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Editorial

Escape Ovulation in HRT-Frozen Embryo Transfer Cycles and Use of Gn-RH Antagonists-An Opinion

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Stimulated frozen embryo transfer cycles (FET), also called hormone replacement (HRT) FET cycles, utilise a high dose of oestrogen from the start of a natural menstrual cycle. This helps to build the endometrium and suppress ovulation. Suppression of ovulation is caused by suppressing follicle-stimulating hormone (FSH) and luteinising hormone (LH) from the anterior pituitary. Escape ovulation, which is unexpected follicular development in HRT-FET, is uncommon but an event that happens on a regular basis. This inevitably influences the timing of the embryo transfer hence the outcomes.

Escape ovulation is an event which can be encountered in 1.9 - 7.4% of HRT-FET cycles without pituitary suppression [1] either with gonadotrophin agonists (GnRH-a) or antagonists. If recognised, escape ovulation leads to the cancellation of the treatment. If unrecognised, however, it would directly affect the outcome and influence the pregnancy rates due to possible mistiming of the embryo transfer (ET). Recognising or avoiding escape ovulation may therefore improve the outcomes in HRT-FET cycles.

Although a potential option, endocrine monitoring of HRT-FET cycles may not necessarily help recognise such events. Late-follicular phase serum oestradiol and luteinising hormone (LH) levels do not seem to predict outcomes [2]. Serum progesterone assessments, on the other hand, may be used to detect escape ovulation.

However, given the low incidence of escape ovulation, it is questionable whether this measurement (progesterone assessment) significantly improves pregnancy outcomes when additional preventive measures are taken to avoid follicular growth and escape ovulation, such as a high dose of estrogen supplementation from Day 1 of the cycle onwards [3] and ultrasound scan examinations to exclude a growing follicle.

Use of GnRH agonists during HRT-FET cycles

In addition to oestrogen administration, GnRH-a can be added to an HRT-FET protocol to prevent spontaneous ovulation [4]. In one randomised controlled trial (RCT), such an approach was associated with increased clinical pregnancy and live birth rates, mainly due to lower cycle cancellation rates [5].

More recently, another retrospective study failed to show any benefit of using GnRH-a in frozen embryo transfer cycles [1]. In addition, HRT-FET cycles without GnRH-a co-treatment seem more patient-friendly, given the avoidance of the cost and potential side effects associated with these drugs [3].

GnRH antagonists to avoid escape ovulation

With their high potency and fewer side effects, GnRH antagonists have been introduced into *in-vitro* fertilisation (IVF) and emerged as an alternative to GnRH-a. They suppress the pituitary activity directly and prevent FSH and LH secretion. Unlike GnRH-a, these potent GnRH antagonists cause immediate, rapid gonadotropin suppression by competitively blocking GnRH receptors in the anterior pituitary gland, thereby preventing endogenous GnRH from inducing LH and FSH release from the pituitary. Furthermore, suppression of GnRH antagonists can be quickly reversed. This different pharmacologic mechanism of action makes GnRH antagonists a more logical choice to use in IVF to prevent premature LH surges.

Therefore, in an HRT-FET cycle, GnRH antagonists can down-regulate pituitary activity just like GnRH-a to avoid escape ovulation. Compared to a GnRH-a downregulated cycle, the benefits would be a shorter cycle length, shorter length of time to inject and no side effects as there will be no down-regulation. Therefore, antagonists are more user-friendly than agonists. Antagonists would provide a further measure to ensure that escape ovulation would not occur. This would help better control an HRT- FET cycle, potentially increasing the chances of successful implantation.

Antagonist administration in an HRT-FET cycle, therefore, would ideally start on the 5th or the sixth day of the oestrogen intake; the dose used is the same as in IVF (0.25 mg/day) and would continue until progesterone administration is started.

Bibliography

1. Van de Vijver A., *et al*. "Cryopreserved embryo transfer in an artificial cycle: Is GnRH agonist down-regulation necessary?" *Reproductive BioMedicine Online* 29.5 (2014): 588-594.
2. Bocca S., *et al*. "Impact of serum estradiol levels on the implantation rate of cleavage stage cryopreserved-thawed embryos transferred in programmed cycles with exogenous hormonal replacement". *Journal of Assisted Reproduction and Genetics* 32.3 (2015): 395-400.
3. Mackens S., *et al*. "Frozen embryo transfer: a review on the optimal endometrial preparation and timing". *Human Reproduction* 32 (2017): 2234-2242.
4. Keltz MD., *et al*. "Baseline cyst formation after luteal phase gonadotropin-releasing hormone agonist administration is linked to poor *in vitro* fertilisation outcome". *Fertility and Sterility* 64.3 (1995): 568-572.
5. El-Toukhy T., *et al*. "Pituitary suppression in ultrasound-monitored frozen embryo replacement cycles. A randomised study". *Human Reproduction* 19.4 (2004): 874-879.

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