the present study, the patients in Group 2 (10–15 oocytes) benefited from this strategy, as the NNT was 8. However, we did not evaluate the increasing cost of treatment, as this was not an objective of this study. Thus, there is a need for more studies to evaluate the cost effectiveness of the freeze-all policy.

In conclusion, it seems that the potential advantage of the freeze-all policy is closely related to ovarian response. The results of this study show that although the freeze-all policy may be related to better IVF outcomes in normal responders, these potential advantages decrease with worsening ovarian response. Patients with poorer ovarian response do not benefit from the freeze-all strategy. As there are no currently available non-invasive clinical tools to select which patients will be submitted to a freeze-all strategy, the implementation of an iET would ultimately benefit patients with respect to IVF outcomes.

Acknowledgments The English language editing of this manuscript was provided by the Journal Prep.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Cobo A, de los Santos MJ, Castellò D, Gámiz P, Campos P, Remohí J. Outcomes of vitrified early cleavage-stage and blastocyst-stage embryos in a cryopreservation program: evaluation of 3,150 warming cycles. Fertil Steril. 2012;98:1138–46.
2. Wong KM, Mastenbroek S, Repping S. Cryopreservation of human embryos and its contribution to in vitro fertilization success rates. Fertil Steril. 2014;102:19–26.
3. Albertini DF. Phasing in and out of the FREEZE-ALL mentality: Was Mother Neture right after all? J Assist Reprod Genet. 2015;32:169–70.
4. Roque M. Freeze-all policy: Is it time for that? J Assist Reprod Genet. 2015;32:171–6.
5. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. High ongoing pregnancy rates after deferred transfer through bipronuclear oocyte cryopreservation and post-thaw extended culture. Fertil Steril. 2009;92:1594–9.
6. Barnhart KT. Are we ready to eliminate the transfer of fresh embryos in in vitro fertilization? Fertil Steril. 2014;102:1–2.
7. Siristatidis C, Sergentanis TN, Kanavidis P, Trivella M, Mavromatis I, Psaltopoulou T, et al. Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer—a systematic review and meta-analysis. Hum Reprod Update. 2013;19:105–23.
8. Nikas G, Develioglu OH, Toner JP, Jones Jr HW. Endometrial pinopodes indicate a shift in the window of receptivity in IVF cycles. Hum Reprod. 1999;14:787–92.
9. Richter KS, Shipley SK, McVearry I, Tucker MJ, Widra EA. Cryopreserved embryo transfers suggest that endometrial receptivity may contribute to reduced success rates of later developing embryos. Fertil Steril. 2006;86:862–6.
10. Horcajadas JA, Riesewijk A, Polman J, van Os R, Pellicer A, Mosselman S, et al. Effect of controlled ovarian hyperstimulation in IVF on endometrial gene expression profiles. Mol Hum Reprod. 2005;11:195–205.
11. Fatemi HM, Popovic-Todorovic B. Implantation in assisted reproduction: a look at endometrial receptivity. Reprod Biomed Online. 2013;27:530–8.

12. Achache H, Ravel A. Endometrial receptivity markers, the journey to successful embryo implantation. Hum Reprod Update. 2006;12:731–46.
13. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. Fertil Steril. 2011;96:344–8.
14. Roque M, Lattes K, Serra S, Solà I, Geber S, Carreras R, et al. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. Fertil Steril. 2013;99:156–62.
15. Devroey P, Polyzos NP, Blockeel C. An OHSS-Free Clinic by segmentation of IVF treatment. Hum Reprod. 2011;26:2593–7.
16. Blockeel C, Drakopoulos P, Santos-Ribeiro S, Polyzos NP, Tournaye H. A fresh look at the freeze-all protocol: a SWOT analysis. Hum Reprod. 2016;31:491–7.
17. Aflatoonian A, Oskouian H, Ahmadi S, Oskouian L. Can fresh embryo transfers be replaced by cryopreserved-thawed embryo trasnfers in assisted reproductive cycles? A randomized controlled trial. J Assist Reprod Genet. 2010;27:357–63.
18. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in high responders. Fertil Steril. 2011;96:516–8.
19. Rodriguez-Purata J, Lee J, Whitehouse M, Duke M, Grunfeld L, Sandler B, et al. Reproductive outcome is optimized by genomic embryo screening, vitrification, and subsequent transfer into a prepared synchronous endometrium. J Assist Reprod Genet. 2016;33:401–12.
20. Chen ZJ, Shi Y, Sun Y, Zhang B, Liang X, Cao Y, et al. Fresh versus frozen embryos for infertility in the polycystic ovary syndrome. N Engl J Med. 2016;375:523–33.
21. Roque M, Valle M, Guimarães F, Sampaio M, Geber S. Freeze-all policy: fresh vs. frozen-thawed embryo transfer. Fertil Steril. 2015;103:1190–3.
22. Braga DP, Setti AS, Sávio Figueira RC, Azevedo MC, Iaconelli A Jr, Lo Turco EG, Borges E Jr. Freeze-all, oocyte vitrification, or fresh embryo transfer? Lessons from an egg-sharing donation program. Fertil Steril 2016.
23. Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L, et al. ESHRE consensus on the definition of "poor response" to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011;26:1616–24.
24. Geber S, Sales L, Sampaio MA. Laboratory techniques for human embryos. Reprod Biomed Online. 2002;5:211–8.
25. Geber S, Moreira AC, de Paula SO, Sampio M. Comparison between two forms of vaginally administered progesterone for luteal phase support in assisted reproduction cycles. Reprod Biomed Online. 2007;14:155–8.
26. Kuwayama M, Vajta G, Kato O, Leibo SP. Highly efficient vitrification method for cryopreservation of human oocytes. Reprod Biomed Online. 2005;11:300–8.
27. Almodin CG, Minguetti-Camara VC, Paixao CL, Pereira PC. Embryo development and gestation using fresh and vitrified oocytes. Hum Reprod. 2010;25:1192–8.
28. Clarke JF, van Rumste MME, Farquhar CM, Johnson NP, Mol BWJ, Herbison P. Measuring outcomes in infertility trials: can we rely on clinical pregnancy rates? Fertil Steril. 2010;94:1647–51.
29. Polyzos NP, Sunkara SK. Sub-optimal responders following controlled ovarian stimulation: an overlooked group? Hum Reprod. 2015;30:2005–8.
30. Drakopoulos P, Blockeel C, Stoop D, Camus M, de Vos M, Tournaye H, et al. Conventional ovarian stimulation and single embryo transfer for IVF/ICSI. How many oocytes do we need to maximize cumulative live birth rates utilization of all fresh and frozen embryos? Hum Reprod. 2016;31:370–6.
31. AbdelHafez FF, Desai N, Abou-Setta AM, Falcone T, Goldfarb J. Slow freezing, vitrification and ultra-rapid freezing of human embryos: a systematic review and meta-analysis. Reprod Biomed Online. 2010;20:209–22.
32. Weinerman R, Mainigi M. Why we should transfer frozen instead of fresh embryos: the translational rationale. Fertil Steril. 2014;102:10–8.
33. Herrero L, Martínez M, Garcia-Velasco JA. Current status of human oocyte and embryo cryopreservation. Curr Opin Obstet Gynecol. 2011;23:245–50.
34. Pavone ME, Innes J, Hirshfeld-Cytron J, Kazer R, Zhang J. Comparing thaw survival, implantation and live birth rates from cryopreserved zygotes, embryos and blastocysts. J Hum Reprod Sci. 2011;4:23–8.
35. Edgar DH, Gook DA. A critical appraisal of cryopreservation (slow cooling versus vitrification) of human oocytes and embryos. Hum Reprod Update. 2012;18:536–54.
36. Group P, Alviggi C, Andersen CY, Buehler K, Conforti A, De Placido G, et al. A new more detailed stratification of low responders to ovarian stimulation: from a poor response to a low prognosis concept. Fertil Steril. 2016;105:1452–3.
37. Ubaldi F, Bourgain C, Tournaye H, Smitz J, Van Steirteghem A, Devroey P. Endometrial evaluation by aspiration biopsy on the day of oocyte retrieval in the embryo transfer cycles in patients with serum progesterone rise during follicular phase. Fertil Steril. 1997;67:521–6.
38. Kolibianakis E, Bourgain C, Albano C, Osmanagaoglu K, Smitz J, Van Steirteghem A, et al. Effect of ovarian stimulation with recombinant follicle-stimulating hormone, gonadotropin releasing hormone antagonists, and human chorionic gonadotropin on endometrial maturation on the day of oocyte pick-up. Fertil Steril. 2002;78:1025–9.
39. Labarta E, Martínez-Conejero JA, Alamá P, HOrcajadas JA, Pellicer A, Simón C, et al. Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis. Hum Reprod. 2011;26:1813–25.
40. Ji J, Liu Y, Tong XH, Luo L, Ma J, Chen Z. The optimum number of oocytes in IVF treatment: an analysis of 2455 cycles in China. Hum Reprod. 2013;28:2728–34.
41. Roque M, Valle M, Guimarães F, Sampaio M, Geber S. Cost-effectiveness of the freeze-all policy. JBRA Assist Reprod. 2015;19:125–30.