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ARTICLE

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

Enrico Papaleo [a], Luca Pagliardini [b], Valeria Stella Vanni [a], Diana Delprato [a], Patrizia Rubino [b], Massimo Candiani [a,c], Paola Viganò [b,*]

[a] *Centro Scienze Natalità, Obstetrics and Gynecology Dept, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milano, Italy;* [b] *Division of Genetics and Cell Biology, Reproductive Sciences Lab, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20132, Milano, Italy;* [c] *Vita-Salute San Raffaele University, Via Olgettina 58, 20132 Milano, Italy*

* Corresponding author. *E-mail address:* vigano.paola@hsr.it (P Viganò).

Enrico Papaleo obtained his medical degree at the University of Milan, Italy, in 1999, and completed his residency in obstetrics and gynaecology at the University Vita-Salute San Raffaele, Milan, Italy, in 2005. Since 2011, he has been Director of the IVF Unit 'Centro Scienze Natalità', Obstetrics and Gynaecolgy Dept., IRCCS San Raffaele, Milan, Italy. He has been a member of ESHRE since 2003. His current interests focus on new approaches for ovulation induction in infertile patients, polycystic ovary syndrome, management of endometriosis in IVF and embryo transfer and identification of novel prognostic markers of outcome for women undergoing assisted reproduction techniques.

Abstract 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.

KEYWORDS: Blastocyst, Cost analysis, Freeze-all, IVF

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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

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