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A direct healthcare cost analysis of the cryopreserved versus fresh transfer policy at the blastocyst stage

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KEY MESSAGE

Vitrification at blastocyst stage of all embryos obtained in a cycle of IVF is economically valuable for a publicly-funded healthcare system due to the reduction in the number of subsequent transfers required to obtain a baby. This strategy may be applied in all IVF units, with similar or even better outcomes when comparing fresh and frozen cycles.

A B S T R A C T

A cost analysis covering direct healthcare costs relating to IVF freeze-all policy was conducted. Normal- and high- responder patients treated with a freeze-all policy (n = 63) compared with fresh transfer IVF (n = 189) matched by age, body mass index, duration and cause of infertility, predictive factors for IVF (number of oocytes used for fertilization) and study period, according to a 1:3 ratio were included. Total costs per patient (€6952 versus €6863) and mean costs per live birth were similar between the freeze-all strategy (€13,101, 95% CI 10,686 to 17,041) and fresh transfer IVF (€15,279, 95% CI 13,212 to 18,030). A mean per live birth cost-saving of €2178 (95% CI −1810 to 6165) resulted in a freeze-all strategy owing to fewer embryo transfer procedures (1.29 ± 0.5 versus 1.41 ± 0.7); differences were not significant. Sensitivity analysis revealed that the freeze-all strategy remained cost-effective until the live birth rate is either higher or only slightly lower (≥–0.59%) in the freeze-all group compared with fresh cycles. A freeze-all policy does not increase costs compared with fresh transfer, owing to negligible additional expenses, i.e. vitrification, endometrial priming and monitoring, against fewer embryo transfer procedures required to achieve pregnancy.

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http://dx.doi.org/10.1016/j.rbmo.2016.09.008

Introduction

Cryopreservation of human embryos is now a routine procedure in assisted reproduction technique laboratories. With advances in cryopreservation and warming techniques, the quality and implantation potential of cryopreserved embryos are similar to those of fresh embryos (Cobo et al., 2012; Wong et al., 2014). In fact, over the past decade, the number of frozen–thawed embryo transfer (FET) cycles has increased steadily (de Mouzon et al., 2010) and success rates after FET are on par with, or even superior to, those of fresh embryo transfer (Roy et al., 2014; Shapiro et al., 2011a, 2011b; Wong et al., 2014; Zhu et al., 2011). This has legitimized the development of so-called freeze-all strategies in IVF, in which the entire cohort of embryos is electively cryopreserved and the transfer is delayed, in contrast with fresh transfer IVF in which only supernumerary embryos are cryopreserved. This approach is already considered as the preferred method for managing conditions as common as high risk of ovarian hyperstimulation syndrome (OHSS) (Devroey et al., 2011), the need for pre-implantation genetic diagnosis (PGD), pre-implantation genetic screening (PGS) and impairment in endometrial receptivity owing to progesterone elevation during ovarian stimulation (Venetis et al., 2013).

Moreover, the hypothesis of adopting the elective freeze-all strategy in routine clinical practice is also gaining attention (Evans et al., 2014; Maheshwari and Bhattacharya, 2013). In fact, growing evidence shows that ovarian stimulation itself, which causes supraphysiologhic hormonal levels, may decrease endometrial receptivity (Bourgain and Devroey, 2003; Check et al., 1999; Devroey et al., 2004; Nikas et al., 1999; Ochsenkuhn et al., 2012; Richter et al., 2006; Roque, 2015; Roque et al., 2013, 2015; Shapiro et al., 2008, 2014a). On the basis of this biological rationale, the transfer of a cryopreserved embryo into a more physiologic environment would result in greater pregnancy rates compared with fresh embryo transfer, and the outcomes of currently available studies seem to support the elective freeze-all strategy (Maheshwari and Bhattacharya, 2013; Roque, 2015; Roque et al., 2013, 2015; Shapiro et al., 2011a, 2011b, 2013; Zhu et al., 2011).

Furthermore, accumulating clinical evidence has suggested that the peri-implantation environment after ovarian stimulation increases the risk of abnormal placentation, leading to increased rates of ectopic pregnancy, antepartum haemorrhage, preterm birth, small for gestational age, low-birth weight newborns and perinatal mortality compared with FET, even if results are still controversial and confounders as relevant as age, smoking, parity, previous uterine surgery and pre-existing medical illness have not been fully controlled (Ishihara et al., 2014; Maheshwari et al., 2012; Shapiro et al., 2012). On the other hand, there are still some open issues about the freeze-all policy. First, FET may be neither feasible nor necessary for all patients, i.e. patients with poor-quality embryos, patients who underwent mild ovarian stimulation or patients with advanced age and indication to a short time-to-pregnancy. In addition, as already pointed out by several investigators (Blockeel et al., 2016; Maheshwari and Bhattacharya, 2013; Shapiro et al., 2014a, 2014b), no study has currently evaluated the cost-effectiveness of a freeze-all strategy compared with fresh transfer IVF. Controlling health costs represents a priority in most Western societies (Tilburt and Cassel, 2013), and the relevance of cost-effectiveness assessment of infertility care interventions is particularly crucial (ESHRE Capri Workshop Group, 2015).

It is estimated that, in developed countries, 1–5% of all births are generated from assisted reproduction technique treatments (Chambers et al., 2014; Sutcliffe and Ludwig, 2007). Hence, the costs of a shift towards a freeze-all policy should urgently be assessed, considering the additional expenses associated with cryopreservation, endometrial priming and monitoring before FET (Blockeel et al., 2016). Therefore, we aimed to investigate the costs of the freeze-all strategy in normal- and high-responder patients (four or more oocytes collected) (Drakopoulos et al., 2016; Polyzos and Sunkara, 2015). We designed a retrospective single-centre case-control study and conducted a real-life cost analysis comparing patients treated with a freeze-all cycle owing to contraindications to fresh embryo transfer with patients undergoing fresh embryo transfer. The two groups were matched by age, cause of infertility, predictive factors for IVF (body mass index [BMI], duration of infertility, number of oocytes used for fertilization) and study period.

Materials and methods

Study design and target population

This is a non-interventional, retrospective, case-control, observational, single-centre cohort study of normal- and high-responder patients undergoing blastocyst culture conducted at the IVF Unit of San Raffaele Hospital between 1 January 2012 to 31 December 2013. A total of 252 patients aged between 18 and 42 years, with BMI between 19 and 25 Kg/m^2, basal FSH less than 8 U/L, anti-Müllerian hormone (AMH) between 1.1 and 3.9 ng/dl and four or more oocytes retrieved were included.

Of these patients, 189 underwent a fresh embryo transfer (control group), and eventually the supernumerary embryos were cryopreserved, wereas 63 patients (cases) underwent cryopreservation of all embryos. This strategy was carefully chosen for clinical contraindication to fresh embryo trasfer: patients for OHSS risk (n = 25); patients for high progesterone levels on the day of HCG trigger (>1.5 ng/dl) (n = 15); patients for detection of sacto and hydrosalpinx (n = 12); patients for suspected endometrial pathology (polyp or hyperplasia not previously detected) (n = 11).

The two groups were matched according to a 1:3 ratio by age (±6 months), cause of infertility and predictive factors for IVF (BMI ± 3 Kg/m^2, duration of infertility, number of oocytes used for fertilization), study period (the following women fulfilling the criteria for selection and matching).

Ovarian stimulation, oocyte retrieval, fertilization and embryo culture

Ovarian stimation was carried ot according to clinical practice and as previously described (Restelli et al., 2014). When one or more follicles had reached a diameter of 16 mm or wider, ovulation was triggered with 10,000 IU of highly purified HCG. In the case of risk of OHSS (presence of 25 follicles with a diameter of 12 mm or more on day of ovulation induction), GnRH agonist 0.2 mg was used as an alternative to highly purifed HCG.

Oocytes were collected 36 h after ovulation induction. After 2- to 3-h incubation in human serum albumin (HSA)-supplemented fertilization medium (Sage In-Vitro Fertilization, Inc. Trumbull, CT, USA) under oil, selected oocytes were allocated to fresh insemination or ICSI. For ICSI, denudation of the cumulus oophorus was performed as previously described (Calzi et al., 2012; Corti et al., 2013; Restelli et al., 2014; Rubino et al., 2016). Inseminated or injected oocytes were

grouped and cultured in microdrops of equilibrated HSA-supplemented fertilization medium or of serum substitute supplement (SSS, Irvine, CA, USA)-supplemented cleavage medium (Sage In-Vitro Fertilization, Inc. Trumbull, CT, USA) under oil. Sixteen–eighteen hours after insemination or ICSI, all oocytes were checked for fertilization as previously described (Calzi et al., 2012; Corti et al., 2013; Restelli et al., 2014) and embryos were cultured until blastocyst stage in SSS-supplemented blastocyst medium (Sage In-Vitro Fertilization, Inc. Trumbull, CT, USA). Blastocyst evaluation was conducted in accordance with the Istanbul Consensus (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011) as previously described (Restelli et al., 2014).

Oocyte and blastocyst vitrification and warming procedures

Supernumerary oocytes and day 5–7 blastocysts were cryopreserved by means of the Cryotop device and solutions (Kitazato BioPharma Co., Japan) as previously described (Ubaldi et al., 2015). Each Cryotop was used for a maximum number of one embryo or three oocytes. After warming (Ubaldi et al., 2015), blastocysts were placed in blastocyst medium (Sage In-Vitro Fertilization, Inc. Trumbull, CT, USA), supplemented with 20% SSS (Irvine, CA, USA), whereas oocytes were placed in cleavage medium (Sage In-Vitro Fertilization, Inc. Trumbull, CT, USA), supplemented with 20% SSS (Irvine, CA, USA).

Embryo transfer and supplementation

The number of blastocysts transferred in both fresh and cryopreserved cycles was established according to the American Society for Reproductive Medicine guidelines (Practice Committee of American Society for Reproductive Medicine and Practice Committee of Society for Assisted Reproductive Technology, 2013). Vitrified–warmed transfer was conducted after endometrial priming with oestradiol valerate at 6 mg per day taken orally; both groups underwent luteal phase support with progesterone 600 mg per day administered vaginally and continued to week 12 of pregnancy (treatment was discontinued only in the case of spontaneous abortion).

Pregnancy outcomes and follow-up

Follow-up and data collection were carried out until 24 months after oocyte retrieval. Ongoing pregnancy was defined as the presence of at least one viable fetus beyond 12 weeks of gestation; live birth was defined as the delivery of a live born infant (>24 weeks of gestation).

Cost analysis

The outcome measures of the economic evaluation were the costs and effectiveness of the two different strategies included in the study. All treatment-related direct healthcare costs were included in the analysis, whereas costs supported by the individuals (transports, absences from work, accompanying partner's expenses if present) and costs related to pregnancy assistance were excluded from the model.

In the study setting (i.e. the Italian public health system), direct costs for healthcare procedures are calculated on the basis of a diagnosis-related group system. Costs for the IVF procedures were therefore derived from the regional diagnosis-related group register (http://www.regione.lombardia.it). Costs incurred for oocyte collection were €2211 and included costs of the ultrasound, serum monitoring tests, and cost of patient sedation and pain control drugs administered in the hospital. Costs for each embryo transfer attempt were €2265, with a further €18 for endometrial ultrasound monitoring in the case of cryopreserved embryo transfer attempts. Costs of the domiciliary drugs were obtained through the consultancy of the website of the official Italian Institute for drugs (Agenzia Italiana del Farmaco) (http://www.agenziafarmaco.gov.it); mean costs for fresh cycle medications and FET medications were equal to €1437 and €34, respectively. Costs for the cryopreservation and warming of blastocysts and oocytes were calculated on the basis of the total cost for cryopreservation and warming material (Vitrification and Warming KIT, Kitazato Biopharma Co, Japan) used in our laboratory during the study period divided by the total number of embryos and oocyte triplets cryopreserved or warmed in the same period. From these calculations, we determined a cost equal to €45 (that included the cryotop cost) for each embryo or oocyte triplet cryopreserved, whereas warming an embryo or oocyte triplet cost €12. Effectiveness was expressed as the cumulative live birth rate (CLBR) after a complete IVF–ICSI cycle, which comprised a single oocyte collection and a variable number of embryo transfers, related to the number of blastocysts obtained.

Statistical analysis

The main clinical outcome of the study was the CLBR per started cycle. Secondary clinical outcome was cumulative ongoing pregnancy rate. The study design was a non-inferiority trial and the sample size was calculated on the basis of expected CLBR in patients who started a fresh cycle of 40% and stating as clinically relevant a 50% relative reduction in women with a freeze-all cycle. Setting type I and II errors to 0.05 and 0.10 and planning a 3:1 matching, the calculated number of women to be recruited was about 58 patients with a freeze-all cycle and 174 patients with a fresh cycles. Sample size calculation was conducted using G*power 3 (http://www.gpower.hhu.de/). Data are presented as means ± SD, number (percentage), median (interquartile range [IQR]) or percentage [95% confidence interval (95% CI)]. Data were compared using the chi-squared test, Fisher exact test, Student's t-test and non-parametric Wilcoxon test as appropriate (SPSS 17.0 for Windows, Chicago, IL, USA). A logistic regression model was used to calculate the odds ratio of ongoing pregnancy and CLBR adjusted for age. A binomial distribution model was used to calculate the 95% CI of proportions. The 95% CIs for mean cost per-live birth were calculated on the basis of the 95% CI of CLBR. One-way sensitivity analysis was conducted keeping constant the number of executed transfer procedures in each group and the CLBR of the fresh cycles group, and varying the CLBR for the freeze-all group. $P < 0.05$ was considered statistically significant.

Ethical approval

All patients routinely provide informed consent for their clinical data and anonymized records to be used for research purposes. Local Institutional Review Board approval for the use of clinical data for research studies was obtained on 9 February 2012.

Results

Baseline characteristics

Data from 189 patients who underwent a fresh cycle and 63 patients who underwent a freeze-all cycle were available for evaluation.

Table 1 – Baseline characteristics of the study groups.

Characteristics	Fresh (n = 189)	Freeze-all (n = 63)	*P*-value
Age (years)	36.0 ± 3.5	35.1 ± 3.4	NS
Body mass index (kg/m^2)	22.0 ± 2.7	21.3 ± 2.7	NS
Duration of infertility (years)	3.1 ± 0.8	3.0 ± 0.8	NS
Current smoking	32 (16.9%)	12 (19%)	NS
Previous pregnancies	53 (28%)	11 (17.5%)	NS
Previous ovarian surgery	12 (6.3%)	6 (9.5%)	NS
Cycle length (days)	29.8 ± 4.2	32.3 ± 11.7	0.01
Day 3 serum FSH (IU/ml)	6.9 ± 1.8	6.4 ± 2.5	NS
Anti-Müllerian hormone (ng/ml)	2.8 ± 2.0	3.5 ± 2.5	0.02
Total antral follicle count	13.2 ± 6.0	14.2 ± 7.9	NS

Data are expressed as mean ± SD or number (percentage).
NS = not statistically significant.

Baseline characteristics of the women in the two study groups are shown in **Table 1**. No statistically significant differences emerged with the exception of cycle length and AMH concentration. Women in the freeze-all study group presented longer cycle length (32.3 ± 11.7 days versus 29.8 ± 4.2 days for the fresh cycle group) ($P = 0.01$) and higher AMH concentration (3.5 ± 2.5 versus 2.8 ± 2.0 ng/ml for the fresh cycle group) ($P = 0.02$), possibly reflecting the causes for the indication to a freeze-all cycle.

Clinical IVF outcomes

The cycle outcomes for the two study groups are presented in **Table 2**. The number of oocytes retrieved was significantly higher in the freeze-all group, with the median number of retrieved oocytes equal to 13 (IQR 8–20) compared with 11 oocytes (IQR 9–14) for the fresh cycles group ($P = 0.02$). The median number of oocytes used in each cycle was the same for the two study groups, as this parameter was used as criteria for the case-control matching. No differences in fertilization rate, total number of blastocysts obtained per cycle, blastocysts quality, mean number of transferred blastocysts per transfer and mean number of transfers per patient were observed between the two study groups. The cumulative ongoing pregnancy rate per started cycle in the fresh and freeze-all groups was 56.1% (95% CI 49.0 to 63.0%) and 60.3% (95% CI 48.0 to 71.5%), respectively. After adjusting for age, the odds ratio for cumulative ongoing pregnancy rate for freeze-all cycles compared with fresh cycles was 1.11 (95% CI 0.62 to 2.00). The CLBR did not differ between the two study groups as it was 45.5% (95% CI 38.6 to 52.6%) and 52.4% (95% CI 40.3 to 64.2%) in the fresh cycle and freeze-all group, respectively, resulting in a risk difference of cumulative live birth of +6.9 % (95% CI –7.2 to +20.6) for the freeze-all group. The age-adjusted odds ratio of CLBR for freeze-all cycles compared with fresh cycles was 1.20 (95% CI 0.67 to 2.15). Percentages of multiple deliveries were similar for the fresh cycle group (18.6%) and freeze-all group (18.2%).

Cost analysis

All the costs included in the analysis are presented in **Table 3**. The mean costs per cycle were similar for the two different strategies, with €6952 and €6863 for fresh and freeze-all group, respectively. The freeze-all strategy was more cost-effective, with a mean cost per live birth equal to €13,101 (95% CI 10,686 to 17,041) compared with €15,279 (95% CI 13,212 to 18,030) for the fresh cycle group, although the difference was not significant. The mean per-live birth cost-saving resulting from using the freeze-all strategy was therefore €2178 (95% CI –1810 to 6165). A sensitivity analysis, which assumed different live birth outcomes for the freeze-all group, revealed that the freeze-all strategy remained cost-effective until the difference in live birth ratio between the freeze-all group and the fresh cycle group is –0.59% or greater (**Figure 1**), i.e. until the CLBR in the freeze-all group is either higher or only slightly lower than the fresh cycle group.

Discussion

To the best of our knowledge, our study is the first cost-analysis of a freeze-all policy in assisted reproduction techniques. It shows that no significant differences exist in the costs of a freeze-all embryo strategy, in which the entire cohort of embryos is cryopreserved for subsequent FET, compared with fresh transfer IVF, in which the best available blastocysts are transferred in the fresh cycle and only

Table 2 – IVF and intracytoplasmic sperm injection cycle outcome in the two study groups.

Characteristics	Fresh (n = 189)	Freeze-all (n = 63)	OR (95% CI)
Oocytes retrieved (number)	11 (9–14)	13 (8–20)[a]	
Oocytes used	9 (7–10.5)	9 (7–10)	
Fertilisation rate	74.6 (72.2–77.0)	71.0 (66.8–75.3)	
Number of blastocysts (total)	3.3 ± 1.4	3.3 ± 1.7	
Blastocysts quality (total)			
A	139 (22.1%)	44 (21.3%)	
B	245 (38.9%)	74 (35.7%)	
C	246 (39.0%)	89 (43.0%)	
Number of transferred blastocysts / transfer	1.6 ± 0.5	1.5 ± 0.5	
Mean number of transfers / patient	1.4 ± 0.7	1.3 ± 0.5	
Cumulative ongoing pregnancy rate	56.1 (49.0–63.0)	60.3 (48.0–71.5)	1.11 (0.62–2.00)[b]
Cumulative live birth rate	45.5 (38.6–52.6)	52.4 (40.3–64.2)	1.20 (0.67–2.15)[b]

Data are expressed as mean ± SD, number (percentage), median (interquartile range) or percentage (95% confidence interval).
[a] $P = 0.02$.
[b] Corrected for age.

Table 3 – Costs in the two study groups.

Items	Costs per unit (€)	Total costs for all the patients (€)		% of the total costs	
		Fresh (n = 189)	Freeze-all (n = 63)	Fresh (n = 189)	Freeze-all (n = 63)
Fresh cycle medications	1437[a]	275,713	90,551	20.98	20.94
Oocyte retrieval	2211	417,879	139,293	31.80	32.22
Embryo transfer	2265	597,960	183,465	45.51	42.43
Oocyte cryopreservation/warming		3580	3796	0.27	0.88
Cryopreservation solutions	16	992	1087	0.08	0.25
Warming solutions	12	761	708	0.06	0.16
Cryotops	29	1827	2001	0.14	0.46
Blastocyst cryopreservation and warming		14,953	11,019	1.14	2.55
Cryopreservation solutions	16	4741	3260	0.36	0.75
Warming solutions	12	1483	1756	0.11	0.41
Cryotops	29	8729	6003	0.66	1.39
Cryopreserved embryo transfer medications	34	2554	2755	0.19	0.64
Cryopreserved embryo transfer monitoring	18	1360	1468	0.10	0.34
Total costs		1,313,999	432,347		
Mean cost per patient		6952	6863		
Mean cost per live birth (95% CI)[b]		15,279 (13,212–18,030)	13,101 (10,686–17,041)		

Costs are reported in Euros and rounded to the nearest integer.

[a] Mean cost per patient.

[b] The 95% CIs were calculated based on the 95% CI of the live birth ratio.

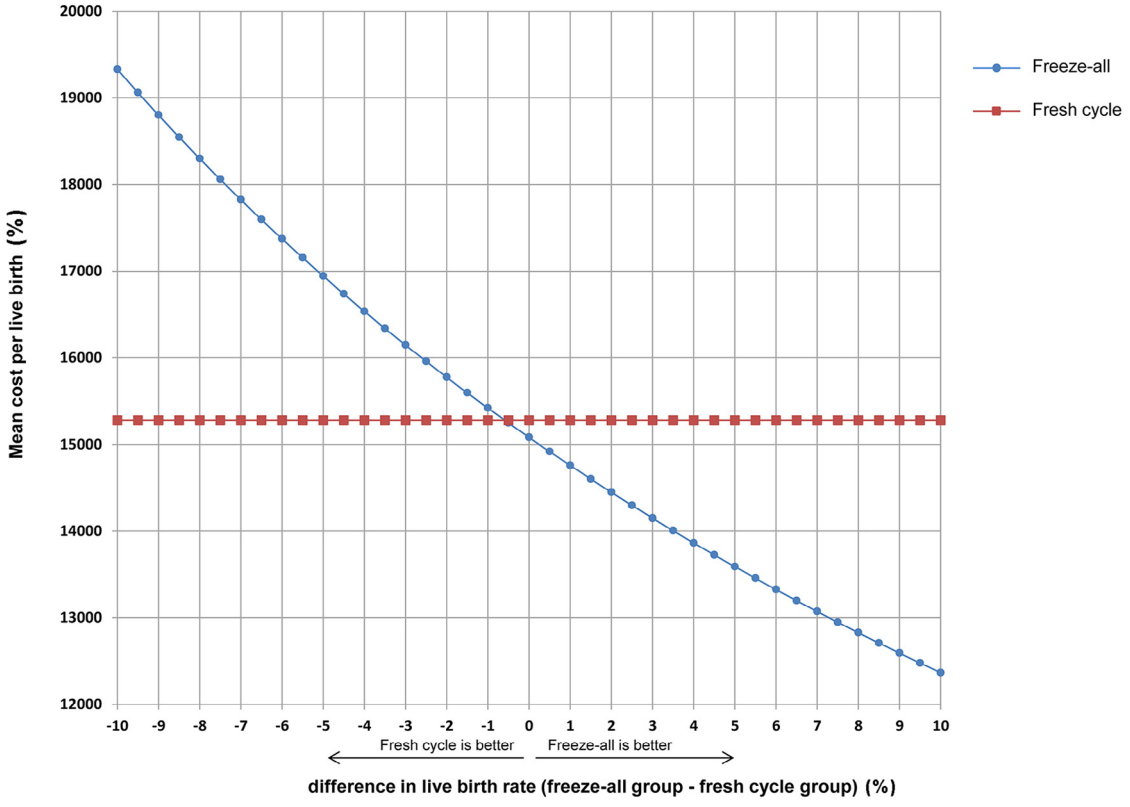

Figure 1 – Sensitivity analysis according to percentage difference in live birth rate. The live birth rate and the mean cost per live birth for the fresh cycle group (red squared line) have been kept constant, changing the cumulative live birth rate for the freeze-all group and consequently the related cost per live birth (blue dotted line). The number of executed transfers in both groups was not modified.

supernumerary embryos are cryopreserved. The freeze-all strategy is already considered the preferred method for managing patients at high risk of OHSS, for patients needing PGD and PGS, and for patients with abnormal progesterone elevation at the end of ovarian stimulation in IVF. Recent evidence, however, also supports the elective adoption of the freeze-all policy in routine clinical practice in IVF. In fact, some centres have already adopted elective vitrification and subsequent vitrified–warmed single blastocyst transfer as routine management of cases with previous failed fresh embryo transfer cycles or a history of tubal infertility and ectopic pregnancy (Kato et al., 2012; Shapiro et al., 2014b). In general, clinical and technical issues have to be clarified before this strategy is routinely adopted. On the one hand, the freeze-all policy has so far mainly been applied to restricted groups of patients, and high-quality randomized controlled trials aimed at assessing the benefits of a freeze-all approach in different infertile populations are currently still ongoing (Blockeel et al., 2016). On the other hand, extensive cost-effectiveness analyses should also be conducted (Blockeel et al., 2016; Maheshwari and Bhattacharya, 2013). In fact, incremental costs are expected for a strategy of elective cryopreservation compared with fresh embryo transfer, owing to additional expenses associated with cryopreservation, extra workload, endometrial priming and monitoring before FET (Blockeel et al., 2016; Maheshwari and Bhattacharya, 2013). Interestingly, our analysis shows no significant difference in the mean direct costs of a freeze-all policy compared with fresh transfer cycles in normal- and high-responder patients undergoing blastocyst culture. In particular, both mean costs per patient (i.e. per started cycle) and mean costs per live birth were comparable between the freeze-all strategy and fresh transfer IVF using the 'real-life' data from our centre. More specifically, a mean per-live birth cost-saving of €2178 resulted from using the freeze-all strategy, but the difference was not significant. This observation is partially due to the fact that, if a freeze-all strategy is adopted, a lower number of embryo-transfer attempts is required to achieve pregnancy. Our results show that embryo transfer procedures account for over 40% of all costs in both strategies, and that mean number of transfers is slightly lower in the freeze-all group compared with fresh transfer IVF (1.29 ± 0.5 versus 1.40 ± 0.7), even if the difference is not significant. If a very low cost is assumed for the embryo transfer procedures, even equal to zero, however, the freeze-all strategy remains cost-saving in our analysis owing to the higher number of pregnancies achieved (data not shown).

As this analysis is based on real IVF data and true healthcare costs, the major strength of our study is its data-driven approach. To some extent, this may raise the concern that our results may have only limited validity, as they may vary with the variation of healthcare costs, i.e. among different settings and countries. On the other hand, assuming a greater efficacy of the freeze-all strategy in terms of pregnancies achieved, lower costs associated with this strategy should also be observed in situations and conditions different from Italy.

In fact, medications used for endometrial priming and endometrial monitoring before FET only account for less than 1% of total costs in a freeze-all strategy. Costs associated with vitrification of embryos as well do not represent an issue: in fact, in normal- and high-responder patients in whom supernumerary blastocysts are expected and vitrified, a fresh embryo transfer attempt only implies the vitrification of one or two fewer blastocysts compared with a freeze-all policy.

Intuitively, the global cost of treatment is strictly related to the performance of each technique in terms of CLBR. To determine the robustness of our cost analysis, we therefore conducted a sensitivity analysis and showed that the freeze-all strategy remained cost-effective until the difference in CLBR between the freeze-all group and the fresh cycle group is –0.59% or greater. In contrast, a sensitivity analysis for varying single-step costs would be of little significance.

Although pregnancy outcomes in our study are comparable between the freeze-all strategy and fresh transfer IVF, Zhu et al. (2011) conversely found an increased clinical pregnancy rate with cryopreserved blastocysts compared with fresh transfer. Similar results were also confirmed by two subsequent randomized controlled trials (Shapiro et al., 2011a, 2011b), including normal- and high-responder patients, in which a significant increase in pregnancy rates occurred with the freeze-all strategy at the blastocyst stage compared with fresh embryo transfer. As a non-significant trend for both improved cumulative ongoing pregnancy rate and CLBR is also observed in our study, our result is most likely due to the small number of patients included. Hence, larger studies might be able to strengthen our results.

The main limitation of our study is that we only report on direct healthcare costs. With recent evidence suggesting that cryopreserved embryo transfer might lead to decreased maternal and perinatal morbidity compared with fresh embryo transfer (Barnhart, 2014; Ishihara et al., 2014; Li et al., 2015; Maheshwari et al., 2012), it is very likely that an analysis covering indirect costs would prove a freeze-all policy to be more cost-effective. In this context, the reduction in the incidence of severe OHSS associated with treatment segmentation would also likely reveal the freeze-all strategy to be cost-saving, owing to reduced need of medication and hospitalization (Devroey et al., 2011). In addition, if a better performance of the cryopreserved embryo transfer in terms of implantation and pregnancy rates will be confirmed, this strategy will encourage single embryo transfer and help to decrease the incidence of twin pregnancies, with an obvious advantage on indirect costs. One further limitation of our analysis could be represented by the heterogeneity of the two populations in terms of basal AMH and number of oocytes retrieved. The number of oocytes used for fertilization (a criterium used for matching) and the number of embryos transferred, however, were similar between the two groups, thereby at least partially controlling for the potential bias. Finally, it is relevant to notice that in our study, blastocysts were cryopreserved by vitrification, so our results already apply to the currently preferable, and also most expensive, cryopreservation technique (Gvakharia and Adamson, 2011; Li et al., 2015). Therefore, as the freeze-all strategy might be evolving into mainstream therapy in IVF, our first cost analysis reassures the adoption of this policy, as the mean direct costs per-cycle and per-live birth are similar compared with fresh transfer IVF. Further larger, prospective studies extending the analysis to indirect costs and also providing data on poor responder patients are, however, needed.

ARTICLE INFO

Article history:
Received 26 April 2016
Received in revised form 15 September 2016
Accepted 21 September 2016
Declaration: The authors report no financial or commercial conflicts of interest.

Keywords:
Blastocyst
Cost analysis
Freeze-all
IVF

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