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REVIEW

The freeze-all strategy after IVF: which indications?

BIOGRAPHY

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KEY MESSAGE

Deferred strategy could be proposed as a 'rescue' strategy to improve safety and enhance live birth rate or, as a 'scheduled' strategy, based on women characteristics, to ensure better conditions for transfer and to limit the adverse effects of ovarian stimulation.

ABSTRACT

The freeze-all strategy is gaining popularity worldwide as an alternative to the conventional fresh embryo transfer. It consists of cryopreservation of the entire embryo cohort and the embryo transfer in a subsequent cycle that takes place separately from ovarian stimulation. The freeze-all strategy was initially a 'rescue' strategy for women at high risk of ovarian hyperstimulation syndrome; however, this approach has been extended to other indications as a scheduled strategy to improve implantation rates. This assumes that ovarian stimulation can alter endometrial receptivity in fresh cycles owing to the effect of supraphysiological levels of steroids on endometrial maturation. The procedure, however, has not been associated with increased live birth rates in all infertile couples, and concerns have been raised about the occurrence of several adverse perinatal outcomes. It is, therefore, crucial to identify in which subgroups of patients a freeze-all strategy could be beneficial. The aim of this review is to summarize current scientific research in this field to highlight potential indications for this strategy and to guide clinicians in their daily practice.

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INTRODUCTION

The use of frozen embryo transfers has steadily increased over the past decade, and this approach to assisted reproductive technology (ART) is now practised worldwide (*European IVF-Monitoring Consortium for the European Society of Human Reproduction and Embryology, 2016*). Several factors underlie the growing success of this procedure, such as improvements in cryopreservation techniques, particularly the vitrification processes (*Wong et al., 2014*), and the expansion of 'elective single embryo transfer' (*Pandian et al., 2005*). These advances have contributed to a large increase in the number of embryos available for transfer. The current trend, however, is not just to freeze the supernumerary embryos, but to freeze the entire embryo cohort to achieve a deferred embryo transfer. This is referred to as the 'deferred embryo transfer' strategy or the 'freeze-all' strategy (*Blockeel et al., 2016*; *Bourdon et al., 2018a*). It differs from the fresh embryo transfer approach because the process of embryo transfer is separate to the process of ovarian stimulation and oocyte retrieval.

The use of this strategy is steadily increasing in ART cycles with various indications (*Bourdon et al., 2017*; *Blockeel et al., 2019*). It was initially developed to counter the risk of late pregnancy-induced ovarian hyperstimulation syndrome (OHSS) in patients who experienced an excessive ovarian response to stimulation (*Bodri et al., 2010*; *Manzanares et al., 2010*). This was considered to be a 'rescue' strategy, as the freeze-all strategy was decided during ovarian stimulation. The indications for a 'rescue' freeze-all strategy were then extended to other clinical conditions, such as the existence of endometrial anomalies, e.g. thin endometrium, polyps, associated metrorrhagia, submucosal leiomyomas and endometritis, or elevated progesterone levels on the last day of stimulation. The aim was to limit the risk of implantation failure (*Venetis et al., 2013*; *De Ziegler et al., 2016*), or was used as a 'scheduled' strategy before the beginning of ovarian stimulation in various indications, including preimplantation genetic testing (PGT). In these cases, embryos remain frozen while awaiting the results of the genetic tests (*Evans et al., 2014*; *Rodriguez-Purata et al., 2016*; ESHRE PGT Consortium Steering Committee *et al*., *2020*), or in the presence of endometriosis (*Bourdon et al., 2018c*). On the basis of the hypothesis that ovarian stimulation with IVF and intracytoplasmic sperm injection (ICSI) cycles could have a negative effect on endometrial receptivity, generalization of the freeze-all strategy to the overall IVF/ICSI population has since been implemented in a number of centres (*Shi et al., 2018*; *Wei et al., 2019*) in an effort to improve reproductive outcomes. The results of several recent randomized controlled trials (RCTs) and meta-analyses on live birth rates (LBR), either the LBR after the first embryo transfer or the cumulative LBR, are, however, controversial, with some studies showing no benefit of the freeze-all strategy compared with the fresh embryo transfer strategy, and others reporting better outcomes (*Chen et al., 2016*; *Wong et al., 2017*; *Shi et al., 2018*; *Vuong et al., 2018*; *Roque et al., 2019*; *Wei et al., 2019*). Moreover, some concerns about an increased risk of adverse perinatal outcomes in deferred embryo transfers have been expressed, including hypertensive disorders of pregnancy (HDP), large for gestational age (LGA) or high birth weight (HBW) newborns (*Chen et al., 2016*; *Maheshwari et al., 2018*; *Zhang et al., 2018*; *Roque et al., 2019*; *Wei et al., 2019*). It seems, therefore, premature to apply the freeze-all policy to all ART cycles. On the basis of currently available evidence, it should only be a consideration in specific indications to limit the risks from ovarian stimulation and to optimize the chances of a live birth. Here, we attempt to establish in which clinical circumstances a freeze-all strategy should be recommended. To this end, an overview of each potential indication, as a 'rescue' strategy or a 'scheduled' one, will be presented to discuss how best to proceed in daily practice.

SCIENTIFIC BASIS OF DEFERRED TRANSFER: INFLUENCE OF OVARIAN STIMULATION ON THE ENDOMETRIUM

The major difference between freeze-all and fresh embryo transfer strategies is the timing of the embryo transfer relative to ovarian stimulation. At the end of ovarian stimulation, 'supraphysiological' concentrations of oestradiol and progesterone are usually reached, and these could alter the endometrium receptivity, as suggested by numerous published studies (*Check et al., 1999*; *Nikas et al., 1999*). In the fresh embryo transfer policy, the embryo transfer takes place just after the ovarian stimulation whereas, in the freeze-all policy, cryopreservation of the entire embryo cohort after the oocyte retrieval allows the embryo transfer to be carried out well after ovarian stimulation, under more physiological conditions.

In a natural cycle, the endometrium is receptive for only a limited time span, outside of which embryonic implantation cannot take place. This window of implantation lies between day 6 and day 10 after ovulation (*Lessey, 2011*; *Valdes et al., 2017*; *Neykova et al., 2020*), and steroids (oestradiol and progesterone) play a key role in inducing structural and molecular changes in the endometrium that allow the embryo to implant itself (*Noyes et al., 1975*; *Simon et al., 2003*; *Young, 2013*).

A major source of concern in ART cycles is that ovarian stimulation may disturb the dynamics of endometrium maturation (*Ubaldi et al., 1997*; *Lass et al., 1998*; *Nikas et al., 1999*; *Bourgain and Devroey, 2003*). Indeed, several studies have shown that, after ovarian stimulation, the endometrium is able to reach its receptivity phase sooner. An advance of the maturation of the endometrium by 2–4 days has been shown to occur based on a large number of endometrial biopsies carried out on the day of oocyte retrieval compared with biopsies carried out in natural cycles (*Ubaldi et al., 1997*; *Lass et al., 1998*). Several markers of the implantation window, such as the 'nucleolar channel system' (*Zapantis et al., 2013*) or the formation of pinopodes at the apical pole of the epithelium (*Nikas et al., 1999*), were found to occur earlier than normal. Other studies have found that endometrial secretions before embryo transfer are altered relative to natural cycles (*Boomsma et al., 2010*; *Li and Jin, 2013*). Embryos transferred after ovarian stimulation seem to be exposed to an environment that differs from that of a natural cycle (*Bourgain and Devroey, 2003*). Similarly, immunological differences (*Orvieto et al., 1999*; *Junovich et al., 2011*) and changes in gene expression (*Mirkin et al., 2004*; *Horcajadas et al., 2005*; *2008*; *Liu et al., 2008*; *Haouzi et al., 2009*) have been shown to occur in the endometrium

after ovarian stimulation compared with the endometrium in natural cycles. For instance, *Haouzi et al. (2009)* found that only 46% of the activated genes linked to the acquisition of a receptive endometrium were identical in natural and stimulated cycles (*Haouzi et al., 2009*). Yet, the functional consequences of these changes in gene expression on embryo implantation have remained unclear to date (*Mirkin et al., 2004*; *Simon et al., 2005*). Several teams have even developed endometrial receptivity assays based on the evaluation of the impregnation of progesterone, or the presence of specific microRNAs or immune modifications, in an attempt to optimize endometrial receptivity, thereby hypothetically increasing ART implantation rates (*Tan et al., 2018*; *Haouzi et al., 2020*; *Lédée et al., 2020*).

As the endometrium seems to undergo a series of histological, immunological and genetic changes owing to increased oestrogen and progesterone serum levels during ovarian stimulation, it has been hypothesized that implantation rates could be improved by transferring the embryo in the next cycle, in an endometrium that is not exposed to 'supraphysiological' levels of steroids (*Yu Ng et al., 2000*; *Bourgain and Devroey, 2003*). Indeed, deferred transfer of an embryo to a subsequent 'natural' or 'artificial' cycle would allow for resynchronization of the endometrium and the transferred embryo. To obtain a receptive endometrium for the frozen–thawed embryo transfer, several options are routinely carried out: the natural cycle; the ovulated cycle with mild ovarian stimulation; and the artificial cycle with the use of exogenous oestradiol and progesterone (*Ghobara et al., 2017*). These three methods were considered to be equally successful in terms of live birth rates until recently (*Groenewoud et al., 2013*; *Ghobara et al., 2017*), after the results of few observational studies suggesting decreased live birth rates, increased miscarriage rates and adverse perinatal outcomes for children conceived after artificial frozen embryo transfer cycles (*Hatoum et al., 2018*; *Ginström Ernstad et al., 2019*; *Saito et al., 2019*; *Wang et al., 2020*). More data provided by RCTs are needed to disentangle the effect of the endometrial preparation protocol on ART outcomes, from confounding factors such as the maternal characteristics, the cryopreservation technique or other features of the ART cycle.

WHAT IS THE EFFECT ON LIVE BIRTH RATES?

Currently, the cumulative LBR seems to be the most pertinent outcome to evaluate the success of the ART, including the results of fresh and frozen embryo transfer cycles (*Maheshwari et al., 2015*). To date, only few studies comparing the freeze-all and the fresh embryo transfer strategies have reported this outcome, and results failed to demonstrate any advantage of the freeze-all strategy in the overall IVF population (*Ferraretti et al., 1999*; *Shapiro et al., 2011*; *Chen et al., 2016*; *Vuong et al., 2018*; *Zacà et al., 2018*; *Wei et al., 2019*; *Li et al., 2019*; *Roque et al., 2019*; *Boynukalin et al., 2020*). In a recent meta-analysis from Roque *et al*. (2019) pooling the results of five RCTs (2674 patients), no significant difference was found between the two groups (RR 1.04; 95% CI 0.97 to 1.11) in cumulative LBR (*Roque et al., 2019*). The same conclusions were drawn in another recent RCT, including 1650 ovulatory women (*Wei et al., 2019*), and in large retrospective cohort studies (*Zacà et al., 2018*; *Li et al., 2019*; *Boynukalin et al., 2020*). Subgroup analysis, however, highlighted a potential benefit of the freeze-all strategy on cumulative LBR, in specific clinical scenarios, such as in high-responders (*Boynukalin et al., 2020*) or in blastocyst-stage embryo transfer (*Zacà et al., 2018*), underlining the need for more data to discriminate the clinical situations in which freeze-all could be really advantageous in terms of cumulative LBR. Another important outcome when comparing two different ART strategies is the time to pregnancy. Unfortunately, few studies have focused on this issue (*Vuong et al., 2018*; *Stormlund et al., 2020*), reporting an increase in the time to pregnancy in the freeze-all approach. On the basis of these findings, it seems inappropriate to implement the freeze-all strategy in all patients undergoing ART. The clinical scenarios in which the freeze-all could offer an improvement in pregnancy outcomes or safety will be discussed.

FREEZE-ALL: A 'RESCUE' STRATEGY?

The decision to opt for a freeze-all strategy could be decided during ongoing ovarian stimulation, as a 'rescue' strategy, to improve the safety, enhance the chances of a live birth, or both. These potential 'rescue' indications are detailed below.

Risk of ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome is an iatrogenic complication in ART which, in rare cases, can lead to death (*Smith et al., 2015*). Two types of OHSS have been identified, based on the delay in appearance: early OHSS occurs 3–7 days after triggering ovulation. It is induced mostly by the injection of exogenous HCG (triggering ovulation) (*Lyons et al., 1994*; *Mathur et al., 2000*); late OHSS manifests about 12 days after the embryonic transfer. It is induced by the secretion of endogenous HCG with pregnancy (*Lamazou et al., 2011*; *Smith et al., 2015*). The incidence of moderate and severe OHSS has been estimated to be 3–6% and 0.1–2%, depending on the study (*Lamazou et al., 2011*; *Papanikolaou et al., 2011*; *Nastri et al., 2015*; *Barbosa et al., 2016*). In high-risk women presenting with polycystic ovary syndrome (PCOS), the incidence is even higher, reaching 5–10% (*Chen et al., 2016*; *Lambalk et al., 2017*). This syndrome is secondary to an exacerbated response to ovarian stimulation by gonadotrophins, which leads to the release of various vasoactive substances that induce an increase in the permeability of the capillaries, a release of fluid from the vascular sector to a third sector, and haemoconcentration (*Goldsman et al., 1995*). The administration of HCG has been shown to drive the release of vascular endothelial growth factor (VEGF), which is one of these key vasoactive substances (*Neulen et al., 1995*; *Geva and Jaffe, 2000*; *Cerrillo et al., 2009*). Therefore, the exogenous HCG that triggers ovulation plays a major role in the occurrence of OHSS, and the endogenous HCG secreted by the trophoblast with pregnancy greatly exacerbates it, in the case of a fresh embryo transfer. Ovulation trigger by a gonadotrophin releasing hormone agonist (GnRHa), instead of the HCG exogenous treatment, has been proposed to avoid early OHSS (*Devroey et al., 2011*; *Fatemi et al., 2014*; *Borges et al., 2016*; *Mourad et al., 2017*). Indeed, use of GnRHa as a trigger leads to a reduction of the steroidogenesis and early luteolysis, which then prevents the secretion of

vasoactive substances responsible for OHSS (*Kol, 2004*; *Tannus et al., 2017*). As reported by *Cerrillo et al. (2009)*, the follicular fluid vascular endothelial growth factor concentration was significantly lower in response to GnRHa compared with triggering with HCG. As a result of this quick luteolysis, the luteal phase is defective after GnRHa trigger, thereby explaining lower pregnancy rates and higher miscarriage rates in the case of fresh embryo transfer and standard luteal phase support (*Humaidan et al., 2005*; *Kolibianakis et al., 2005*). Intensive luteal phase support protocols were, therefore, developed, sometimes requiring small boluses of HCG, providing satisfying reproductive outcomes but also residual risks of OHSS resulting from both the use of exogenous HCG and the secretion of endogenous HCG in case of pregnancy after the fresh embryo transfer (*Humaidan et al., 2010*; *2013*; *Radesic and Tremellen, 2011*; *Iliodromiti et al., 2013*; *Santos-Ribeiro et al., 2020*). For all these reasons, the 'rescue' freeze-all strategy, with cryopreservation of the entire embryo cohort, is a validated approach for avoiding late OHSS and optimizing the chances of pregnancy (*Devroey et al., 2011*; *Blockeel et al., 2016*; *ESHRE guideline: ovarian stimulation for IVF/ICSI, 2019*). In case of agonist stimulation protocols, as HCG trigger is the only option, the freeze-all strategy can be applied to avoid late OHSS in women with a high risk of OHSS, although it does not prevent the risk of early OHSS (*ESHRE guideline: ovarian stimulation for IVF/ICSI, 2019*). Adjuvants treatments (dopamine agonists, GnRH antagonists) have also been studied as secondary prevention interventions for OHSS in women at high-risk (*Tang et al., 2016*; *Mourad et al., 2017*; *Nelson, 2017*; *ESHRE guideline: ovarian stimulation for IVF/ICSI, 2019*; *Shrem et al., 2019*).

Ultimately, the best way to avoid OHSS and to maximize patient safety is to prevent its occurrence by identifying patients at risk. Indeed, screening patients for risk factors is a crucial step, as this allows selection of the most appropriate treatment, i.e. antagonist ovarian stimulation protocol; for example, women with PCOS or women who have previously experienced OHSS (*Mourad et al., 2017*; *Nelson, 2017*). A recent RCT that included women with PCOS showed that the freeze-all strategy resulted in significantly lower OHSS rates (10/746 [1.3%] versus 54/762 [7.1%], respectively; absolute difference 95% CI –5.7, –7.7 to –3.7) and significantly higher chances of live birth after the first embryo transfer (368/746 [49.3%] versus 320/762 [42.0%], respectively, $P = 0.004$), compared with the fresh embryo transfer strategy. These findings in patients with PCOS or hyper-responder patients were confirmed by a recent meta-analysis (*Roque et al., 2019*), which highlighted increased LBR and decreased OHSS rates in the freeze-all group (RR 1.16, 95% CI 1.05 to 1.28); $P = 0.004$; and RR 0.42, 95% CI 0.19 to 0.96; $P = 0.04$, respectively). Altogether, these findings suggest that the freeze-all approach is the optimal strategy for patients at risk of OHSS, including women with PCOS, allowing both reduction of the OHSS risk as well as improvement of the chances of a live birth.

Endometrial, tubal and uterine factors discovered during ovarian stimulation

Specific uterine anomalies detected over the course of the ovarian stimulation, such as endometrial anomalies, e.g. polyps, associated metrorrhagia, submucosal leiomyomas and endometritis, tubal anomalies, e.g. hydrosalpinx, can compromise implantation (*De Ziegler et al., 2016*; *Tsiami et al., 2016*). Indeed, although morphological evaluation of the pelvis is recommended before IVF, some anomalies may not be discovered until later during the stimulation, in which case it is preferable to defer the embryo transfer in a freeze-all strategy until after the observed anomaly has been corrected.

Hydrosalpinx, for example, is a common condition among women of reproductive age, with negative consequences on ART outcomes (*Wainer et al., 1997*; *Savaris and Giudice, 2007*). Surgical treatment with proximal tubal occlusion or salpingectomy can reduce the risk of early pregnancy loss and it increases live birth rates compared with no intervention (*Barbosa et al., 2016*; *Dreyer et al., 2016*; *Harb et al., 2019*). Therefore, in case of late discovery of hydrosalpinges during the stimulation, a freeze-all strategy is likely to provide the best chance for infertile women to obtain a live birth, as it allows surgical treatment between ovarian stimulation and embryo transfer. Similarly, in case of leiomyomas that distort the uterine cavity or in case of large endometrial polyps, a surgical resection before the embryo transfer can improve the live birth rate (*Saravelos et al., 2011*; *Izhar et al., 2019*).

Endometrial thickness has also been proposed as a key element for successful implantation; a thin endometrium has been associated with lower chances of a live birth after a fresh embryo transfer (*Liu et al., 2018*; *Ribeiro et al., 2018*). For instance, a large retrospective study of more than 40,000 embryo transfers concluded that the clinical pregnancy rates and the live birth rates decreased whereas the pregnancy loss rates increased significantly with each millimeter decline in the endometrial thickness below 8 mm in fresh ART cycles (*Liu et al., 2018*). The association between a thin endometrium and a decrease in the chances of a live birth after a fresh embryo transfer has also been reported in other large retrospective cohort studies, with thresholds ranging from 7 to 10 mm (*Gallos et al. 2018*; *Oron et al. 2018*; *Ribeiro et al. 2018*). Conversely, in a subgroup analysis of an RCT, no significant effect of the endometrial thickness on LBRs in fresh embryo transfer cycles was described above 8 mm (*Vuong et al. 2019*). Therefore, in case of a thin endometrium during ovarian stimulation, a deferred transfer can be an option to investigate the endometrial anomaly before proceeding to the embryo transfer.

Finally, several cervical anatomical features or cervical stenosis are not diagnosed upstream of the embryo transfer. This may lead to the inability of inserting the embryo transfer catheter, making freeze-all a good option while waiting to solve the problem. Although evidence evaluating the need to differ ovarian stimulation is lacking, a strategy of deferring the embryo transfer until after correction of the observed anomalies seems to be clinically relevant.

Inadequate serum progesterone levels

Elevated progesterone at the end of the follicular phase seems to have a deleterious effect on implantation and pregnancy rates. In a meta-analysis involving 55,199 fresh cycles and 7229 frozen embryo transfer cycles, it was shown that a high level of progesterone (≥0.8 ng/ml) on trigger day significantly reduced the probability of becoming pregnant after a fresh transfer compared with a frozen transfer (*Venetis et al.,*

2013). In another study of oocyte-donation cycles, recipients of oocytes from donors with high progesterone levels (≥1.2 ng/ml) at the end of the follicular phase had similar outcomes as those who received oocytes from donors with normal or low progesterone levels (Melo et al., 2006), This suggests a negative effect of high progesterone levels on the endometrium rather than on the oocyte or embryo quality. In the same way, Healy et al. (2016) underscored that, in the case of transfer of good-quality blastocysts, the chances of becoming pregnant were identical for the fresh and the frozen approach if the levels of progesterone remained below 2 ng/ml. Conversely, above this threshold, the implantation and pregnancy rates were reduced in the fresh transfer group compared with the frozen transfer group (Healy et al., 2016).

Various serum progesterone level cut-offs have been reported, and the effect of the increase in progesterone seems to differ according to clinical presentations. For instance, in high responders, levels over 1.8 ng/ml had no clinical effect in a retrospective cohort study of 2850 women (Requena et al., 2014). In two other retrospective studies, the duration of progesterone elevation had a greater influence on the success rates than the quantitative rise above a certain cut-off (Huang et al., 2012; Santos-Ribeiro et al., 2019). Vuong et al. (2019), however, in a secondary analysis of an RCT concluded that, in case of a serum progesterone level higher than 1.14 ng/ml on the day of trigger, the chances of a live birth were significantly increased after a freeze-all strategy compared with a fresh embryo transfer (Vuong et al., 2019). Although the available data show discrepancies in the clinical effect of different serum progesterone levels on the day of ovulation trigger, a 'rescue' freeze-all strategy with vitrification of the entire embryo cohort can be an option to avoid the detrimental endometrial consequences of elevated progesterone concentrations.

In the same way, but much less studied, low serum progesterone levels before a fresh embryo transfer could also have a detrimental effect on reproductive outcomes, thereby making the freeze-all approach a potential option to try improving ART success rates. To our knowledge, only two observational studies have focused on this issue (Santos-Ribeiro et al., 2014; Thomsen et al., 2018), and highlighted decreased live birth rates below progesterone thresholds of 0.5 ng/ml on the day of HCG administration and 18 ng/ml on the day of embryo transfer, respectively. Yet, caution is needed to interpret such observational data, as many confounding factors are not taken into account and may bias the evaluation of the effect of low progesterone levels on live birth rates in fresh embryo transfer cycles (Venetis et al., 2018). Moreover, no RCT has ever addressed the question of the benefits of the freeze-all strategy over the fresh embryo transfer approach to improve ART results, when progesterone levels are below a certain threshold during ovarian stimulation.

Finally, the cost–effectiveness ratio of deferring the embryo transfer in case of inadequate progesterone levels during ovarian stimulation or before embryo transfer remains to be evaluated.

Embryological reasons: slow-developing blastocysts

Embryo transfer at the blastocyst stage is becoming more accepted and it is frequently preferred in ART centres worldwide, especially in the context of a single embryo transfer strategy (Gardner, 2000; Glujovsky et al., 2016). In most cases, embryos reach the blastocyst stage 5 days after fertilization, although slower embryos can reach expanded blastocele formation on day 6 or even on day 7, under the same culture conditions (Ivec et al., 2011; Hammond et al., 2018). Currently available data indicate that ART outcomes differ for blastocysts developing on day 5 compared with slower developing day-6 blastocysts. In a recent meta-analysis, the transfer of day-5 blastocysts was associated with significantly higher pregnancy rates compared with the transfer of day-6 blastocysts (Bourdon et al., 2019). In addition, a recent time-lapse imaging study showed that embryos that required relatively little time to reach the full blastocyst stage in fresh embryo transfer were associated with a significantly increased LBR per transfer than embryos that were slow to reach the blastocyst stage (Fishel et al., 2018). Although these results support the notion that the intrinsic embryo implantation potential in day-6 blastocysts is impaired (Bourdon et al., 2020a), an asynchrony between the endometrium and day-6 blastocysts is also a possibility, as suggested by Healy et al. (2017) who reported significantly lower live birth rates in fresh day-6 compared with fresh day-5 blastocyst transfers, whereas this difference was not found with frozen embryo transfer (Healy et al., 2017). Progesterone is known to be crucial for preparation of the endometrium for implantation by allowing it to become receptive to the embryo. In case of fresh day-6 blastocyst transfer, the embryo is transferred 1 day later than a fresh day-5 blastocyst, and thus to an endometrium exposed to 1 more day of progesterone, which could lead to suboptimal embryo–endometrium synchrony. Although no RCT to date has compared the implantation chances of day-6 blastocysts in a fresh and a deferred embryo transfer strategy, the results from a recent meta-analysis revealed lower implantation rates in fresh day-5 blastocyst transfers compared with frozen day-6 blastocyst transfers (Bourdon et al., 2019). Therefore, the freeze-all approach should be considered for cycles where there is a potential embryo–endometrium asynchrony caused by delays in blastocyst development.

SCHEDULED FREEZE-ALL STRATEGY

The freeze all strategy can be decided upstream of the ovarian stimulation. This decision can be taken, based on specific characteristics of the infertile couple, to try to ensure better conditions for the embryo transfer and to limit the adverse effects of ovarian stimulation.

Patients undergoing preimplantation genetic testing

Preimplantation genetic testing aims to analyse the DNA from embryos for human leukocyte antigen typing or to determine genetic abnormalities (ESHRE PGT Consortium Steering Committee et al., 2020), including PGT for aneuploidy (PGT-A), PGT for monogenic defects and PGT for chromosomal structural rearrangements. The embryo biopsy can be carried out at different embryonic stages, and a freeze-all strategy can be applied while waiting for the results of the genetic analysis (ESHRE PGT Consortium Steering Committee et al., 2020). Notably, the PGT-A technology has been applied to ART procedures to select the most competent embryos for transfer, to increase IVF/ICSI live birth rates. Although RCTs have clearly shown that PGT-A associated

embryo biopsy at cleavage stage and fluorescence in-situ hybridization (FISH) technology do not increase pregnancy rates, and in some instances even lowers them (*Mastenbroek et al., 2011*), recent advances in IVF (extended embryo culture, trophectoderm biopsy and vitrification), along with advances in the genetic technologies, now indicate ample scope for aneuploidy to be detected at the blastocyst stage (*Dahdouh et al., 2015*), even if the improvement in live birth rate for the overall ART population remains to be proved (*Munné et al., 2019*). After a blastocyst embryo biopsy (day 5 or day 6), two transfer strategy options for euploid embryos are available in clinical practice: a freeze-all strategy, with all of the blastocysts frozen after biopsy in anticipation of PGT-A, or a fresh embryo transfer of a blastocyst biopsied at day 5, cultured overnight to await the PGT-A results for a fresh embryo transfer of euploid embryos on day 6 as soon as the PGT-A results become available. Nevertheless, a RCT has reported that the freeze-all strategy significantly improved the ongoing pregnancy rate (80% versus 61%) and the live birth rate (77% versus 59%) compared with a fresh embryo transfer strategy after PGT-A of blastocyst embryos (*Coates et al., 2017*). Indeed, in light of the time required to carry out an embryo genome-wide analysis, a robust freeze-all strategy is preferable with this technique (*Coates et al., 2017*). Nevertheless, only one RCT has evaluated this freeze-all embryo transfer strategy (*Coates et al., 2017*). Therefore, further RCTs are needed to confirm the superiority of a freeze-all strategy in PGT-A associating embryo biopsy at the blastocyst stage compared to a fresh strategy.

Endometriosis and adenomyosis

Endometriosis affects about 6–10% of all reproductive-age women, and at least one-third of them are infertile (*Giudice and Kao, 2004*). IVF/ICSI is a therapeutic option for many women who are infertile as a result of endometriosis, and it generally yields satisfactory results (*Hamdan et al., 2015*; *Maignien et al., 2016*; *2020*). Recent observations have highlighted a potential benefit of freeze-all strategy in this specific population. For instance, in a cohort study of 270 endometriosis-affected women, a significantly higher cumulative live birth rate was observed among patients who underwent a freeze-all strategy compared with patients who underwent a fresh embryo transfer (29.6% versus 15.6%; $P = 0.01$), after matching them for age, the number of previous IVF cycles and the endometriosis phenotype (*Bourdon et al., 2018c*). The proposed hypothesis is that endometrial receptivity can become even more disturbed in endometriosis-affected patients after ovarian stimulation: the eutopic endometrium has been shown to undergo biochemical and structural changes (*Borghese et al., 2008*; *Santulli et al., 2014*). These may be exacerbated by supraphysiological levels of steroids related to ovarian stimulation. Therefore, a reliance on deferred embryo transfer could restore optimal receptivity for implantation, thereby improving the pregnancy rate and obstetrical issues. In the same way, adenomyosis is an oestrogen-dependent disease that can result in pelvic pain and infertility. A close relationship seems to exist between endometriosis and adenomyosis (*Chapron et al., 2017*). Few data on the benefit of the freeze-all strategy in women with adenomyosis undergoing ART are available. As is the case for women with endometriosis, however, the eutopic endometrium in adenomyosis-affected women also undergoes hormonal and molecular changes (*Mehasseb et al., 2011*; *Benagiano and Brosens, 2012*). In addition, it has been reported that GnRHa pretreatment increased the litter size compared with untreated mice with adenomyosis in a mouse model of adenomyosis (*Guo et al., 2017*). In humans, GnRHa pretreatment in association with hormonal replacement therapy before frozen embryo transfer also seems to have a positive effect on the chances of pregnancy (*Park et al., 2016*; *Stanekova et al., 2018*; *Zhu et al., 2019*). Consequently, the use of a freeze-all strategy in endometriosis, adenomyosis patients, or both, could be a promising strategy to improve ART outcomes. RCTs are nonetheless required.

Repeated IVF/ICSI failures

Repeated IVF/ICSI failure is a common occurrence in ART, and it can be attributed to interlinked causes, such as embryonic defects or multifactorial causes (*Margalioth et al., 2006*). It may also be caused by a failed implantation process, possibly related to the endometrial changes that impair endometrial receptivity in fresh autologous IVF/ICSI cycles (*Bourgain and Devroey, 2003*; *Lédée et al., 2011*). On the basis of this hypothesis, a freeze-all strategy could be a relevant alternative, as it could provide a more physiologic environment for embryo transfer and thus improve implantation. Indeed, several studies advocate a freeze-all strategy to increase the chances of a live birth in women with repeated IVF/ICSI failures, although the results have so far been mixed (*Shapiro et al., 2014*; *Magdi et al., 2017*; *Bourdon et al., 2018a*). *Shapiro et al. (2014)* concluded that women with at least one failed fresh blastocyst transfer have a significantly greater probability of a live birth with the 'freeze-all' and subsequent thawed approach than with another fresh cycle (*Shapiro et al., 2014*). Along these lines, *Magdi et al. (2017)* conducted a prospective cohort study of women with recurrent implantation failure, defined as a failure to achieve a clinical pregnancy after at least three fresh or frozen cycles with a cumulative transfer of at least four good-quality embryos in women under 40 years of age, and they found a statistically significantly higher implantation rate of 39.9% in the deferred embryo transfer cycle group compared with 15.9% in the fresh embryo transfer group (*Magdi et al., 2017*). Conversely, another cohort study found no significant differences between fresh and deferred embryo transfer strategies in live birth and cumulative live birth rates for women with a history of at least two or more consecutive IVF/ICSI cycle failures (*Bourdon et al., 2018a*). Similarly, a cohort study of 433 poor responders, with at least one previous failed cycle with fresh embryo transfer, found no significant differences in the pregnancy rates between the freeze-all and the fresh embryo transfer strategy (*Roque et al., 2018*). The lack of RCT to date involving this specific subgroup of women (*Roque et al., 2019*), and the absence of a standardized definition for recurrent IVF/ICSI failures (*El-Toukhy and Taranissi, 2006*; *Rinehart, 2007*; *Coughlan et al., 2014*), prevent solid conclusions being drawn. Nevertheless, in light of the absence of efficient strategies in case of recurrent failures (*Coughlan, 2018*), the freeze-all policy could be a valuable option that patients should be made aware of (*Shapiro and Garner, 2017*), while waiting for substantiation by a large, multicentre, prospective RCT.

Risk of thromboembolic diseases

IVF is associated with an increased risk of thromboembolic diseases (pulmonary

embolism and venous thrombosis), with a doubling of risks during pregnancies resulting from ART (OR 2.18, 1.63 to 2.92) compared with the background pregnant population, according to a recent meta-analysis (*Sennström et al., 2017*). This is a result of a five to 10-fold increased risk during the first trimester (*Chan, 2009*; *Rova et al., 2012*; *Henriksson et al., 2013*; *Hansen et al., 2014*; *Galambosi et al., 2017*). The risk factors comprise the presence of OHSS (RR 95% CI 5.4, 2.1 to 13.7), with an incidence of about 0.2% (*Magnusson et al., 2018*), as well as prior history of polycystic ovarian syndrome (RR 95% CI 4.8, 1.7 to 13.4) (*Hansen et al., 2014*). Moreover, unusual sites of thrombosis, such as the upper limbs or the neck, have been reported with OHSS (*Chan, 2009*).

Explanations for this increased risk of thromboembolic diseases comprise normal physiological changes in pregnancy that are the result of a hypercoagulative state. This state correlates with oestradiol levels. Increased oestradiol levels in the context of IVF can influence the state of hypercoagulability. Indeed, the acquired resistance to the anticoagulant action of activated protein C (APC) increases significantly during hyperstimulation and remains high during luteal treatment. The change in the oestradiol level between baseline and hyperstimulation correlates with changes in APC (*Curvers et al., 2001*). More recently, early changes in laboratory markers of thrombotic risk (especially thrombin generation) in the first trimester of pregnancy have been evaluated in women undergoing natural cycle IVF (*Bagot et al., 2019*). This study confirmed the correlation between high oestradiol and progesterone levels and markers of hypercoagulability. Moreover, the results showed that the prothrombotic state developed very early during the first trimester (*Bagot et al., 2019*).

Few studies to date have evaluated the difference in thromboembolic risk between fresh and frozen embryo transfer. The risk of a thromboembolic event does not appear to be increased during pregnancies derived from frozen embryo transfer (*Rova et al., 2012*) given that the ovarian stimulation does not take place before the transfer and because the risk of OHSS is absent. These results, however, were based on a small sample of women in the frozen embryo transfer cycle group. More recently, *Olausson et al. (2020)* published data from the nationwide Swedish registry-based cohort study of women who gave birth after various types of embryo transfer and after natural pregnancies (*Olausson et al., 2020*). They confirmed the high risk of thromboembolic event in women giving birth after a fresh embryo transfer compared with women giving birth after natural conception (for venous thromboembolism, events/incidence per 1000 ongoing pregnancies: 45/1.77, 95% CI 1.29 to 2.37; hazard ratio 8.96, 95% CI 6.33 to 12.67; for pulmonary embolism: 8/0.32, 95% CI 0.14 to 0.62; HR 8.69, 95% CI 3.83 to 19.71). Conversely, the incidence of a thromboembolic event in women giving birth after a frozen embryo transfer was not increased during the first trimester compared with natural conception (for venous thromboembolism: 3/0.61; 95% CI 0.94 to 9.35; HR 2.97). No pulmonary embolism event occurred in the frozen embryo transfer group. These results suggest that frozen embryo transfer could be safer than fresh embryo transfer. The hypothesis for explaining this result could be the difference between hormonal levels and induced coagulation markers. Frozen embryo transfer replicates the same hormonal and coagulation state of natural conception. By contrast, fresh embryo transfer is preceded by an elevated level of oestradiol and consequently a hypercoagulation state. Therefore, a freeze-all strategy could be the best option to limit the thromboembolic risks induced by ART treatments in women who are at high risk of a thromboembolic event.

WHAT IS THE EFFECT OF OBSTETRIC AND PERINATAL OUTCOMES?

The safety of the freeze-all strategy in terms of obstetric and perinatal outcomes is another important source of concern. Interpretation of the broad range of data in this regard is made difficult as numerous factors can influence pregnancy outcomes, including maternal characteristics, ovarian stimulation protocols, luteal phase support modalities, techniques for cryopreservation and thawing, number and stage of transferred embryos, and the protocols for endometrial preparation in frozen embryo transfer. Until recently, most observations were based on the results of observational studies comparing fresh versus frozen embryo transfer. These suffered from biases, the main ones being that women in the latter group tend to be younger, have a better response to ovarian stimulation, produce more embryos, and have better prognoses (*Maheshwari et al., 2018*). Yet, several recent RCTs and meta-analysis report a number of consistent findings.

Miscarriages

No differences have been found between freeze-all and fresh embryo transfer strategies (*Roque et al., 2019*).

Preterm delivery

Contrary to most retrospective cohort studies and meta-analyses in the past few years (*Pelkonen et al., 2010*; *Pinborg et al., 2010*; *2013*; *Kato et al., 2012*; *Sazonova et al., 2012*), no differences have been reported in the risk of delivery before 37 weeks of gestation among pregnancies resulting from freeze-all compared with fresh embryo transfer cycles in recent RCTs and meta-analysis (*Chen et al., 2016*; *Shapiro et al., 2016*; *Shi et al., 2018*; *Vuong et al., 2018*; *Zhang et al., 2018*; *Roque et al., 2019*; *Wei et al., 2019*). Such differences have several explanations. First, observational studies compare the outcomes of fresh embryo transfer with frozen embryo transfer, without distinguishing between embryo transfer after a freeze-all policy or subsequent frozen embryo transfer after a fresh transfer; this introduces a comparison bias between women who do not have the same ART prognosis and embryos of lowest quality in the latter group. Most observational studies were carried out on cleavage-stage embryos and after slow freezing, whereas recent studies include blastocyst-stage embryo transfer and embryo vitrification, which could also explain differences on perinatal outcomes.

Fetal growth: birthweight

Most studies have revealed a higher risk of a low birthweight (LBW) and small for gestational age (SGA) (*Maheshwari et al., 2018*; *Sha et al., 2018*; *Vuong et al., 2018*) in fresh embryo transfer compared with freeze-all cycles. For instance, in a recent meta-analysis, *Maheshwari et al., (2018)* found that the risk of having a SGA baby and a baby with birth weight less than 2500 g were significantly less in singleton pregnancies subsequent to frozen thawed embryo transfer

compared with those after fresh embryo transfer (RR 0.61; 95% CI 0.56 to 0.67, 10 studies/142462 patients and RR 0.72; 95% CI 0.67 to 0.77, 20 studies/280044 patients, respectively). By contrast, a higher risk of a HBW and LGA was found in freeze-all strategies (*Maheshwari et al., 2018*; *Sha et al., 2018*; *Zhang et al., 2018*; *Wei et al., 2019*), with relative risk estimates of 1.85 (95% CI 1.46 to 2.33, three studies/161267 participants) and 1.54 (95% CI 1.48 to 1.61, seven studies/138263 participants), respectively, in the meta-analysis by *Maheshwari et al. (2018)*. The exact mechanism underlying such differences in the birthweights of newborns remains to be fully elucidated, although several explanations have been forwarded. Supraphysiological levels of steroid hormones during ovarian stimulation may alter endometrial receptivity at the time of the fresh embryo transfer and thus lead to abnormal implantation and placentation, ultimately affecting fetal growth (*Evans et al., 2014*; *Weinerman and Mainigi, 2014*; *Senapati et al., 2018*; *Wu et al., 2020*; *Zhu et al., 2019*). The evidence for an oestradiol-mediated effect on placentation and fetal growth has been corroborated by a recent retrospective study showing that an elevated level of oestradiol on the day of HCG trigger was an independent risk factor for term LBW in singleton pregnancies achieved after fresh embryo transfer (*Pereira et al., 2017*). Conversely, a retrospective study at a centre that uses a freeze-all strategy in case of a high level of oestradiol at trigger did not find a difference in the rate of LBW among the four study groups defined according to the level of oestradiol on the trigger day (*Bourdon et al., 2020b*). This indirectly underscores the fact that fetal growth is probably determined by elevated levels of oestradiol during ovarian stimulation. Moreover, another study of frozen embryo transfer has emphasized the crucial role of oestradiol levels in implantation, as a significant decrease was found in mean birthweight of singleton pregnancies achieved after prolonged exposure to oestradiol (>36 days) in hormonal replacement therapy (HRT) cycles (*Bourdon et al., 2018b*). In addition, several studies have highlighted an increased risk of ischaemic placental disease (*Johnson et al., 2019*) and altered placental vasculature in fresh cycles compared with frozen cycles, thereby emphasizing the potential contribution of placental dysfunction to restricted fetal growth. Finally, results from oocyte donation models in which the endometrium of the recipients is not exposed to ovarian stimulation are in line with these findings showing no difference in the birthweights of newborns obtained after fresh versus frozen embryo transfer (*Galliano et al., 2015*; *Vidal et al., 2017*). Although these observations may account for the higher proportion of SGA and LBW in fresh cycles, the higher proportion of HBW after freeze-all cycles, even compared with natural pregnancies (*Wennerholm et al., 2013*), remains to be fully elucidated. Recent evidence seems to underscore the potential effect of the vitrification–thawing process itself on fetal development. For instance, significant epigenetic changes have been noted in the placenta of pregnancies from frozen embryo transfer compared with spontaneous pregnancies (*Hiura et al., 2017*). Moreover, in several animal models, epigenetic dysregulations affecting genes involved in growth and development have been observed after cryopreservation (*Wang et al., 2010*; *Riesco and Robles, 2013*; *Ghosh et al., 2017*). Evidence from the oocyte donation model, however, indicates that the cryopreservation method *per se* does not have a major effect on fetal birthweights, as no significant difference was found between siblings obtained after replacement of fresh and frozen embryo transfer (*Vidal et al., 2017*). Another important issue to be considered is the endometrial priming in frozen embryo transfer, as different obstetric outcomes have been observed in recent RCTs using different endometrial preparation methods. In the study by *Shi et al. (2018)*, most frozen embryo transfer cycles were carried out in natural cycles, and they did not find differences in the mean birthweight of singletons, or in the rate of macrosomia. Conversely, other studies using endometrial preparations involving oestradiol found significantly increased mean birthweights and proportions of LGA in the deferred embryo transfer groups (*Chen et al., 2016*; *Vuong et al., 2018*; *Zhang et al., 2018*). Furthermore, recent retrospective cohort studies comparing several endometrial priming methods for frozen embryo transfer found increased risks of LGA and macrosomia in the programmed cycle groups compared with the natural or stimulated cycle groups (*Ginström Ernstad et al., 2019*; *Saito et al., 2019*). This could also explain why birthweight differences were not found in oocyte recipients undergoing fresh or frozen embryo transfer, as women in oocyte donation programmes mostly undergo HRT in both types of cycles. Future research is still required to understand the detailed mechanisms underlying the impact of HRT on fetal growth in frozen embryo transfer.

Gestational hypertension: preeclampsia

Several studies have shown an increased risk of HDP, including preeclampsia, in freeze-all cycles compared with fresh cycles (*Chen et al., 2016*; *Maheshwari et al., 2018*; *Sha et al., 2018*; *Roque et al., 2019*; *Wei et al., 2019*). For example, *Maheshwari et al. (2018)* highlighted a 1.29 increase in the risk of developing HDP (95% CI 1.07 to 1.56, five studies/98656 participants), and *Roque et al. (2019)* found a 1.79 increase in the risk of developing preeclampsia (95% CI 1.03 to 3.09, three studies/4447 participants), after a frozen embryo transfer compared with a fresh embryo transfer. These findings may also be related to the use of HRT as an endometrial priming method for frozen embryo transfer, as the results of *Shi et al. (2018)* who mostly carried out natural cycles, did not reach the same conclusions as the aforementioned studies. Indeed, recent work has shown that programmed frozen embryo transfer cycles are at higher risks of HDP than stimulated or natural frozen embryo transfer cycles (*Ginström Ernstad et al., 2019*; *Saito et al., 2019*). This is in accordance with the recent observation that the risk of preeclampsia was increased in pregnancies achieved without the corpus luteum, as in programmed frozen embryo transfer cycles (*von Versen-Höynck et al., 2019*). The lack of circulating angiogenic and immunoregulatory factors usually produced by the corpus luteum was suggested to be involved in this increase (*Conrad et al., 2019*), as a result of maternal abnormal vascular adaptation during early gestation that can lead to adverse obstetric outcomes (*von Versen-Höynck et al., 2020*). These results are also supported by the high rates of HDP reported in oocyte donation pregnancies (*Storgaard et al., 2017*; *Blazquez et al., 2018*), which were mostly obtained after hormone replacement therapy cycles. In addition to the often promoted immunological theory (*Gundogan et al., 2010*; *Levron et al., 2014*), the absence of the corpus luteum could be another

mechanism explaining the increased risk of pregnancy complications in egg-donor recipients.

Other obstetric and perinatal outcomes

With other pregnancy outcomes, such as gestational diabetes mellitus (*Sha et al., 2018*; *Shi et al., 2018*; *Vuong et al., 2018*; *Wei et al., 2019*), placenta praevia (*Wei et al., 2019*), antepartum haemorrhage (*Maheshwari et al., 2018*), congenital anomalies (*Maheshwari et al., 2018*; *Shi et al., 2018*; *Zhang et al., 2018*; *Roque et al., 2019*; *Wei et al., 2019*), and perinatal mortality (*Chen et al., 2016*; *Maheshwari et al., 2018*; *Shi et al., 2018*; *Vuong et al., 2018*), no differences have been reported between the freeze-all and the fresh embryo transfer strategies.

Long-term health outcomes

Although little is known about the long-term health outcomes in children born after frozen embryo transfer compared with fresh embryo transfer, the few available data aare, somehow, reassuring (*Pelkonen et al., 2015*; *Spangmose et al., 2019*; *Vuong et al., 2020*). With physical health, a large registry cohort study including 1825 children born after frozen embryo transfer and 2933 children born after fresh embryo transfer, showed that most health indicators were similar among the two groups during a 3-year follow-up (*Pelkonen et al., 2015*). For instance, the most common discharge diagnoses, including gastroenteritis and colitis, otitis, upper and lower respiratory diseases, asthma and allergies were similar between the two ART groups, as well as the risk of hospital admission after adjusting for premature births (adjusted OR 1.01; 0.88 to 1.17). With neurodevelopmental health, a recent long-term follow-up study of 267 babies born after the first embryo transfer based on a RCT comparing the freeze-all versus the fresh embryo transfer strategy, pointed out comparable childhood development in the two study groups, with a mean age of 37 months among children at the end of the follow-up (*Vuong et al., 2020*). Moreover, *Spangmose et al. (2019)* found similar academic performances at 15–16 years of age, in adolescents conceived after frozen embryo transfer compared with children conceived after fresh embryo transfer, based on a national registry cohort study of 6495 singletons. Data on the long-term consequences for children born this way are urgently needed, as studies on this topic and the increasing proportions of frozen embryo transfer cycles worldwide, are lacking.

COST-EFFECTIVENESS CONSIDERATIONS

The cost-effectiveness analysis for the freeze-all strategy is highly challenging as it requires integrating multiple parameters. On the one hand, the use of GnRHa trigger with the freeze-all approach leads to a drastic decrease in the rate of OHSS (*Fatemi et al., 2014*) and the additional costs associated with OHSS management. Ovarian stimulation may, therefore, be stronger to increase the number of oocytes retrieved, ultimately leading to higher cumulative LBR (*Polyzos et al., 2018*; *Zhu et al., 2018*). The potentially improved obstetric and perinatal outcomes (miscarriages, SGA, LBW) should also be taken into account (*Maheshwari et al., 2018*; *Roque et al., 2019*; *Wei et al., 2019*). On the other hand, the freeze-all strategy brings cost-increment through the need of additional treatments for endometrial preparation, and the use of embryo cryopreservation techniques (*Blockeel et al., 2016*). Finally, the economic context of the country and the presence of a public or private insurance funding for ART also need to be considered. Currently, few studies have evaluated the cost-effectiveness of the freeze-all versus the fresh embryo transfer strategy (*Roque et al., 2015*; *Papaleo et al., 2017*; *Le et al., 2018*) Although difficult to interpret, the results do not seem to underline an increase in the costs of the freeze-all policy compared with the fresh one. Yet, further RCTs with cost-effectiveness analysis are needed to evaluate the cost-effectiveness of the freeze-all strategy in different clinical indications, such as patients at risk of OHSS.

SUGGESTIONS FOR CLINICAL PRACTICE

Freeze-all with a deferred embryo transfer can be scheduled before the beginning of the stimulation or during ovarian stimulation, as dictated by the clinical situation (FIGURE 1).

Which ovarian stimulation protocol and which molecule should be used for ovulation trigger?

In practice, use of ovarian stimulation antagonist protocols is preferred. These are more flexible as they allow the ovulation to be triggered with GnRHa, HCG, or both. Use of GnRHa trigger,

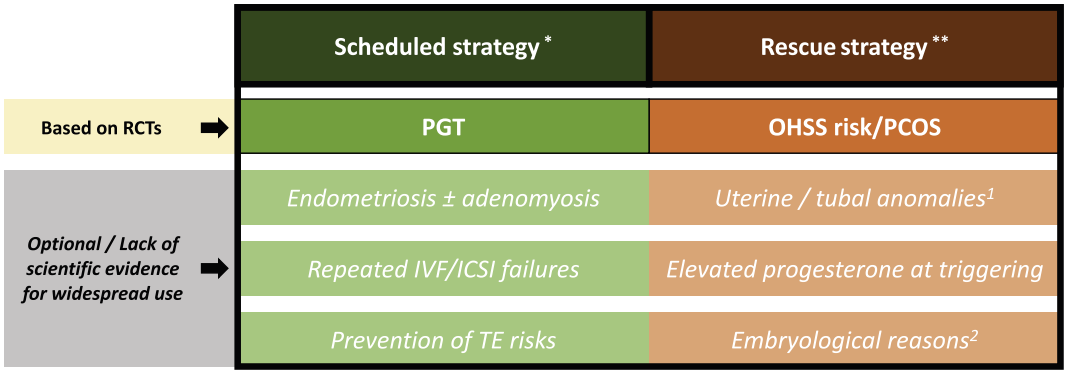

FIGURE 1 When and for which clinical situations should a freeze-all strategy be used? [a]The decision to opt for a freeze-all strategy is taken before the beginning of ovarian stimulation; [b]the decision to opt for a freeze-all strategy is taken during ovarian stimulation; [c]treatable uterine/tubal anomalies discovered during ovarian stimulation; [d]only day-6 blastocysts obtained after prolonged embryo culture. ICSI, intra-cytoplasmic sperm injection; OHSS, ovarian hyperstimulation syndrome; PCOS, polycystic ovary syndrome; PGT, preimplantation genetic testing; RCT, randomized controlled trial; TE, thromboembolic diseases.

in addition to being compatible with the freeze-all strategy, allows OHSS to be fully avoided in women with a risk of OHSS, including PCOS (*ESHRE guideline: ovarian stimulation for IVF/ICSI, 2019*). Nevertheless, in case of ovarian stimulation with an agonist protocol, trigger with HCG is the only available option available. In this situation, the freeze-all strategy remains useful to limit the risk of late OHSS (*ESHRE guideline: ovarian stimulation for IVF/ICSI, 2019*).

Furthermore, aside from women with a risk of OHSS, a GnRHa trigger alone or in association with HCG (double trigger) in antagonist protocols could also be an option in case of the freeze-all strategy to optimize the number of mature oocytes retrieved. Indeed, several RCTs have reported increased maturation rates after trigger with GnRHa plus HCG compared with HCG alone (*Humaidan et al., 2005*; *Krishna et al., 2016*; *Ali et al., 2020*). In light of these preliminary data, and given the risk of failure of GnRHa when used alone for ovulation trigger even minimal (*Meyer et al., 2015*; *Popovic-Todorovic et al., 2019*), the double trigger could be a valuable alternative to exclusive GnRHa trigger for women with no risk of OHSS who are undergoing a freeze-all strategy. Supplemental evidence is needed, however, before implementing this approach in the daily practice.

How to inform patients

From the patients' perspective, one could suppose that couples would naturally opt for the embryo transfer strategy minimizing their time to pregnancy, therefore favouring the fresh embryo transfer approach (*Vuong et al., 2018*; *Stormlund et al., 2020*). Surprisingly, in a cohort study of 165 patients focusing on their preferences about the embryo transfer strategy (*Stormlund et al., 2019*), the freeze-all strategy was favoured by most. Indeed, despite concerns about the delay in embryo transfer, most of the participants were in favour of the freeze-all strategy after being informed of the advantages and disadvantages of both embryo transfer policies. Therefore, practitioners have a major role to play in adequately informing the couples in the initial treatment process, to facilitate their adequation to an individualized treatment including a freeze-all approach, according to the clinical situation.

When to carry out frozen embryo transfer

The transfer of a frozen embryo can be carried out as soon as the first menstrual cycle after ovarian stimulation without it negatively affecting the chances of a live birth (*Santos-Ribeiro et al., 2016*; *Lattes et al., 2017*; *Ozgur et al., 2017*; *Bourdon et al., 2018d*). The deferred embryo transfer after a freeze-all strategy can also be scheduled at any time, as several studies have reported similar pregnancy rates irrespective of the number of cycles between the oocyte retrieval and the embryo transfer (*Santos-Ribeiro et al., 2016*; *Ozgur et al., 2017*; *Lattes et al., 2017*; *Bourdon et al., 2018d*).

How to carry out frozen embryo transfer: embryo stage, freezing technique and endometrial preparation protocols

Another key issue in the freeze-all strategy is the embryo stage at freezing. Although no RCTs to date have specifically studied this point, the available data tend to indicate that the blastocyst stage is superior compared with the cleavage stage, in ovulatory patients. Indeed, two large RCTs that included cleavage stage embryos did not find any advantage for the freeze-all versus the fresh embryo transfer strategy (*Shi et al., 2018*; *Vuong et al., 2018*), whereas a RCT including blastocysts concluded that the freeze-all strategy was superior (*Wei et al., 2019*). The proposed hypotheses are that embryo transfer to the uterine cavity after 5 days of culture is thought to provide better embryo–endometrium synchrony, thus leading to higher chances of implantation as it more closely mimics the sequence of events in natural conception (*Maheshwari et al., 2016*); and extended embryo culture to the blastocyst stage is the best way to identify developing embryos that have successfully activated their embryonic genome, thereby improving the transfer of viable embryos (*Harton et al., 2013*). Moreover, the freeze-all strategy cannot be implemented in daily practice without an efficient vitrification technology. Indeed, vitrification has clearly demonstrated its superiority compared with slow-freezing, allowing to cool and warm embryos with far less damage than slow-freeze, and providing high embryo survival rates. This procedure, however, requires technical expertise to guarantee satisfying reproductive outcomes (*Nagy et al., 2020*), thereby making the experience of the laboratory staff in vitrifying the embryos a fundamental requirement of a 'routine' freeze-all approach.

Aside from the embryo stage and the freezing technology, another key aspect is the method of endometrial priming for embryo transfer. Adequate endometrial preparation is required for a successful outcome. To promote favourable conditions for implantation, various options, ranging from a natural cycle to an ovulated cycle with mild ovarian stimulation, or an artificial cycle with endometrial preparation using oestradiol and progesterone, have been used and proven to be effective to prepare the endometrium for implantation (*Ghobara et al., 2017*). Recent reviews and meta-analysis have compared different cycle regimens for frozen embryo transfer, and no regimen was superior to another (*Groenewoud et al., 2016*; *Ghobara et al., 2017*). Yet, as the risks of LGA or macrosomia and HDP seem to be higher in artificial cycles compared with stimulated and natural cycles (*Ginström Ernstad et al., 2019*; *Saito et al., 2019*), the latter should be used as much as possible in ovulatory women to improve obstetrical outcomes, despite the fact that they are technically more challenging to manage in large ART centres.

In conclusion, depending on the clinical setting, IVF freeze-all cycles could provide significant advantages over fresh cycles. Evidence shows that women for whom freeze-all is clearly recommended are patients at risk of OHSS, including PCOS, and those undergoing PGT (FIGURE 1). Although scientific evidence is lacking, it seems reasonable to provide this as an option to other groups of patients undergoing IVF/ICSI, notably as a 'rescue' strategy, in women with treatable tubal or uterine anomalies discovered during ovarian stimulation, in patients with elevated serum progesterone levels on the day of the ovulation trigger, or when only day-6 blastocysts are available after a prolonged embryo culture (FIGURE 1). Moreover, there are many reasons for scheduling a deferred embryo transfer. These include women having endometriosis or adenomyosis-related infertility, women experiencing repeated IVF/ICSI failures or women at substantial thromboembolic risk; however, further evidence is needed to support this strategy. At present, the current scientific background is not sufficiently robust to generally apply

this technique to all patients requiring ART. In particular, data comparing the cumulative live birth rates and the time to obtain a live child between the fresh and the freeze-all strategy are lacking. Furthermore, although current research supports the notion that freeze-all strategy is safe, particularly in light of the decreased risks of SGA and LBW, the data reveal higher rates of LGA, HBW and HDP, which is concerning, as these complications are associated with increased risks of adverse neonatal outcomes (*Khambalia et al., 2017*; *Doty et al., 2019*). Information about obstetric and perinatal outcomes and childhood outcomes are limited. Hence, future follow-up studies are needed to obtain a global assessment of the effects of the freeze-all strategy.

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