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The effect of elevated progesterone levels before HCG triggering in modified natural cycle frozen-thawed embryo transfer cycles

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KEY MESSAGE

Isolated elevated late follicular phase progesterone concentrations were found in over one-fifth of patients undergoing modified natural cycle frozen-thawed embryo transfer. These elevated progesterone concentrations, however, seem to be without any consequence for live birth and pregnancy rates.

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ABSTRACT

Recent studies suggest that elevated late follicular phase progesterone concentrations after ovarian stimulation for IVF may result in embryo–endometrial asynchrony, reducing the chance of successful implantation after fresh embryo transfer. It remains unclear to what extent elevated late follicular phase progesterone levels may occur in unstimulated cycles before frozen–thawed embryo transfer, or what affect they may have on outcomes. In this cohort study, 271 patients randomized to the modified natural cycle arm of a randomized controlled trial comparing two endometrial preparation regimens underwent late follicular phase progesterone and LH testing. A receiver operating characteristic curve was constructed to identify a progesterone cut-off level with the best predictive value for live birth (progesterone level ≥4.6 nmol/l). A total of 24.4% of patients revealed an isolated elevated serum progesterone of 4.6 nmol/l or greater, and 44.3% showed an elevated progesterone level in association with a rise in LH. Neither endocrine disruption affected outcomes, with live birth rates of 12.9% versus 10.6% (OR 0.6, 95% CI 0.19 to 1.9) and 11.9% versus 17.5% (OR 1.6, 95% CI 0.79 to 3.1), respectively. Whether monitoring of progesterone and LH in natural cycle frozen–thawed embryo transfer has added clinical value should studied further.

Introduction

The incidence and effect of elevated late follicular phase progesterone levels on IVF treatment outcomes continue to be debated (Fatemi and Van Vaerenbergh, 2015; Weinerman and Mainigi, 2014). Several studies of patients undergoing ovarian stimulation for IVF have shown that an elevated late follicular phase progesterone level is associated with diminished pregnancy rates and an increased risk of obstetric complications (Bosch et al., 2010; Venetis et al., 2015). Elevated late follicular phase progesterone levels are usually defined as a serum progesterone of 4.77 nmol/l or more (≥1.5 ng/l) on completion of ovarian stimulation, before administration of HCG to trigger final oocyte maturation (Bosch et al., 2010; Venetis et al., 2015).

The underlying mechanism for this phenomenon remains unclear, but supraphysiological oestrogen levels arising from ovarian stimulation may be indirectly implicated (Farhi et al., 2010; Joo et al., 2010). Both abnormal oestrogen and progesterone levels lead to a spectrum of alterations in the endometrium, such as changes in histological features as well as gene and cytokine expression related to endometrial receptivity (Boomsma et al., 2010; Bosch et al., 2010; Labarta et al., 2011; Lass et al., 1998; Ubaldi et al., 1997). In patients undergoing ovarian stimulation for IVF, these features are observed earlier when progesterone levels are elevated before HCG has been administered. This suggests an acceleration in the maturation of the endometrium that may lead to an asynchrony between optimal receptivity and timing of embryo transfer, resulting in lower pregnancy rates (Ubaldi et al., 1997; Van Vaerenbergh et al., 2011). Whether the changes in the endometrium are the result of an elevated progesterone alone or perhaps a combination of supra-physiological hormone levels and other ovarian stimulation related factors remains unclear.

As natural cycle frozen–thawed embryo transfer requires no ovarian stimulation, it provides the opportunity to avoid the assumed negative effects of ovarian hyperstimulation on the endometrium. In natural cycle frozen–thawed embryo transfer, endocrine control of the menstruation cycle is not altered, and the endometrium should not be exposed to supra-physiological oestrogen and progesterone levels. This premise underlies the recommendation by some to freeze all embryos when an elevated late follicular phase progesterone is measured, and to delay transfer to an unstimulated cycle (Polotsky et al., 2009; Shapiro et al., 2010).

In modified natural cycle frozen–thawed embryo transfer, an injection with HCG is given to trigger ovulation of the dominant follicle. The continuing presence of the dominant follicle on ultrasound is taken to indicate that LH surge and luteinization have yet to occur. Progesterone levels, however, start to rise about 12 h before the start of the LH surge, so it is possible that at the time of HCG administration, progesterone levels are elevated (Hoff et al., 1983). Given that maturation of the endometrium is induced by progesterone, significant progesterone elevation before HCG injection might lead to desynchronization between the endometrium and the embryo, and thereby diminishing pregnancy rates.

This concern has led some to monitor progesterone levels in patients undergoing modified natural cycle frozen–thawed embryo transfer, and cancel the cycle if progesterone levels are elevated (Weissman et al., 2009, 2011). The incidence and effect of elevated progesterone levels before ovulation triggering in modified natural cycle frozen–thawed embryo transfer, however, remain to be elucidated. As elevated progesterone levels have been shown to be related to multifollicular development, we investigated the frequency of premature progesterone elevations in modified natural cycle frozen–thawed embryo transfer cycles and whether they are associated with detrimental effects on clinical outcomes in this context.

Materials and methods

Patients and procedures

Included patients were recruited for the purpose of a multi-centre randomized controlled trial ('ANTARCTICA' trial, NTR1586) (Groenewoud et al., 2012b, 2016). Patients were randomized between an artificial frozen embryo transfer cycle and a modified natural cycle frozen–thawed embryo transfer. Participants meeting the inclusion criteria for this trial were aged 18–40 years, had a regular cycle and had cryopreserved embryos derived from of one of their first three fresh IVF or IVF and intracytoplasmic sperm injection (IVF–ICSI) cycles. Patients with a uterine anomaly or a contraindication for medication used in the artificial frozen embry transfer cycle were excluded, as were patients undergoing treatment with donor gametes. Patients randomized to modified natural cycle frozen–thawed embryo transfer were considered eligible for the analyses of the present study. Ethical approval for the randomized controlled trial was obtained from the institutional review board of the Isala Clinics in Zwolle on 4 March 2009 (reference number NL23273.075.09).

Patients randomized to the modified natural cycle frozen–thawed embryo transfer arm underwent ultrasound monitoring of the dominant follicle and the endometrium to plan thawing and transferring

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