

Article

Should we continue to measure endometrial thickness in modern-day medicine? The effect on live birth rates and birth weight

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KEY MESSAGE

This study reaffirms the usefulness of endometrial thickness as a potential prognostic tool for live birth rates and neonatal birthweight in contemporary IVF, particularly when considered together with other ovarian stimulation monitoring methods, such as the late-follicular endocrine profile.

ABSTRACT

The evaluation of endometrial thickness (EMT) is still part of standard cycle monitoring during IVF, despite the lack of robust evidence of any value of this measurement to predict little revalidation in contemporary medical practice; other tools, however, such as endocrine profile monitoring, have become increasingly popular. The aim of this study was to reassess whether EMT affects the outcome of a fresh embryo transfer in modern-day medicine, using a retrospective, single-centre cohort of 3350 IVF cycles (2827 women) carried out between 2010 and 2014. In the multivariate regression analysis,

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EMT was non-linearly associated with live birth, with live birth rates being the lowest with an EMT less than 7.0 mm (21.6%; $P < 0.001$) and then between 7.0 mm and 9.0 mm (30.2%; $P = 0.008$). An EMT less than 7.0 mm was also associated with a decrease in neonatal birthweight z-scores (-0.40; 95% CI -0.69 to -0.12). In conclusion, these results reaffirm the use of EMT as a potential prognostic tool for live birth rates and neonatal birthweight in contemporary IVF, namely when considered together with other ovarian stimulation monitoring methods, such as the late-follicular endocrine profile.

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Introduction

Over the years, much has been published on potential sonographic markers for endometrial receptivity. Although it remains a controversial issue, endometrial thickness (EMT) is the most widely used prognostic factor for endometrial receptivity during assisted reproductive techniques (Kasius et al., 2014).

Several mechanisms are responsible for modifications caused to the morphology and histology of the endometrium before embryo implantation. Specifically, previous studies have shown that endometrial proliferation is dependent on reproductive age, hormonal levels of oestradiol and the expression of endometrial receptors (Paulson, 2011; Zhang et al., 2005).

Debate on the predictive value measuring EMT before administering HCG for ovulation triggering in assisted reproduction techniques is ongoing. Some investigators have shown a linear correlation between pregnancy rates and EMT (Al-Ghamdi et al., 2008; Chen et al., 2010; Richter et al., 2007; Rinaldi et al., 1996); however, others have posited that pregnancy rates may even decline above a thickness of 14 mm (Weissman et al., 1999), after which miscarriage rates may increase. Moreover, in a retrospective study (Lamanna et al., 2008) including 606 women undergoing a long-agonist protocol, the investigators reported a parabolic trend in pregnancy rate across EMT categories (with lower pregnancy rate in EMT extremes below 8 mm and above 14 mm, respectively). In 2014, a meta-analysis of 22 studies concluded that the measurement of EMT was a valuable predictor for clinical pregnancy, with lower clinical pregnancy rates below the frequently mentioned cut-off of 7 mm, which progressively increased until 10 mm of EMT (Kasius et al., 2014). On the basis of these results, one could conclude that a thick endometrium may not necessarily predict pregnancy but, conversely, a thin endometrium may be associated with lower pregnancy rates, possibly owing to a thinner functional layer that exposes the embryo to the higher oxygen concentrations of the blood from the spiral arteries during implantation (Casper, 2011).

Adequate endometrial development seems to be of paramount importance for placentation, given that previous studies have shown an association between abnormal glandular or vascular development and defective-placentation disorders, including placental abruption, low birth weight (LBW), fetal growth restriction, pregnancy-related hypertensive disorders and pregnancy loss (Palatnik et al., 2016; Pelinck et al., 2010a, 2010b; Rombauts et al., 2014; Toal et al., 2007). Most of the previously mentioned studies relate EMT to pregnancy rate with no mention of the potential effect on neonatal morbidity (Holden et al., 2017; Ma et al., 2017; Yuan et al., 2016), despite the common knowledge that assisted reproduction techniques are associated with preterm birth and LBW (Declercq et al., 2015; Jackson et al., 2004; Poikkeus et al., 2007; Schieve et al., 2002). The contributing factors of LBW after assisted reproduction techniques are immense, with little agreement on the main underlying causes. Multiple studies have pointed to either certain relevant baseline characteristics of the population seeking assisted reproduction techniques or specificities in the

stimulation protocols and laboratory procedures (Bower and Hansen, 2005; Doyle et al., 1992; Helmerhorst et al., 2004; Jackson et al., 2004; Ludwig et al., 2006; Putterman et al., 2003; Schieve et al., 2002; Wang et al., 2005). Specifically, subfertility itself is a risk factor for LBW (Axmon and Hagmar, 2005; Basso and Baird, 2003; Bergh et al., 1999; Draper et al., 1999; Pandian et al., 2001), with conflicting results on whether specific causes of infertility pose a higher risk than others (Doyle et al., 1992; Wang et al., 2005). Some evidence also suggests a detrimental effect of the hyperestrogenic milieu on neonatal outcomes, given that neonates resulting from minimal-stimulation IVF may have higher birth weights compared with conventional IVF newborns (Pelinck et al., 2010a, 2010b). Furthermore, others have associated EMT less than 10 mm with an increased risk of adverse perinatal outcomes, including preterm delivery, LBW and fetal demise (Chung et al., 2006), an association which may be explained by a reduced selective capacity of thinner endometria (Oron et al., 2016).

Monitoring of both the endometrial and ovarian responses to ovarian stimulation with transvaginal ultrasound has become an important predictor of the success of assisted reproduction techniques (McWilliams and Frattarelli, 2007). Also, many agree that a concomitant hormonal assessment may also be beneficial in predicting assisted reproduction technique outcome (Hardiman et al., 1990; Loumaye et al., 1997; Rizk and Smitz, 1992), although it is not universally applied (Murad, 1998; Vandekerckhove et al., 2014) because supraphysiologic hormone levels during ovarian stimulation seem to be the underlying mechanism causing a so-called 'endometrium-embryo asynchrony' (Al-Azemi et al., 2012; Kyrou et al., 2009; Roque et al., 2013; Shapiro et al., 2011). More specifically, it has been reported that abnormal serum progesterone levels may be associated with lower ongoing pregnancy rate and live birth rates (Bosch et al., 2010; Kolibianakis et al., 2002; Santos-Ribeiro et al., 2014).

The main aim of this study was to estimate the predictive value of EMT in live birth and the neonatal outcomes of fresh embryo transfers in contemporary medicine, accounting specifically for the endocrine profile of the patient during the late-follicular phase.

Material and methods

Study design

This retrospective, single-centre, cohort study included assisted reproduction technique treatment cycles carried out at the Universitair Ziekenhuis, Brussels, between January 2010 and December 2014. Only cycles in which patients underwent a gonadotrophin-releasing hormone (GnRH) antagonist down-regulated stimulation protocol followed by a fresh embryo transfer were included. To minimize confounding derived from women with a baseline poor prognosis, we excluded cycles in women aged 40 years or older and managed natural cycles. The exclusion criteria also included those who underwent cycles with known uterine abnormalities (including uterine malformations and intrauterine disease diagnosed during ultrasound or a preceding

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