

Frozen embryo transfer: a review on the optimal endometrial preparation and timing

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STUDY QUESTION: What is the optimal endometrial preparation protocol for a frozen embryo transfer (FET)?

SUMMARY ANSWER: Although the optimal endometrial preparation protocol for FET needs further research and is yet to be determined, we propose a standardized timing strategy based on the current available evidence which could assist in the harmonization and comparability of clinic practice and future trials.

WHAT IS KNOWN ALREADY: Amid a continuous increase in the number of FET cycles, determining the optimal endometrial preparation protocol has become paramount to maximize ART success. In current daily practice, different FET preparation methods and timing strategies are used.

STUDY DESIGN, SIZE, DURATION: This is a review of the current literature on FET preparation methods, with special attention to the timing of the embryo transfer.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Literature on the topic was retrieved in PubMed and references from relevant articles were investigated until June 2017.

MAIN RESULTS AND THE ROLE OF CHANCE: The number of high quality randomized controlled trials (RCTs) is scarce and, hence, the evidence for the best protocol for FET is poor. Future research should compare both the pregnancy and neonatal outcomes between HRT and true natural cycle (NC) FET. In terms of embryo transfer timing, we propose to start progesterone intake on the theoretical day of oocyte retrieval in HRT and to perform blastocyst transfer at hCG + 7 or LH + 6 in modified or true NC, respectively.

LIMITATIONS REASONS FOR CAUTION: As only a few high quality RCTs on the optimal preparation for FET are available in the existing literature, no definitive conclusion for benefit of one protocol over the other can be drawn so far.

WIDER IMPLICATIONS OF THE FINDINGS: Caution when using HRT for FET is warranted since the rate of early pregnancy loss is alarmingly high in some reports.

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Introduction

More efficient cryopreservation strategies (i.e. vitrification) (Loutradi *et al.*, 2008) and reassuring safety data (Belva *et al.*, 2008; 2016) have progressively increased the use of frozen embryo transfer (FET) (European IVF-Monitoring Consortium (EIM) *et al.*, 2016), namely beyond cases with a surplus amount of good quality embryos following an elective single embryo transfer policy (Peeraer *et al.*, 2014). The use of an antagonist protocol with agonist triggering followed by a 'freeze-all' strategy and transfer of the embryo(s) in a subsequent FET cycle is a promising option with high live birth rates (Blockeel *et al.*, 2016). Although elective embryo cryopreservation was mainly developed for patients with an increased risk of developing ovarian hyperstimulation syndrome (Devroey *et al.*, 2011), its use has now been also extended to cycles with pre-implantation genetic diagnosis/screening, late-follicular progesterone elevation (Bosch *et al.*, 2010; Roque *et al.*, 2015; Healy *et al.*, 2016) and embryo-endometrial asynchrony (Shapiro *et al.*, 2008). Moreover, there is an ongoing debate whether frozen embryos transferred in a 'more physiologic' non-stimulated endometrium, may not only result in higher pregnancy rates (Shapiro *et al.*, 2011; Roque *et al.*, 2013), but also potentially decrease maternal and neonatal morbidity (Evans *et al.*, 2014; Ishihara *et al.*, 2014).

Materials and Methods

In the following review, we gather the available evidence in search for the best preparation protocol for FET. Literature on the topic was retrieved in PubMed and references from relevant articles were investigated until June 2017.

Results

FET preparation methods

FET preparation methods can largely be divided into artificial and natural cycles (NCs). In the artificial cycle, also referred to as a HRT cycle, endometrial proliferation and follicular growth suppression is achieved by estrogen supplementation. Meanwhile, in the NC, solely menstrual cycle monitoring is performed usually without any pharmacological intervention prior to ovulation.

Hormonal replacement treatment

Although originally developed to allow embryo transfers in recipients of donated oocytes, the HRT protocol has proven to be successful in the general population as well (Younis *et al.*, 1996), thus extending its advantages in terms of minimal monitoring and easy scheduling to those performing IVF overall. However, the universal application of HRT cycles may have potential disadvantages including an increased cost, inconvenience and the potential adverse events associated with estrogen supplementation (e.g. increased thrombotic risk).

Estrogen supplementation. Most HRT protocols empirically opt to supplement estrogens for 2 weeks in an attempt to mimic the NC (Lutjen *et al.*, 1984). However, it seems that such an extended period may be unnecessary and that 5–7 days may suffice for adequate endometrial proliferation (Navot *et al.*, 1986). Limiting the length of the estrogen supplementation would be beneficial in terms of cost and

time to pregnancy and deserves further attention in upcoming studies. Caution, however, is warranted, given that a higher miscarriage rate with shorter estrogen supplementation has also been previously reported (Borini *et al.*, 2001). Conversely, if necessary, estrogen supplementation may also be safely prolonged if necessary without compromising pregnancy outcome (Soares *et al.*, 2005).

Estrogens may be administered orally, vaginally and parentally (transdermal route) and both natural as well as synthetic estrogens may be used (Scott *et al.*, 1991b). A meta-analysis concluded that the type of estrogen supplementation and route of administration had no effect on the success rates of FETs (Glujovsky *et al.*, 2010). The conversion between different supplementation methods may be estimated as follows: 0.75 mg of micronised estradiol (oral administration) = 1.25 g of estradiol gel (transdermal administration) = 1 mg of estradiol valerate (oral or vaginal administration). The standard dose of estradiol valerate is 6 mg daily (Cobo *et al.*, 2012), although different step up protocols—mimicking the rising estradiol levels of a NC—are also frequently used (Soares *et al.*, 2005; Escribá *et al.*, 2006; van de Vijver *et al.*, 2014).

Exogenous mild ovarian stimulation instead of direct estrogen supplementation has been proposed aiming to increase the circulation of serum estrogen and potentially enhance endometrial receptivity. However, a recent systematic review concluded that, when compared to NC, ovarian stimulation with gonadotropins or clomiphene citrate did not seem to enhance live birth pregnancy rates (Yarali *et al.*, 2016). Interestingly, when compared to HRT, gonadotropins or letrozole ovarian stimulation did seem to have a slightly increased chance for live birth. However, until well-designed prospective studies are performed, no definitive recommendation on the use of ovarian stimulation during FET can be made.

Monitoring during estrogen supplementation. In daily clinical practice, an ultrasound scan is usually planned following an initial period of estrogen priming in order to measure endometrial thickness and exclude the presence of a pre-ovulatory follicle, corpus luteum or luteinized endometrium prior to starting progesterone supplementation. The optimal endometrial thickness in HRT FET cycles has been described to be between 9 and 14 mm (El-Toukhy *et al.*, 2008). Conversely, given that a previous meta-analysis has associated endometrial thickness ≤ 7 mm in fresh IVF cycles with a lower chance of pregnancy, this cut-off value is generally extrapolated to FET as well; however, the actual value of this arbitrary cut-off and whether the same limit can be extrapolated to frozen cycles requires further research (Dain *et al.*, 2013; Kasius *et al.*, 2014).

There is limited information available regarding the need for endocrine monitoring during HRT. Specifically, late-follicular serum estradiol and luteinizing hormone (LH) do not seem to predict outcome (Remohi *et al.*, 1997; Banz *et al.*, 2002; Griesinger *et al.*, 2007; Niu *et al.*, 2008; Bocca *et al.*, 2015). Serum progesterone assessments may be used to detect escape ovulation, an event which can be encountered in 1.9–7.4% of HRT FET cycles without pituitary suppression (Dal Prato *et al.*, 2002; van de Vijver *et al.*, 2014). However, given the low incidence, it is questionable whether this measurement significantly improves pregnancy outcome, definitely when additional preventive measures are taken to avoid follicular growth and escape ovulation (e.g. high dose of estrogen supplementation from Day 1 of the cycle onwards).

GnRH agonist. Besides the administration of estrogen, a GnRH agonist can be added to a HRT protocol in order to prevent spontaneous ovulation (Keltz et al., 1995). In one randomized controlled trial (RCT), the use of such an approach was associated with increased clinical pregnancy and live birth rates, mainly due to lower cycle cancellation rates (El-Toukhy et al., 2004). However, endocrine cycle monitoring was not performed in that study, and the incidence of premature ovulation was not reported. The results of this trial are also in contradiction with those of subsequent systematic reviews and meta-analyses, which failed to demonstrate any benefit in terms of clinical pregnancy and cancellation rates (Ghobara and Vandekerckhove, 2008; Glujovsky et al., 2010). More recently, another retrospective study also failed to show any benefit of the use of a GnRH agonist (van de Vijver et al., 2014). Conversely, HRT FET cycles without GnRH agonist co-treatment seem to be more patient-friendly given the avoidance of the cost and potential side effects associated with these drugs.

Progesterone supplementation. Once the proliferation of the endometrium with the administration of estrogens is considered sufficient, progesterone is initiated to promote the final phase of endometrial preparation prior to embryo transfer. An additional injection of hCG on the day of progesterone initiation showed no better implantation or pregnancy rates (Ben-Meir et al., 2010). Regarding progesterone supplementation itself, there is little agreement on the ideal route of administration and dose. Often, micronized progesterone is administered vaginally (Bourgain et al., 1990). When compared to intramuscular (IM) injections, patients seem to prefer the vaginal route owing to its quick, easy and painless administration (Levine, 2000). However, there is no RCT comparing IM and vaginal routes in HRT FET cycles. Retrospective data are conflicting, being in favor of the IM route (Haddad et al., 2007; Kaser et al., 2012) or showing no significant differences in terms of outcome (Shapiro et al., 2014). A recent double-blinded placebo-controlled RCT demonstrated non-inferiority and a similar safety profile for the oral administration of dydrogesterone in fresh cycles (Tournaye et al., 2017). However, more data are needed to confirm the safety and efficacy of oral dydrogesterone in HRT FET. As for the optimal progesterone dose specifically in HRT FET cycles, one retrospective study concluded that doubling the dose of vaginal progesterone gel in patients with oligomenorrhoea significantly increased live birth rates (Alsbjerg et al., 2013).

The use of measuring serum progesterone during the luteal phase in HRT FET cycles requires further investigation as well. The currently available results are contradictory as progesterone levels >20 ng/ml (possibly due to an escape ovulation and subsequent embryo-endometrial asynchrony) on the day of transfer have been associated with decreased ongoing pregnancy and live birth rates (Kofinas et al., 2015), while an optimal mid-luteal progesterone range between 22 and 31 ng/ml has also been proposed (Yovich et al., 2015). The administration route and dose also needs to be taken into account when performing such endocrine monitoring. Furthermore, another potential confounding factor is intercourse during a FET cycle, since it has been shown that it significantly reduces serum progesterone levels in women administering vaginal progesterone gel (Merriam et al., 2015).

No consensus has been reached yet on when to stop progesterone administration following a positive pregnancy test in HRT FET. The

estimated onset of placental steroidogenesis, the so-called luteoplacental shift, occurs during the fifth gestational week (Scott et al., 1991a). A meta-analysis has demonstrated that, following a fresh embryo transfer, progesterone can be discontinued once a positive pregnancy test is detected (Liu et al., 2012). However in HRT FET cycles, as no corpus luteum—and, hence, no endogenous progesterone production—is present, the best moment remains to be elucidated.

Natural cycle

In a NC FET, there is no medical intervention, except of endocrine and ultrasound monitoring during the proliferative phase, to schedule the transfer when the endometrium is synchronized to the developmental stage of the embryo. Although the advantage is the absence of estrogen supplementation, this protocol entails more frequent visits to the clinic, less cycle control and flexibility and holds a higher risk of cycle cancellation [up to 6% (Sathanandan et al., 1991)].

Proliferative phase monitoring. The starting point to assess embryo-endometrial synchronization is the ovulation of the dominant follicle, which in a NC can either be triggered exogenously (i.e. modified NC, in which ovulation is triggered by hCG as soon as a dominant follicle of e.g. >16 mm is observed) or by serial blood (or, albeit less accurately, urine) sampling until a LH peak is observed (i.e. true NC, in which ovulation occurs spontaneously). Although the serum hormone levels in such cases are often exhaustively assessed (Casper et al., 2016), the role of such endocrine monitoring in addition to the usual ultrasound monitoring is a subject of much debate in both true and modified NC FETs (Groenewoud et al., 2012, 2017; Lee et al., 2014). Furthermore, the definition of what constitutes an LH surge is not unanimous. Historically, an LH surge has been described as an increase of the level of LH beyond 180% of the mean level observed in the previous 24 h (Frydman et al., 1982). In a clinical setting, however, varying definitions are used, including a concentration of 180% above the latest serum value available in that patient with a continued rise thereafter (Testart et al., 1981) to a level of 10 IU/l or more (Groenewoud et al., 2017).

Regarding endometrial thickness, the optimal threshold for NC FET remains unknown and the extrapolation of findings in fresh and HRT FET cycles should also be approached with caution in this case given the lack of data.

Spontaneous versus triggered ovulation. Two small RCTs revealed conflicting results: while the first (Weissman et al., 2011) did not find any significant differences between spontaneous and exogenously-triggered ovulation cycles, another (Fatemi et al., 2010) was interrupted prematurely due to the fact that an interim analysis revealed remarkably lower pregnancy rates in women who were administered hCG (14.3% versus 31.4%, respectively). One of the posited reasons for this difference was that the research groups had considered different timings to perform the embryo transfer (specifically, a 1-day difference between both studies). Second, it is possible that in the prematurely interrupted study there could have been a higher embryo-endometrial asynchrony in the modified NC study group as FET timing was the same for both arms, despite known differences in the timing of spontaneous versus triggered ovulation (Kosmas et al., 2007). Third, some women from the modified NC group in this same study already had an LH rise on the day of hCG administration which

was associated with significantly lower pregnancy rates (suspected to be because of higher grade of embryo-endometrial asynchrony), while serum progesterone >1 ng/ml was an exclusion criterion in the study by Weissman *et al.* Finally, luteal phase support (LPS) was given only in the RCT performed by Weissman *et al.*

Three retrospective studies comparing true versus modified NC failed to demonstrate significant differences in clinical outcomes (Weissman *et al.*, 2009; Chang *et al.*, 2011; Tomás *et al.*, 2012), however a recent large retrospective analysis did show a significant difference in clinical pregnancy rate (CPR) in favor of the true NC FET (without LPS) versus the modified NC FET (with LPS) even after adapting the transfer policy to the type of ovulation trigger and excluding patients that administered hCG despite a LH surge (46.9% versus 29.7%, $P < 0.001$) (Montagut *et al.*, 2016). Thus, until further prospective studies comparing true with modified NC are performed, the question on what seems the best approach remains unanswered.

Progesterone supplementation. The prevalence of a luteal phase defect in NCs in normo-ovulatory subfertility patients has been historically described to be around 8% (Rosenberg *et al.*, 1980), with mid-luteal serum progesterone levels <10 ng/ml being considered to reflect a NC luteal phase defect (Jordan *et al.*, 1994).

The use of LPS in true NC FET is supported by one RCT (Bjuresten *et al.*, 2011) where micronized vaginal progesterone (MVP) was initiated in the evening after FET. Our retrospective analysis (Montagut *et al.*, 2016) did not show a significant difference in CPR when comparing true NC FET with or without MVP; on the contrary, there was a trend favouring one not to supplement (CPR 46.9% versus 39.9%). Here, however, MVP was started sooner, immediately on the day after the LH surge. Hence, the discrepancy between the studies might reflect the importance of the correct timing to start LPS. Another retrospective study investigating true NC FET LPS by two IM injections of hCG (the day of FET and 6 days later) failed to show any difference in outcome (Lee *et al.*, 2013).

For modified NC FET, both prospective (Eftekhari *et al.*, 2013) and retrospective (Kyrou *et al.*, 2010) studies failed to show any difference in terms of pregnancy outcome with or without LPS. Due to prolonged half-life of hCG used as trigger, it makes biological sense that no LPS may be needed, although not all researchers agree (Kim *et al.*, 2014).

Overall, the moment to start LPS in a NC FET is unclear although one may postulate that immediately after the LH surge or hCG trigger may be too soon and affect the window of implantation (WOI). Until further data are accrued on this subject it seems likely that different protocols will continue to be used in daily practice (Weissman *et al.*, 2011; Tomás *et al.*, 2012).

HRT or NC?

Retrospective data have left physicians with conflicting information in terms of clinical outcome (Ghobara and Vandekerckhove, 2008; Givens *et al.*, 2009; Chang *et al.*, 2011; Groenewoud *et al.*, 2013; Guan *et al.*, 2016). Recently, a large, multi-center, non-inferiority trial studying modified NC versus HRT has failed to show any significant difference in live birth, clinical or ongoing pregnancy rates (Groenewoud *et al.*, 2016). Furthermore, the costs of both treatment modalities were comparable. However, this study did not assess the potential benefit of FET performed without exogenous ovulation triggering and concerns were raised due to the overall low success rate reported and the high miscarriage rates (Hreinsson *et al.*, 2016). A previous

retrospective analysis has shown a higher miscarriage rate for HRT compared to NC FET, although this could be related to the higher proportion of polycystic ovary syndrome patients in the HRT group (Tomás *et al.*, 2012). Additionally, when comparing HRT FET to fresh embryo transfer, a 1.7-fold higher miscarriage rate has also been described for hormonal substitution FET *per se* (Veleva *et al.*, 2008) and, in cases of repeated implantation failure endometrial transcriptome analysis favored NC over HRT (Altmäe *et al.*, 2016). Current caution and further research is needed; a RCT comparing true NC versus HRT FET in an unbiased population is warranted.

FET timing

The synchronous interaction between a competent embryo and a receptive endometrium is a complex molecular process indispensable for successful implantation (Tabibzadeh, 1998). It is generally considered that once progesterone levels reach a critical threshold, they set into motion a well-timed and orderly secretory transformation of the endometrium leading to receptivity (Franasiak *et al.*, 2016). This receptiveness for blastocyst attachment only occurs for a short period, the WOI (Psychoyos, 1973; Bergh and Navot, 1992). Decidualization, the secretory transformation that the endometrial stromal compartment undergoes to accommodate pregnancy, plays an important role in receptivity as it is thought to contribute to the active selection of embryos attempting implantation (Brosens *et al.*, 2014). Hence, FET timing should assure that the blastocyst seeking implantation meets the optimal receptive/selective endometrial stage during the WOI. Many efforts have been made to identify biomarkers of endometrial receptivity (Coutifaris *et al.*, 2004; Díaz-Gimeno *et al.*, 2011; Edgell *et al.*, 2013), but, so far, no clinically RCT validated test is available in daily practice.

Hormonal replacement treatment

The optimal duration of exposure to progesterone prior to embryo transfer has remained an elusive topic since the start of ART (Nawroth and Ludwig, 2005). When progesterone supplementation in HRT cycles is initiated 3 days before the cleavage embryo transfer, excellent pregnancy rates of up to 40.5% occur (Givens *et al.*, 2009). A limited amount of evidence indicates that even a very short progesterone exposure may suffice to induce endometrial receptivity (Imbar and Hurwitz, 2004; Theodorou and Forman, 2012). Conversely, a study conducted in oocyte recipients showed a higher biochemical pregnancy rate when progesterone supplementation was longer (i.e. transfer of a Day 3 embryo on the 5th day of progesterone supplementation) (Escribá *et al.*, 2006). In line with this, it has been suggested that the risk of early pregnancy loss increases when implantation takes place later in the WOI (Wilcox *et al.*, 1999). A Cochrane Database Review concluded that starting progesterone at a time equivalent to the day of or the day after oocyte retrieval (OR) results in a significantly higher pregnancy rate than if progesterone is initiated a day earlier than the day equivalent to OR (Glujovsky *et al.*, 2010). A recent RCT compared the outcomes of blastocyst transfer with either 5 or 7 days of progesterone supplementation and CPRs once more tended to be in favor of the shorter protocol, although not statistically significant (32.5% versus 27.6%) (van de Vijver *et al.*, 2017). On the other hand, transferring Day 4 embryos on the third day of progesterone supplementation (a time being equivalent to 2 days after OR) was also deleterious (van de Vijver *et al.*, 2016).

Specifically, a higher risk of early pregnancy loss was seen, possibly caused by embryo-endometrial asynchrony or by an insufficient decidualization associated with only 3 days of progesterone administration. Another hypothesis is that, due to a later timing of the WOI, delayed embryos may have a higher chance of encountering a receptive endometrium, allowing them to implant but then being at increased risk for early pregnancy loss.

Taken together, it seems that the starting day of progesterone intake is optimal when equal to the theoretical day of OR or 1 day later (Fig. 1). Given that the WOI is limited in time, this detection of an optimal period is unsurprising and easily understandable; implantation is possible in a quite broad window, but only optimal in a narrower timeframe (Franasiak et al., 2016). Currently, most cleavage stage embryos are transferred around the 4th day of progesterone supplementation, whereas blastocysts are usually transferred on the 6th day of progesterone supplementation. This presumptive embryo transfer timing is in parallel with the timing of fresh embryo transfer after OR: the day of starting progesterone supplementation (considered as P + 0) is set equal to the theoretical day of OR, which is indeed also Day 0 from an embryonic point of view. This should be the preferred terminology as it emphasizes the synchronicity between endometrium and embryo. In a time when embryo transfer may soon become personalized according to a prior diagnostic intervention (e.g. Endometrial Receptivity Array, ERA®, Igenomix) (Díaz-Gimeno et al., 2011), the use of a standardized nomenclature is of utmost importance. Specifically, in repeated implantation failure patients, the WOI is suspected to be narrow and/or displaced

(mostly delayed) (Ruiz-Alonso et al., 2013). Meanwhile, even in the general population, delayed endometrial development has been described in up to 25% of the population (Murray et al., 2004) and an increase in pregnancy rates associated with specific histological endometrial dating patterns and corresponding adjustments in progesterone exposure has been shown (Gomaa et al., 2015).

Natural cycle

In a NC, the WOI is posited to open 6 days after the postovulatory progesterone surge and thought to last ~2–4 days (LH + 7 to LH + 11) (Navot et al., 1991). When using the LH surge to plan embryo transfer one must take into account that the LH surge can occur over a period of 30 h (Acosta et al., 2000). Progesterone rises slightly to 1–3 ng/ml even 12 h to 3 days prior to ovulation, due to the LH-stimulated production by the peripheral granulosa cells (Hoff et al., 1983), with a steep increase in production following ovulation (3–10 ng/ml) due to production by the corpus luteum. The physiological and clinical importance of the pre-ovulatory progesterone elevation is yet to be determined, but is likely to contribute to the induction of the WOI in a NC. However, an accurate mirroring of this finely tuned and tightly regulated molecular system is probably difficult to reproduce artificially and one should acknowledge that all interventions might change the opening, closing, length and functionality of the WOI.

A difference in the timing of FET in true versus modified NC could be considered, as ovulation occurs 36–48 h after hCG administration but varies from 24 to 56 h after a spontaneous LH surge (Kosmas

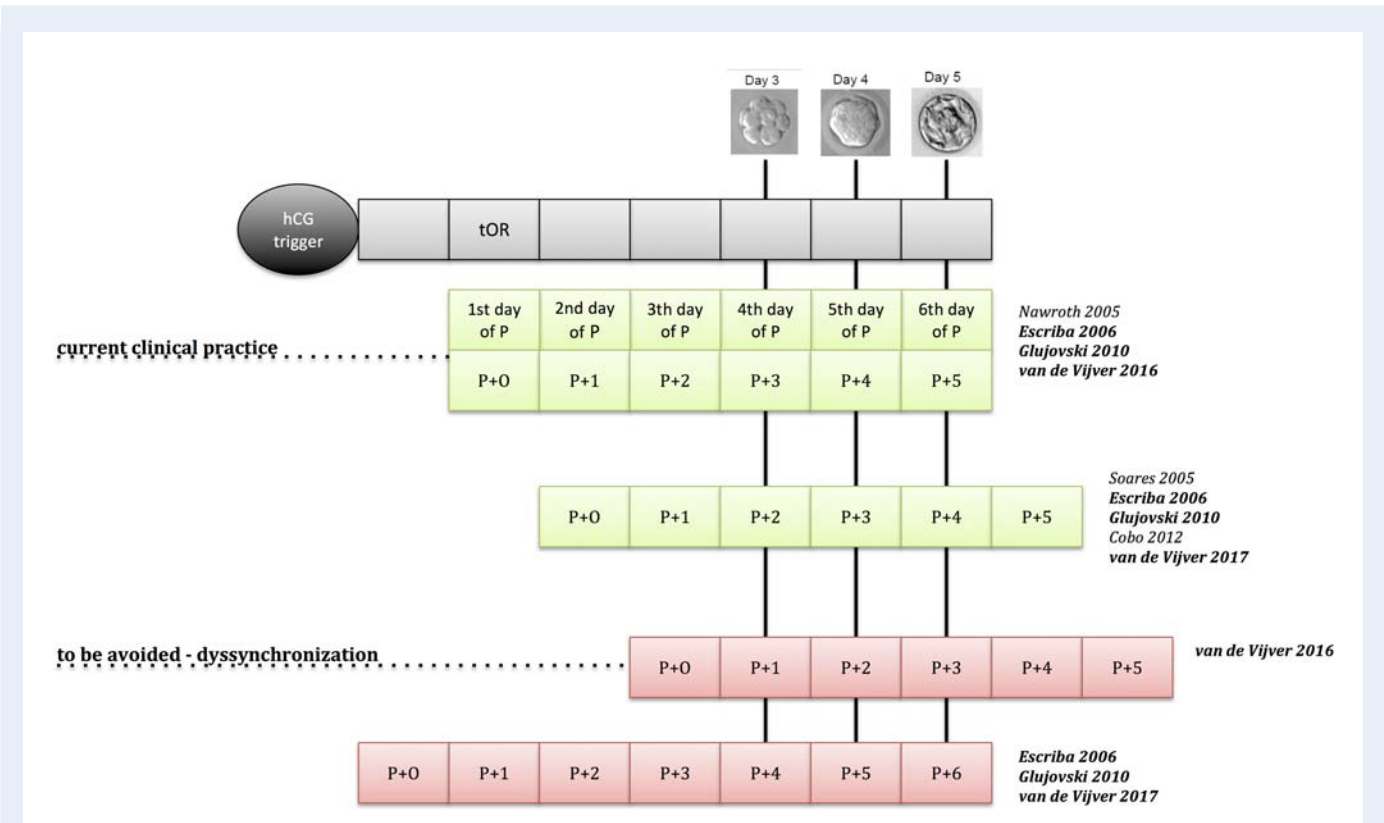


Figure 1 Embryo transfer timing for HRT preparation. tOR, theoretical oocyte retrieval, P, progesterone. In bold: studies with actual comparison of different embryo transfer days.

et al., 2007). For intra-uterine insemination, it has been shown that pregnancy rates are higher when it was performed 36–42 h after hCG trigger, but 18–24 h after spontaneous LH surge (Fuh *et al.*, 1997; Robb *et al.*, 2004). One could draw the parallel to FET and transfer 1-day earlier when a spontaneous LH surge is detected in the serum compared to when ovulation is triggered with hCG. When using urinary LH measurement, this difference in timing might not be beneficial, since a 1-day delay for the detection of peak hormone levels in the urine has been described (Cekan *et al.*, 1986).

We suggest not to administer hCG when a spontaneous LH surge is detected, given the previously noted potential association with a detrimental outcome (Fatemi *et al.*, 2010), even though it has not been confirmed in a recent *post hoc* analysis of the ANTARCTICA trial (Groenewoud *et al.*, 2017). We hypothesize that hCG trigger, as well as additional LPS may impact on the natural course of the endometrium towards receptivity and might cause a shift in the WOI, leading to a more pronounced embryo-endometrial asynchrony. Further research is needed to test this hypothesis and to clearly state what should be the preferred policy in clinical practice.

FET timing proposal

We have observed that in studies assessing the optimal preparation for FET, embryo transfer timing is often described vaguely or confusingly. However, when there was no optimal synchronization, incorrect conclusions on how to best prepare FET could be drawn. We propose the following FET timing strategy and terminology, which could assist in the harmonization and comparability of clinical practice and future trials (Fig. 2):

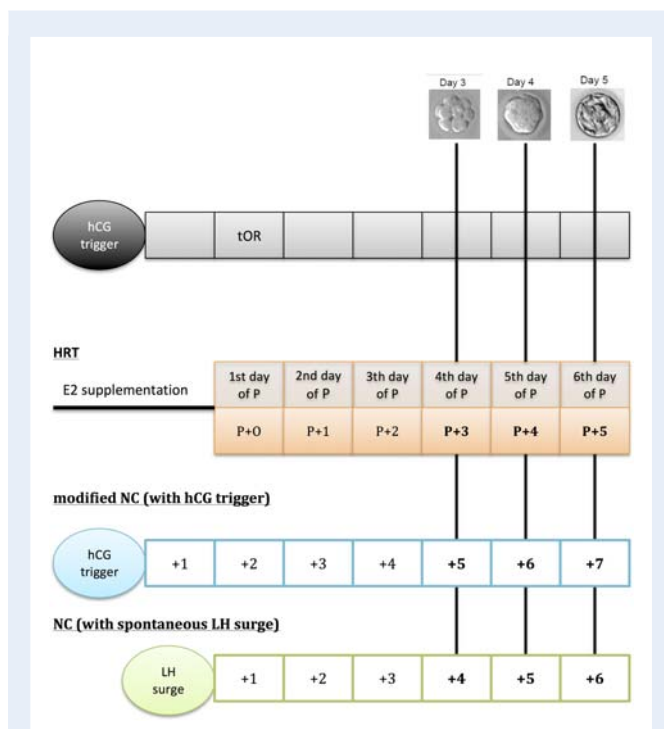


Figure 2 Clinical practice proposal for embryo transfer timing in the different preparation methods. tOR, theoretical oocyte retrieval, E2, estradiol, P, progesterone, NC, natural cycle.

– In HRT:

On day (embryonic age + 1) of progesterone administration, annotated as P+ embryonic age (e.g. a Day 5 embryo on the 6th day of progesterone administration, annotated as P + 5).

– In a modified NC (with hCG trigger):

On day (embryonic age + 2) after hCG injection (e.g. a Day 5 embryo on hCG + 7).

– In a true NC (with spontaneous LH surge):

On day (embryonic age + 1) after LH surge (e.g. a Day 5 embryo on LH + 6).

Specific attention is warranted in situations where embryo thawing is followed by further *in vitro* culture and embryonic development prior to transfer. In such cases, it is likely better to take into account the expected embryonic stage at the moment of transfer instead of the stage in which the embryo was cryopreserved (Cercas *et al.*, 2012; Jin *et al.*, 2013; van de Vijver *et al.*, 2016). No studies have investigated whether the timing of FET should be different for embryos cryopreserved by slow-freezing or vitrification. However, an impact has been described of the method of freezing on post-thaw embryo development and metabolism (Balaban *et al.*, 2008; Cercas *et al.*, 2012) and further research into the potential clinical effects of such differences might optimize embryo-endometrial synchrony.

Conclusion and future perspectives

Although FET is increasingly used for multiple indications, the optimal preparation protocol is yet to be determined. At the basic research level, the evidence points toward the NC being superior to HRT. Hence, future research should compare both the pregnancy and neonatal outcomes between HRT and true NC FET. Furthermore, caution when using HRT is warranted since the rate of early pregnancy loss is alarmingly high in some reports.

In terms of embryo transfer timing, we propose to start progesterone intake on the theoretical day of oocyte retrieval in HRT and to perform blastocyst transfer at hCG + 7 or LH + 6 in modified or true NC, respectively. As individual timing of the WOI becomes increasingly substantiated by diagnostics tools, subsequent time corrections might offer further opportunities to increase FET success rates.

Authors' roles

S.M. wrote the manuscript. S.S.-R. participated in the writing of the manuscript. A.V.D.V., A.R., L.V.L. and H.T. contributed to the interpretation and editing of the manuscript. C.B. is responsible for the concept and final revision of the manuscript.

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References

- Acosta AA, Elberger L, Borghi M, Calamera JC, Chemes H, Doncel GF, Kliman H, Lema B, Lustig L, Papier S. Endometrial dating and determination of the window of implantation in healthy fertile women. *Fertil Steril* 2000;**73**:788–798.
- Alsbjerg B, Polyzos NP, Elbaek HO, Povlsen BB, Andersen CY, Humaidan P. Increasing vaginal progesterone gel supplementation after frozen-thawed embryo transfer significantly increases the delivery rate. *Reprod Biomed Online* 2013;**26**:133–137.
- Altmäe S, Tamm-Rosenstein K, Esteban FJ, Simm J, Kolberg L, Peterson H, Metsis M, Haldre K, Horcajadas JA, Salumets A et al. Endometrial transcriptome analysis indicates superiority of natural over artificial cycles in recurrent implantation failure patients undergoing frozen embryo transfer. *Reprod Biomed Online* 2016;**32**:597–613.
- Balaban B, Urman B, Ata B, Isiklar A, Larman MG, Hamilton R, Gardner DK. A randomized controlled study of human Day 3 embryo cryopreservation by slow freezing or vitrification: vitrification is associated with higher survival, metabolism and blastocyst formation. *Hum Reprod* 2008;**23**:1976–1982.
- Banz C, Katalinic A, Al-Hasani S, Seelig AS, Weiss JM, Diedrich K, Ludwig M. Preparation of cycles for cryopreservation transfers using estradiol patches and Crinone 8% vaginal gel is effective and does not need any monitoring. *Eur J Obstet Gynecol Reprod Biol* 2002;**103**:43–47.
- Belva F, Bonduelle M, Roelants M, Verheyen G, Van Landuyt L. Neonatal health including congenital malformation risk of 1072 children born after vitrified embryo transfer. *Hum Reprod* 2016;**31**:1610–1620.
- Belva F, Henriët S, Van den Abbeel E, Camus M, Devroey P, Van der Elst J, Liebaers I, Haentjens P, Bonduelle M. Neonatal outcome of 937 children born after transfer of cryopreserved embryos obtained by ICSI and IVF and comparison with outcome data of fresh ICSI and IVF cycles. *Hum Reprod* 2008;**23**:2227–2238.
- Ben-Meir A, Aboo-Dia M, Revel A, Eizenman E, Laufer N, Simon A. The benefit of human chorionic gonadotropin supplementation throughout the secretory phase of frozen-thawed embryo transfer cycles. *Fertil Steril* 2010;**93**:351–354.
- Bergh PA, Navot D. The impact of embryonic development and endometrial maturity on the timing of implantation. *Fertil Steril* 1992;**58**:537–542.
- Björsten K, Landgren B-M, Hovatta O, Stavreus-Evers A. Luteal phase progesterone increases live birth rate after frozen embryo transfer. *Fertil Steril* 2011;**95**:534–537.
- Blockeel C, Drakopoulos P, Santos-Ribeiro S, Polyzos NP, Tournaye H. A fresh look at the freeze-all protocol: a SWOT analysis. *Hum Reprod* 2016;**31**:491–497.
- Bocca S, Bondia Real E, Lynch S, Stadtmayer L, Beydoun H, Mayer J, Oehninger S. Impact of serum estradiol levels on the implantation rate of cleavage stage cryopreserved-thawed embryos transferred in programmed cycles with exogenous hormonal replacement. *J Assist Reprod Genet* 2015;**32**:395–400.
- Borini A, Dal Prato L, Bianchi L, Violini F, Cattoli M, Flamigni C. Effect of duration of estradiol replacement on the outcome of oocyte donation. *J Assist Reprod Genet* 2001;**18**:185–190.
- Bosch E, Labarta E, Crespo J, Simón C, Remohí J, Jenkins J, Pellicer A. Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. *Hum Reprod* 2010;**25**:2092–2100.
- Bourgain C, Devroey P, Van Waesberghe L, Smits J, Van Steirteghem AC. Effects of natural progesterone on the morphology of the endometrium in patients with primary ovarian failure. *Hum Reprod* 1990;**5**:537–543.
- Brosens JJ, Salker MS, Teklenburg G, Nautiyal J, Salter S, Lucas ES, Steel JH, Christian M, Chan Y-W, Boomsma CM et al. Uterine selection of human embryos at implantation. *Sci Rep* 2014;**4**:3894.
- Casper RF, Yanushpolsky EH. Optimal endometrial preparation for frozen embryo transfer cycles: window of implantation and progesterone support. *Fertil Steril* 2016;**105**:867–872.
- Cekan SZ, Beksac MS, Wang E, Shi S, Masironi B, Landgren BM, Diczfalussy E. The prediction and/or detection of ovulation by means of urinary steroid assays. *Contraception* 1986;**33**:327–345.
- Cercas R, Villas C, Pons I, Braña C, Fernandez-Shaw S. Vitrification can modify embryo cleavage stage after warming. Should we change endometrial preparation? *J Assist Reprod Genet* 2012;**29**:1363–1368.
- Chang EM, Han JE, Kim YS, Lyu SW, Lee WS, Yoon TK. Use of the natural cycle and vitrification thawed blastocyst transfer results in better in-vitro fertilization outcomes: cycle regimens of vitrification thawed blastocyst transfer. *J Assist Reprod Genet* 2011;**28**:369–374.
- Cobo A, de los Santos MJ, Castellò D, Gámiz P, Campos P, Remohí J. Outcomes of vitrified early cleavage-stage and blastocyst-stage embryos in a cryopreservation program: evaluation of 3,150 warming cycles. *Fertil Steril* 2012;**98**:1138–46.e1.
- Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, McGovern PG, Schlaff WD, Carr BR, Steinkampf MP et al. Histological dating of timed endometrial biopsy tissue is not related to fertility status. *Fertil Steril* 2004;**82**:1264–1272.
- Dain L, Bider D, Levron J, Zinchenko V, Westler S, Dirnfeld M. Thin endometrium in donor oocyte recipients: enigma or obstacle for implantation? *Fertil Steril* 2013;**100**:1289–1295.
- Dal Prato L, Borini A, Cattoli M, Bonu MA, Sciajno R, Flamigni C. Endometrial preparation for frozen-thawed embryo transfer with or without pretreatment with gonadotropin-releasing hormone agonist. *Fertil Steril* 2002;**77**:956–960.
- Devroey P, Polyzos NP, Blockeel C. An OHSS-Free Clinic by segmentation of IVF treatment. *Hum Reprod* 2011;**26**:2593–2597.
- Díaz-Gimeno P, Horcajadas JA, Martínez-Conejero JA, Esteban FJ, Alamá P, Pellicer A, Simón C. A genomic diagnostic tool for human endometrial receptivity based on the transcriptomic signature. *Fertil Steril* 2011;**95**:50–60.e1–15.
- Edgell TA, Rombauts LJF, Salamonsen LA. Assessing receptivity in the endometrium: the need for a rapid, non-invasive test. *Reprod Biomed Online* 2013;**27**:486–496.
- Eftekhar M, Rahsepar M, Rahmani E. Effect of progesterone supplementation on natural frozen-thawed embryo transfer cycles: a randomized controlled trial. *Int J Fertil Steril* 2013;**7**:13–20.
- El-Toukhy T, Coomarasamy A, Khairy M, Sunkara K, Seed P, Khalaf Y, Braude P. The relationship between endometrial thickness and outcome of medicated frozen embryo replacement cycles. *Fertil Steril* 2008;**89**:832–839.
- El-Toukhy T, Taylor A, Khalaf Y, Al-Darazi K, Rowell P, Seed P, Braude P. Pituitary suppression in ultrasound-monitored frozen embryo replacement cycles. A randomised study. *Hum Reprod* 2004;**19**:874–879.
- Escobá M-J, Bellver J, Bosch E, Sánchez M, Pellicer A, Remohí J. Delaying the initiation of progesterone supplementation until the day of fertilization does not compromise cycle outcome in patients receiving donated oocytes: a randomized study. *Fertil Steril* 2006;**86**:92–97.
- European IVF-Monitoring Consortium (EIM), European Society of Human Reproduction and Embryology (ESHRE), Kupka MS, D'Hooghe T, Ferraretti AP, de Mouzon J, Erb K, Castilla JA, Calhaz-Jorge C, De Geyter C, Goossens V. Assisted reproductive technology in Europe, 2011: results generated from European registers by ESHRE. *Hum Reprod* 2016;**31**:233–248.
- Evans J, Hannan NJ, Edgell TA, Vollenhoven BJ, Lutjen PJ, Osianlis T, Salamonsen LA, Rombauts LJF. Fresh versus frozen embryo transfer: backing clinical decisions with scientific and clinical evidence. *Hum Reprod Update* 2014;**20**:808–821.

- Fatemi HM, Kyrou D, Bourgain C, Van den Abbeel E, Griesinger G, Devroey P. Cryopreserved-thawed human embryo transfer: spontaneous natural cycle is superior to human chorionic gonadotropin-induced natural cycle. *Fertil Steril* 2010;**94**:2054–2058.
- Franasiak JM, Ruiz-Alonso M, Scott RT, Simón C. Both slowly developing embryos and a variable pace of luteal endometrial progression may conspire to prevent normal birth in spite of a capable embryo. *Fertil Steril* 2016;**105**:861–866.
- Frydman R, Testart J, Fernandez H, Arvis P, Belaisch JC. [Prediction of ovulation]. *J Gynecol Obstet Biol Reprod (Paris)* 1982;**11**:793–799.
- Fuh KW, Wang X, Tai A, Wong I, Norman RJ. Intrauterine insemination: effect of the temporal relationship between the luteinizing hormone surge, human chorionic gonadotrophin administration and insemination on pregnancy rates. *Hum Reprod* 1997;**12**:2162–2166.
- Ghobara T, Vandekerckhove P. Cycle regimens for frozen-thawed embryo transfer. *Cochrane Database Syst Rev* 2008;1:art. no. CD003414.
- Givens CR, Markun LC, Ryan IP, Chenette PE, Herbert CM, Schriock ED. Outcomes of natural cycles versus programmed cycles for 1677 frozen-thawed embryo transfers. *Reprod Biomed Online* 2009;**19**:380–384.
- Glujovsky D, Pesce R, Fiszbañ G, Sueldo C, Hart RJ, Ciapponi A. Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes. *Cochrane Database Syst Rev* 2010;1:art. no. CD006359.
- Gomaa H, Casper RF, Esfandiari N, Bentov Y. Non-synchronized endometrium and its correction in non-ovulatory cryopreserved embryo transfer cycles. *Reprod Biomed Online* 2015;**30**:378–384.
- Griesinger G, Weig M, Schroer A, Diedrich K, Kolibianakis EM. Mid-cycle serum levels of endogenous LH are not associated with the likelihood of pregnancy in artificial frozen-thawed embryo transfer cycles without pituitary suppression. *Hum Reprod* 2007;**22**:2589–2593.
- Groenewoud ER, Cantineau AEP, Kollen BJ, Macklon NS, Cohen BJ. What is the optimal means of preparing the endometrium in frozen-thawed embryo transfer cycles? A systematic review and meta-analysis. *Hum Reprod Update* 2013;**19**:458–470.
- Groenewoud ER, Cohen BJ, Al-Oraiby A, Brinkhuis EA, Broekmans FJM, de Bruin JP, van den Dool G, Fleisher K, Friederich J, Goddijn M *et al.* A randomized controlled, non-inferiority trial of modified natural versus artificial cycle for cryo-thawed embryo transfer. *Hum Reprod* 2016;**31**:1483–1492.
- Groenewoud ER, Kollen BJ, Macklon NS, Cohen BJ. Spontaneous LH surges prior to HCG administration in unstimulated-cycle frozen-thawed embryo transfer do not influence pregnancy rates. *Reprod Biomed Online* 2012;**24**:191–196.
- Groenewoud ER, Macklon NS, Cohen BJ, ANTARCTICA Study Group. The effect of elevated progesterone levels before HCG triggering in modified natural cycle frozen-thawed embryo transfer cycles. *Reprod Biomed Online* 2017;**34**:546–554.
- Guan Y, Fan H, Styer AK, Xiao Z, Li Z, Zhang J, Sun L, Wang X, Zhang Z. A modified natural cycle results in higher live birth rate in vitrified-thawed embryo transfer for women with regular menstruation. *Syst Biol Reprod Med* 2016;**62**:335–342.
- Haddad G, Saguan DA, Maxwell R, Thomas MA. Intramuscular route of progesterone administration increases pregnancy rates during non-downregulated frozen embryo transfer cycles. *J Assist Reprod Genet* 2007;**24**:467–470.
- Healy MW, Patounakis G, Connell MT, Devine K, DeCherney AH, Levy MJ, Hill MJ. Does a frozen embryo transfer ameliorate the effect of elevated progesterone seen in fresh transfer cycles? *Fertil Steril* 2016;**105**:93–9.e1.
- Hoff JD, Quigley ME, Yen SS. Hormonal dynamics at midcycle: a reevaluation. *J Clin Endocrinol Metab* 1983;**57**:792–796.
- Hreinsson J, Hardarson T, Lind A-K, Nilsson S, Westlander G. Perspectives on results from cryopreservation/thawing cycles. *Hum Reprod* 2016;**31**:2894–2894.
- Imbar T, Hurwitz A. Synchronization between endometrial and embryonic age is not absolutely crucial for implantation. *Fertil Steril* 2004;**82**:472–474.
- Ishihara O, Araki R, Kuwahara A, Itakura A, Saito H, Adamson GD. Impact of frozen-thawed single-blastocyst transfer on maternal and neonatal outcome: an analysis of 277,042 single-embryo transfer cycles from 2008 to 2010 in Japan. *Fertil Steril* 2014;**101**:128–133.
- Jin R, Tong X, Wu L, Luo L, Luan H, Zhou G, Johansson L, Liu Y. Extended culture of vitrified-warmed embryos in day-3 embryo transfer cycles: a randomized controlled pilot study. *Reprod Biomed Online* 2013;**26**:384–392.
- Jordan J, Craig K, Clifton DK, Soules MR. Luteal phase defect: the sensitivity and specificity of diagnostic methods in common clinical use. *Fertil Steril* 1994;**62**:54–62.
- Kaser DJ, Ginsburg ES, Missmer SA, Correia KF, Racowsky C. Intramuscular progesterone versus 8% Crinone vaginal gel for luteal phase support for day 3 cryopreserved embryo transfer. *Fertil Steril* 2012;**98**:1464–1469.
- Kasius A, Smit JG, Torrance HL, Eijkemans MJC, Mol BW, Opmeer BC, Broekmans FJM. Endometrial thickness and pregnancy rates after IVF: a systematic review and meta-analysis. *Hum Reprod Update* 2014;**20**:530–541.
- Keltz MD, Jones EE, Duleba AJ, Polcz T, Kennedy K, Olive DL. Baseline cyst formation after luteal phase gonadotropin-releasing hormone agonist administration is linked to poor in vitro fertilization outcome. *Fertil Steril* 1995;**64**:568–572.
- Kim C-H, Lee Y-J, Lee K-H, Kwon S-K, Kim S-H, Chae H-D, Kang B-M. The effect of luteal phase progesterone supplementation on natural frozen-thawed embryo transfer cycles. *Obstet Gynecol Sci* 2014;**57**:291–296.
- Kofinas JD, Blakemore J, McCulloh DH, Grifo J. Serum progesterone levels greater than 20 ng/dl on day of embryo transfer are associated with lower live birth and higher pregnancy loss rates. *J Assist Reprod Genet* 2015;**32**:1395–1399.
- Kosmas IP, Tatsioni A, Fatemi HM, Kolibianakis EM, Tournaye H, Devroey P. Human chorionic gonadotropin administration vs. luteinizing monitoring for intrauterine insemination timing, after administration of clomiphene citrate: a meta-analysis. *Fertil Steril* 2007;**87**:607–612.
- Kyrou D, Fatemi HM, Popovic-Todorovic B, Van den Abbeel E, Camus M, Devroey P. Vaginal progesterone supplementation has no effect on ongoing pregnancy rate in hCG-induced natural frozen-thawed embryo transfer cycles. *EJOG* 2010;**150**:175–179. Elsevier.
- Lee VCY, Li RHW, Chai J, Yeung TWY, Yeung WSB, Ho PC, Ng EHY. Effect of preovulatory progesterone elevation and duration of progesterone elevation on the pregnancy rate of frozen-thawed embryo transfer in natural cycles. *Fertil Steril* 2014;**101**:1288–1293.
- Lee VCY, Li RHW, Ng EHY, Yeung WSB, Ho PC. Luteal phase support does not improve the clinical pregnancy rate of natural cycle frozen-thawed embryo transfer: a retrospective analysis. *Eur J Obstet Gynecol Reprod Biol* 2013;**169**:50–53.
- Levine H. Luteal support in IVF using the novel vaginal progesterone gel Crinone 8%: results of an open-label trial in 1184 women from 16 US centers. *Fertil Steril* 2000;**74**:836–837.
- Liu X-R, Mu H-Q, Shi Q, Xiao X-Q, Qi H-B. The optimal duration of progesterone supplementation in pregnant women after IVF/ICSI: a meta-analysis. *Reprod Biol Endocrinol* 2012;**10**:107.
- Loutradi KE, Kolibianakis EM, Venetis CA, Papanikolaou EG, Pados G, Bontis I, Tarlatzis BC. Cryopreservation of human embryos by vitrification or slow freezing: a systematic review and meta-analysis. *Fertil Steril* 2008;**90**:186–193.
- Lutjen P, Trounson A, Leeton J, Findlay J, Wood C, Renou P. The establishment and maintenance of pregnancy using in vitro fertilization and embryo donation in a patient with primary ovarian failure. *Nature* 1984;**307**:174–175.
- Merriam KS, Leake KA, Elliot M, Matthews ML, Usadi RS, Hurst BS. Sexual absorption of vaginal progesterone: a randomized control trial. *Int J Endocrinol* 2015;**2015**:685281–685285.

- Montagut M, Santos-Ribeiro S, De Vos M, Polyzos NP, Drakopoulos P, Mackens S, van de Vijver A, Van Landuyt L, Verheyen G, Tournaye H et al. Frozen-thawed embryo transfers in natural cycles with spontaneous or induced ovulation: the search for the best protocol continues. *Hum Reprod* 2016;**31**:2803–2810.
- Murray MJ, Meyer WR, Zaino RJ, Lessey BA, Novotny DB, Ireland K, Zeng D, Fritz MA. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. *Fertil Steril* 2004;**81**:1333–1343.
- Navot D, Laufer N, Kopolovic J, Rabinowitz R, Birkenfeld A, Lewin A, Granat M, Margalioth EJ, Schenker JG. Artificially induced endometrial cycles and establishment of pregnancies in the absence of ovaries. *N Engl J Med* 1986;**314**:806–811.
- Navot D, Scott RT, Droesch K, Veeck LL, Liu HC, Rosenwaks Z. The window of embryo transfer and the efficiency of human conception in vitro. *Fertil Steril* 1991;**55**:114–118.
- Nawroth F, Ludwig M. What is the 'ideal' duration of progesterone supplementation before the transfer of cryopreserved-thawed embryos in estrogen/progesterone replacement protocols? *Hum Reprod* 2005;**20**:1127–1134.
- Niu Z, Feng Y, Sun Y, Zhang A, Zhang H. Estrogen level monitoring in artificial frozen-thawed embryo transfer cycles using step-up regime without pituitary suppression: is it necessary? *J Exp Clin Assist Reprod* 2008;**5**:4.
- Peeraer K, Debrock S, Laenen A, De Loecker P, Spiessens C, De Neubourg D, D'Hooghe TM. The impact of legally restricted embryo transfer and reimbursement policy on cumulative delivery rate after treatment with assisted reproduction technology. *Hum Reprod* 2014;**29**:267–275.
- Psychoyos A. Hormonal control of oovoimplantation. *Vitam Horm* 1973;**31**:201–256.
- Remohi J, Ardiles G, Garcia-Velasco JA, Gaitan P, Simon C, Pellicer A. Endometrial thickness and serum oestradiol concentrations as predictors of outcome in oocyte donation. *Hum Reprod* 1997;**12**:2271–2276.
- Robb PA, Robins JC, Thomas MA. Timing of hCG administration does not affect pregnancy rates in couples undergoing intrauterine insemination using clomiphene citrate. *J Natl Med Assoc* 2004;**96**:1431–1433.
- Roque M, Lattes K, Serra S, Solà I, Geber S, Carreras R, Checa MA. Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis. *Fertil Steril* 2013;**99**:156–162.
- Roque M, Valle M, Guimarães F, Sampaio M, Geber S. Freeze-all policy: fresh vs. frozen-thawed embryo transfer. *Fertil Steril* 2015;**103**:1190–1193.
- Rosenberg SM, Luciano AA, Riddick DH. The luteal phase defect: the relative frequency of, and encouraging response to, treatment with vaginal progesterone. *Fertil Steril* 1980;**34**:17–20.
- Ruiz-Alonso M, Blesa D, Díaz-Gimeno P, Gómez E, Fernández-Sánchez M, Carranza F, Carrera J, Vilella F, Pellicer A, Simón C. The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. *Fertil Steril* 2013;**100**:818–824.
- Sathanandan M, Macnamee MC, Rainsbury P, Wick K, Brinsden P, Edwards RG. Replacement of frozen - thawed embryos in artificial and natural cycles: a prospective semi-randomized study. *Hum Reprod* 1991;**6**:685–687.
- Scott R, Navot D, Liu HC, Rosenwaks Z. A human in vivo model for the luteoplacental shift. *Fertil Steril* 1991a;**56**:481–484.
- Scott RT, Ross B, Anderson C, Archer DF. Pharmacokinetics of percutaneous estradiol: a crossover study using a gel and a transdermal system in comparison with oral micronized estradiol. *Obstet Gynecol* 1991b;**77**:758–764.
- Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C, Thomas S. Evidence of impaired endometrial receptivity after ovarian stimulation for in vitro fertilization: a prospective randomized trial comparing fresh and frozen-thawed embryo transfer in normal responders. *Fertil Steril* 2011;**96**:344–348.
- Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Ross R. Contrasting patterns in in vitro fertilization pregnancy rates among fresh autologous, fresh oocyte donor, and cryopreserved cycles with the use of day 5 or day 6 blastocysts may reflect differences in embryo-endometrium synchrony. *Fertil Steril* 2008;**89**:20–26.
- Shapiro DB, Pappadakis JA, Ellsworth NM, Hait HI, Nagy ZP. Progesterone replacement with vaginal gel versus i.m. injection: cycle and pregnancy outcomes in IVF patients receiving vitrified blastocysts. *Hum Reprod* 2014;**29**:1706–1711.
- Soares SR, Troncoso C, Bosch E, Serra V, Simón C, Remohí J, Pellicer A. Age and uterine receptiveness: predicting the outcome of oocyte donation cycles. *J Clin Endocrinol Metab* 2005;**90**:4399–4404.
- Tabibzadeh S. Molecular control of the implantation window. *Hum Reprod Update* 1998;**4**:465–471.
- Testart J, Frydman R, Feinstein MC, Thebault A, Roger M, Scholler R. Interpretation of plasma luteinizing hormone assay for the collection of mature oocytes from women: definition of a luteinizing hormone surge-initiating rise. *Fertil Steril* 1981;**36**:50–54.
- Theodorou E, Forman R. Live birth after blastocyst transfer following only 2 days of progesterone administration in an agonadal oocyte recipient. *Reprod Biomed Online* 2012;**25**:355–357.
- Tomás C, Alsbjerg B, Martikainen H, Humaidan P. Pregnancy loss after frozen-embryo transfer—a comparison of three protocols. *Fertil Steril* 2012;**98**:1165–1169.
- Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A Phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. *Hum Reprod* 2017;**32**:1019–1027.
- van de Vijver A, Drakopoulos P, Polyzos NP, Van Landuyt L, Mackens S, Santos-Ribeiro S, Vloeberghs V, Tournaye H, Blockeel C. Vitrified-warmed blastocyst transfer on the 5th or 7th day of progesterone supplementation in an artificial cycle: a randomised controlled trial. *Gynecol Endocrinol* 2017:1–4. doi:10.1080/09513590.2017.1318376. [Epub ahead of print].
- van de Vijver A, Polyzos NP, Van Landuyt L, De Vos M, Camus M, Stoop D, Tournaye H, Blockeel C. Cryopreserved embryo transfer in an artificial cycle: is GnRH agonist down-regulation necessary? *Reprod Biomed Online* 2014;**29**:588–594.
- van de Vijver A, Polyzos NP, Van Landuyt L, Mackens S, Stoop D, Camus M, De Vos M, Tournaye H, Blockeel C. What is the optimal duration of progesterone administration before transferring a vitrified-warmed cleavage stage embryo? A randomized controlled trial. *Hum Reprod* 2016;**31**:1097–1104.
- Veleza V, Tiitinen A, Vilks S, Hydén-Granskog C, Tomás C, Martikainen H, Tapanainen JS. High and low BMI increase the risk of miscarriage after IVF/ICSI and FET. *Hum Reprod* 2008;**23**:878–884.
- Weissman A, Horowitz E, Ravhon A, Steinfeld Z, Mutzafi R, Golan A, Levran D. Spontaneous ovulation versus HCG triggering for timing natural-cycle frozen-thawed embryo transfer: a randomized study. *Reprod Biomed Online* 2011;**23**:484–489.
- Weissman A, Levin D, Ravhon A, Eran H, Golan A, Levran D. What is the preferred method for timing natural cycle frozen-thawed embryo transfer? *Reprod Biomed Online* 2009;**19**:66–71.
- Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. *N Engl J Med* 1999;**340**:1796–1799.
- Yarali H, Polat M, Mumusoglu S, Yarali I, Bozdogan G. Preparation of endometrium for frozen embryo replacement cycles: a systematic review and meta-analysis. *J Assist Reprod Genet* 2016;**33**:1287–1304.
- Younis JS, Simon A, Laufer N. Endometrial preparation: lessons from oocyte donation. *Fertil Steril* 1996;**66**:873–884.
- Yovich JL, Conceicao JL, Stanger JD, Hinchliffe PM, Keane KN. Mid-luteal serum progesterone concentrations govern implantation rates for cryopreserved embryo transfers conducted under hormone replacement. *Reprod Biomed Online* 2015;**31**:180–191.