RBM ONLINE

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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.

A B S T R A C T

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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https://doi.org/10.1016/j.rbmo.2017.12.016

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.

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.

Materials 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

hysteroscopy, such as Asherman's syndrome, endometrial polyps, submucosal myomas) and the planned use of either surgically retrieved sperm, donor oocytes, in-vitro maturation or preimplantation genetic diagnosis. Approval and waiver of written informed consent to retrieve and analyse the data was obtained from the Ethical Committee of Universitair Ziekenhuis Brussel (dated 17 May 2017, reference number 1432017369).

Assisted reproduction technique protocol

Ovarian stimulation was started on day 2 of the menstrual cycle with 50–450 IU/day of recombinant FSH (rFSH: Gonal-F®, Merck Pharmaceuticals, Darmstad, Germany; Puregon®, Merck Sharp & Dohme, Whitehouse Station, NJ, USA or Elonva®, Merck Sharp & Dohme) or highly purified human menopausal gonadotrophin (HP-HMG; Menopur®, Ferring Pharmaceuticals, St. Prex, Switzerland). Pituitary down-regulation was achieved with a daily 0.25 mg GnRH antagonist injection of either cetrorelix (Cetrotide®, Merck Pharmaceuticals) or ganirelix (Orgalutran®, Merck Sharp & Dohme) starting on day 7 of the menstrual cycle.

Cycle monitoring was carried out with periodic transvaginal ultrasound and serum oestradiol and progesterone concentration assessments. When at least three follicles measuring 17 mm mean diameter or over were visible, triggering of final oocyte maturation was carried out using either highly purified urinary HCG (5000 UI or 10 000 UI, according to patient weight; Pregnyl®, Merck Sharp & Dohme) or 250 UI of recombinant HCG (Ovitrelle®, Merck Pharmaceuticals). Oocyte retrieval was carried out about 36 h after HCG administration and followed by fertilization by either conventional IVF or intracytoplasmic sperm injection (ICSI).

Main outcomes measures

On the day of, or day before, ovulation triggering, EMT was measured in millimeters. We considered the EMT as the maximal anterior–posterior distance between both endometrial layers about 1 cm from the uterine fundus, subtracting the thickness of intrauterine fluid in the unlikely event that such was detected.

We considered a clinical pregnancy to be one or more gestational sacs diagnosed by ultrasonographic visualization, with any pregnancy loss after this period being defined as a clinical miscarriage. Live birth was defined as the number of deliveries that resulted in at least one live born neonate beyond 24 weeks of gestational age, with twin or higher order pregnancies being considered only once (Zegers-Hochschild *et al*, 2009).

Factors potentially associated with endometrial thickness

The following variables were assessed as potential predictors of EMT: female age, body mass index, total dose of exogenous FSH/highly purified human menopausal gonadotrophin, duration of ovarian stimulation, and late-follicular phase oestradiol and progesterone. To avoid bias by assuming that the relationship between these continuous predictors and EMT was linear, the best-fitting fractional polynomial of each of these variables was compared against their linear function to assess which one better described their association with EMT. This recognized statistical technique is a widely used method that allows an accurate assessment of what type of relationship better explains the association between a continuous variable and any given continuous or dichotomous outcome (Sauerbrei et al., 2006; Sunkara et al., 2011; Templeton et al., 1996).

Evaluation of the relationship between endometrial thickness, live birth and neonatal outcomes

In the present study, EMT was the main exposure variable for live birth. We are aware that the categorization of continuous variables may be of limited value in determining the real effect of a predictor. This is because it simultaneously assumes that values in different intervals have different effects even if close to each other, and that values on the extremes, but within the same interval group, have the same effect. Therefore, our main approach was to assess the relationship of EMT as a continuous variable comparing the best fitting fractional polynomial against the linear function (model 1). Nonetheless, to facilitate the application of the results into everyday clinical practice, EMT was also assigned to the following regular 2-mm-intervalled categories: less than 7.0 mm, 7.0–8.9 mm, 9.0–10.9 mm, 11.0–12.9 mm and 13.0 mm or over (model 2). These intervals were chosen to provide equal intervals as close as possible to the different lower and upper threshold values used across previous studies (Holden et al., 2017; Kasius et al., 2014; Lamanna et al., 2008; Richter et al., 2007).

When assessing the effect of EMT on live birth, we considered the following variables as potential confounders: female age, body mass index (BMI), rank of IVF–ICSI treatment cycle attempt, number of useable embryos (transferred and cryopreserved), number of embryos transferred (single versus multiple), embryo stage at transfer (cleavage day-3 versus blastocyst day-5), quality of the best embryo transferred (1, 2 or 3–4, sub-classified as detailed previously (Montagut et al., 2016)) and both late-follicular phase oestradiol and progesterone levels (determined on the day or day before ovulation triggering).

We also assessed the effect of EMT on neonatal outcomes, specifically gestational age at delivery, preterm birth (<37 weeks), birth weight and LBW (<2500 g). Given the non-linear progression of fetal growth as pregnancy develops, and differences according to fetal sex (Hadlock et al., 1985), the recorded birth weights were standardized using z-scores (Niklasson and Albertsson-Wikland, 2008). The z-scores indicate how many standard deviations an observation was above or below the reference population mean, accounting for gestational age and neonatal sex. Furthermore, given the significant influence of multiple pregnancies on fetal development, only singleton live births were evaluated. For this analysis, we considered the following variables as potential confounders: female age, BMI, parity (nulliparous versus multiparous), and the late-follicular phase oestradiol and progesterone levels.

Other considerations of the statistical analysis

Baseline characteristics were compared between the above-mentioned EMT categories for model 2, with categorical variables presented with relative frequency (%). Continuous variables were presented as means (SD) or medians (interquartile range) according to the normality of the distribution. Comparisons were made using generalized estimating equation (GEE) regression analysis, to account for the possibility of clustering of more than one cycle deriving from the same couple.

The predictors for EMT, live birth and neonatal outcomes were determined using univariable and multivariable GEE regression analysis, adjusting for the potential confounders mentioned previously. In model 2, the median values of each variable in the sample set were chosen as reference values.

$P < 0.05$ was considered to be significant. Stata Software version 13.1 (StataCorp, College Station, Texas, USA) was used for statistical analysis.

Results

Patient baseline demographics and general characteristics of the treatment cycle

A total of 3350 cycles (carried out in 2827 women) were included in the analysis. The baseline demographics and main cycle characteristics according to EMT are presented in **Table 1** and **Table 2**. The distribution of the following characteristics before oocyte retrieval varied significantly among the many EMT categories: BMI ($P < 0.001$), total dose of exogenous gonadotrophins ($P = 0.003$), duration of ovarian stimulation ($P = 0.017$) and late-follicular oestradiol ($P = 0.001$). Conversely, the number of oocytes retrieved, useable embryos produced and characteristics of the embryo(s) transferred (specifically, number, developmental stage and quality) did not vary significantly among the groups.

Factors associated with endometrial thickness

The results of the multivariable regression models for the prediction of EMT are presented in **Supplementary Table S1**. Increases in BMI were associated with a modest increase in EMT ($P < 0.001$); however, increases in late-follicular progesterone were inversely related with EMT ($P = 0.007$). Specifically, each 1 kg/m^2 increase in BMI was linearly associated with a 0.07 mm increase in EMT, and each 1.0 ng/ml increase in progesterone was linearly associated with a 0.25 mm decrease in EMT.

The duration of ovarian stimulation and late-follicular oestradiol were independently and non-linearly associated with an increase in EMT ($P = 0.001$ and $P < 0.001$, respectively) (**Figure 1**). Their effect on EMT, however, were also modest and mostly visible only in the lower limits of these variables. Specifically, the mean EMT seemed to stabilize once a minimum of 7 days of ovarian stimulation and concentration of 1000 pg/ml of oestradiol were reached.

The effect of endometrial thickness on live birth

To assess the effect of EMT on live birth, two logistic regression models were conducted, differing only in how the continuous variables were introduced into the model (either as fractional polynomials [**model 1**] or ordinal categories [**model 2**], respectively. The details of the multivariable regression models are presented in **Supplementary Table S2**. A shown in **Figure 2**, EMT was a non-linear significant predictor of live birth, affecting live birth rates. Furthermore, when specifically using the EMT category that included the median EMT of the sample set (9.6 mm) as the reference value (the 9.0–10.9 mm category from model 2), EMTs less than 7.0 mm ($P < 0.001$) and between 7.0 and 8.9 mm ($P = 0.008$) were both associated with a significant decrease in live birth rates (**Supplementary Table S2** and **Supplementary Figure S1B**).

The collective effect of EMT and the late-follicular endocrine profile on live birth is presented in **Figure 3**. Late-follicular-phase oestradiol had little effect on live birth rates; however, the increase of progesterone contributed significantly ($P < 0.039$) to a reduction in live birth rates within the same EMT measurement. For instance, for a fixed EMT of 10.0 mm, increasing late-follicular progesterone levels of 1.0 ng/ml, 1.5 ng/ml or 2.0 ng/ml were associated with decreasing live birth rates of 34%, 30% and 27%, respectively.

Endometrial thickness and neonatal outcomes

The multivariable EMT regression estimates for gestational age, preterm birth, birth weight z-score and LBW ($n = 939$) are presented in **Table 3**. Although the risk of LBW seemed unaltered by EMT in both models, birth weight z-scores varied significantly ($P = 0.017$) according to EMT (**Figure 4**). Conversely, gestational age and the risk of preterm birth seemed to be unaffected by EMT.

Table 1 – Baseline demographic and cycle characteristics according to endometrial thickness ($n = 3350$).[a]

	<7.0 mm ($n = 284$)	7.0–8.9 mm ($n = 918$)	9.0–10.9 mm ($n = 1159$)	11.0–12.9 mm ($n = 660$)	≥13.0 mm ($n = 329$)	*P*-value
Basic female and treatment cycle characteristics						
Female age (years)						
Median (IQR)	33 (31–36)	32 (29–36)	33 (30–36)	33 (30–36)	33 (29–36)	NS
BMI (Kg/m^2)						
Median (IQR)	22.5 (20.4–26.4)	22.8 (20.6–26.1)	23.4 (21.2–27.3)	23.9 (21.3–28.6)	25.3 (22.0–29.1)	<0.001
Rank of reatment cycle attempt						
Median (IQR)	2 (1–4)	2 (1–5)	2 (1–5)	2 (1–5)	2 (1–7)	NS
Ovarian stimulation and late-follicular phase endocrine profile						
Total dose of exogenous gonadotropins (IU)						
Median (IQR)	1500 (1200–2013)	1600 (1200–2000)	1575 (1200–2000)	1600 (1218–2088)	1688 (1350–2200)	0.003
Duration of ovarian stimulation (days)						
Median (IQR)	9 (8–11)	9 (8–11)	9 (8–11)	10 (9–11)	10 (9–11)	0017
Late-follicular phase oestradiol (pg/ml)						
Median (IQR)	1432 (912–2065)	1493 (1070–2090)	1563 (1141–2153)	1498 (1126–2039)	1649 (1203–2326)	0.001
Late-follicular phase progesterone (ng/ml)						
Median (IQR)	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	0.8 (0.6–1.1)	NS

[a] Comparisons among groups of endometrial thickness made using univariable regression analysis accounting for the clustering of cycles undertaken by the same women.

IQR, interquartile range; NS, non-significant.

Table 2 – Oocyte retrieval, embryo development and cycle pregnancy outcome according to endometrial thickness (*n* = 3350).[a]

	<7.0 mm (*n* = 284)	7.0–8.9 mm (*n* = 918)	9.0–10.9 mm (*n* = 1159)	11.0–12.9 mm (*n* = 660)	≥13.0 mm (*n* = 329)	*P*-value
Ovarian response and embryo production						
Oocytes retrieved						
Median (IQR)	8 (5–13)	9 (5–113)	9 (6–113)	8 (5–112)	8 (6–113)	NS
Useable embryos						
Median (IQR)	2 (2–15)	3 (2–14)	3 (2–14)	3 (2–14)	3 (2–15)	NS
Embryo transfer						
Number of embryos transferred, n (%)						
Single	179 (63.0)	570 (62.1)	690 (59.5)	388 (58.8)	197 (59.9)	NS
Multiple	105 (37.0)	348 (37.9)	469 (40.5)	272 (41.2)	132 (40.1)	
Embryo developmental stage at transfer, n (%)						
Cleavage	172 (60.6)	505 (55.0)	661 (57.0)	403 (61.1)	205 (62.3)	NS
Blastocyst	112 (39.4)	413 (45.0)	498 (43.0)	257 (38.9)	124 (37.7)	
Quality of best embryo transferred, n (%)						
1	186 (65.5)	637 (69.4)	804 (69.4)	468 (70.9)	245 (74.5)	NS
2	81 (28.5)	234 (25.5)	307 (26.5)	168 (25.5)	64 (19.5)	
3–14	17 (6.0)	47 (5.1)	48 (4.1)	24 (3.6)	20 (6.1%)	
Pregnancy and neonatal outcome						
Pregnancy outcome, n (%)						
Positive pregnancy test	92 (32.4)	415 (45.2)	567 (48.9)	341 (51.7)	173 (52.6)	<0.001
Clinical pregnancy	82 (28.9)	374 (40.7)	530 (45.7)	318 (48.2)	160 (48.6)	<0.001
Clinical miscarriage	18/82 (22.0)	85/374 (22.7)	112/530 (21.1)	70/318 (22.0)	48/160 (30.0)	NS
Ectopic pregnancy	2/82 (2.4)	10/374 (2.7)	8/530 (1.5)	4/318 (1.3)	3/160 (1.9)	NS
Stillbirths/elective terminations	0/82 (0)	1/82 (0.3)	2/530 (0.4)	2/318 (0.6)	0/160 (0)	NS
Live birth	62 (21.8)	278 (30.3)	408 (35.2)	242 (36.7)	109 (33.1)	0.001
Singleton	60 (96.8)	255 (91.7)	352 (86.3)	208 (85.9)	91 (83.5)	0.027
Twin/triplet	2 (3.2)	23 (8.3)	56 (13.7)	34 (14.1)	18 (16.5)	
Gestational age (days)[b]						
Median (IQR)	275 (269–1282)	275 (268–1281)	276 (268–1282)	276 (269–1281)	276 (270–1281)	NS
Preterm birth (<37 weeks), n (%)	7/60 (11.7)	27/248 (10.9)	39/344 (11.3)	14/201 (7.)	4/86 (4.7)	NS
Birth weight z-score[b]						
Mean (SD)	−10.7 ± 1.1	−10.4 ± 1.0	−10.3 ± 1.0	−10.3 ± 1.1	−10.4 ± 1.0	0.020
Birth weight (g)[b]						
Median (IQR)	3135 (2845–13350)	3250 (2898–13550)	3270 (2950–13670)	3330 (3010–13650)	3275 (3090–13548)	NS
Low birth weight (<2500 g), n (%)	4/60 (6.7)	24/248 (9.7)	25/344 (7.3)	18/201 (9.0)	3/86 (3.5)	NS
Sex of newborn, n (%)[b]						
Female	30/60 (50.0)	126/248 (50.8)	178/344 (51.7)	99/201 (49.3)	46/86 (53.5)	NS
Male	30/60 (50.0)	122/248 (49.2)	166/344 (48.3)	102/201 (50.7)	40/86 (46.5)	

[a] Comparisons among groups of endometrial thickness made using univariable generalized estimating equation regression analysis accounting for the clustering of cycles undergone by the same women.

[b] Data presented only for singleton deliveries with known date of delivery, birth weight and newborn sex (*n* = 939).

IQR, interquartile range; NS, non-significant.

Discussion

Despite significant advancements in the fields of ultrasonography (Singh et al., 2011; Wang et al., 2010; Zhang et al., 2016), immunology (Seshadri and Sunkara, 2014) and molecular diagnostics (Koot et al., 2016; Ruiz-Alonso et al., 2013), the potential benefit of these novel approaches are yet to be confirmed, leaving most physicians with only the measurement of EMT during ovarian stimulation to aid in the decision of whether or not to carry out a fresh embryo transfer. The main aim of the present study was to investigate whether EMT measurement still plays a role in modern-day medicine. To that extent, our results provide renewed evidence that EMT may affect live birth rates and neonatal outcomes.

In their meta-analysis, Kasius et al. (2014) concluded that the frequently reported cut-off of 7 mm only occurred in 16 out of the 1989 cycles (0.8%) included in the three studies reporting either ongoing pregnancy or live birth rates. Furthermore, although EMT less than 7 mm seemed to be associated with a reduction in live birth rate (OR 0.38), this difference was not statistically significant (95% CI 0.03 to 1.54). In our study, EMT less than 7.0 mm occurred in 8.5% (*n* = 284) of all cycles and was associated with a decrease in live birth rate, results that are more in line with the conclusions of at least three recently published studies with a higher incidence of EMT less than 7 mm as well (Holden et al., 2017; Ma et al., 2017; Yuan et al., 2016). Another potential explanation that may explain the differences between the results of Kasius et al. (2014) and the studies that followed (beyond the six- to 10-fold increase in incidence of EMT <7 mm) may be the fact that ongoing pregnancy rates and live birth rate were considered together in this meta-analysis, a decision that could have produced significant residual confounding. For this reason, an updated meta-analysis integrating these most recent results is currently under

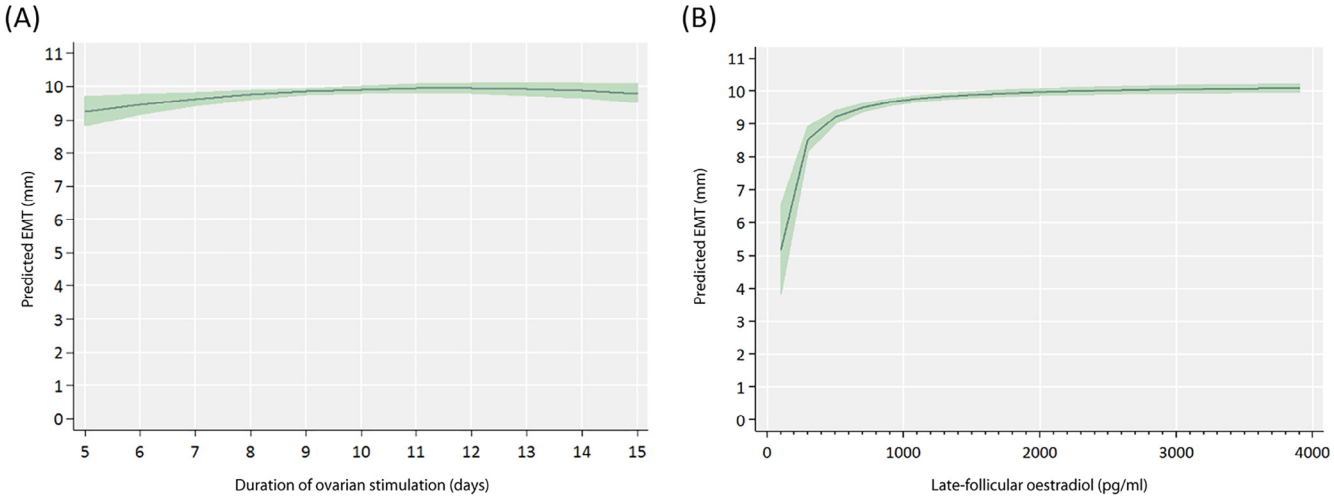

Figure 1 – Predicted endometrial thickness (EMT) according to (A) the duration of ovarian stimulation and (B) late-follicular oestradiol. The figure depicts the predicted mean EMT (teal line) and 95% CI (teal area); The full regression model is detailed in Supplementary Table S1. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

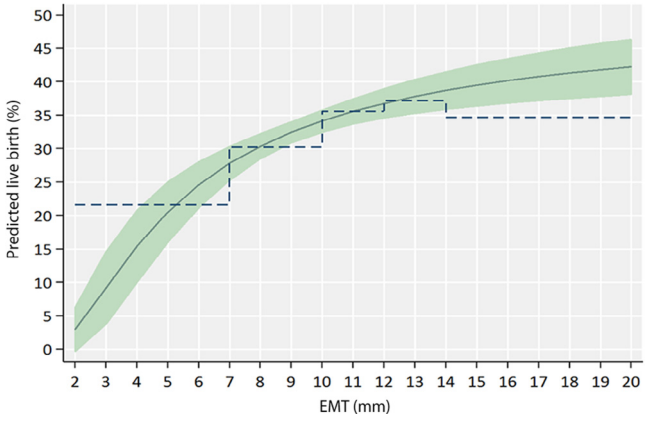

Figure 2 – Predicted live birth rates according to endometrial thickness. The figure depicts the predicted live birth rates after multivariable regression analysis adding endometrial thickness (EMT) as either a continuous (model 1, teal solid line and area for predicted liv birth rate and 95% CI) or categorical-ordinal (model 2, blue dashed line) variable; the full regression models are detailed in Supplementary Table S2. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

way to further understand the discrepancies among the pooled and un-pooled data thus far.

The most common causes for a thin endometrium are either an iatrogenic event, e.g. Asherman's syndrome, infection, e.g. with secondary adhesion development, or exogenous hormonal therapy, e.g. use of oral combined contraceptives, prolonged progesterone therapy and use of clomiphene citrate (Lebovitz and Orvieto, 2014; Senturk and Erel, 2008). A thin endometrium, however, can still occur in other cases for reasons that are less well understood, e.g. high blood flow impedance of the uterine radial arteries (Miwa et al., 2009). Early studies demonstrated that, after ovulation, the spiral arteries constrict preemptively to diminish blood flow to the functional layer (Rossman and Bartelmez, 1957). Nevertheless, a thinned or absent functional layer may subject the embryo to higher vascularity from the basal endometrium, which might explain the reduction of implantation caused by elevated oxygen tension and the production of detrimental reactive oxygen species (Catt and Henman, 2000; Yang et al., 1998).

Given the mounting evidence of a detrimental effect of a thin endometrial lining during IVF, multiple researchers have proposed potential treatment alternatives, including alternative routes for oestradiol administration (Tourgeman et al., 2001) and adjuvant sildenafil (Check et al., 2004; Takasaki et al., 2010), pentoxifylline (Ledee-Bataille et al., 2004; Letur-Konirsch and Delanian, 2003) and granulocyte colony-stimulating factor treatment (Kunicki et al., 2017; Li et al., 2017; Xu et al., 2015), all with controversial results. More recently, stem-cell transplantation has also been shown as a promising alternative (Kunicki et al., 2017; Li et al., 2017; Xu et al., 2015). Future prospective trials may assist physicians in understanding whether postponing the embryo transfer to a subsequent frozen embryo transfer cycle so that further investigations can be carried out e.g. a hysteroscopy, and an alternative treatment used at a later stage, may ultimately optimize assisted reproduction technique outcome.

In contrast to previously published studies (Amir et al., 2007; Gurbuz et al., 2004), we found no association between female age and EMT. This difference in results may be explained by the fact that our study included only women aged younger than 40 years, who were the only group in which the effect of age seemed to become relevant for EMT in the previously mentioned studies. For this reason, we would recommend against extrapolating our results beyond the age group that was included.

Our study also evaluated the potential effect of BMI on EMT. Previously published studies found an association between obesity and hyperinsulinemic state, which may promote the ovarian production of androgens and peripheral conversion of oestrogen in adipocytes (Rachon and Teede, 2010). Furthermore, a relationship between obesity and abnormal endometrial receptivity has also been described (Bellver et al., 2007; Dessolle et al., 2009; DeUgarte et al., 2010), positing that obese women, despite having higher EMTs, might also have impaired implantation. Corroborating previous data (Souter et al., 2011),

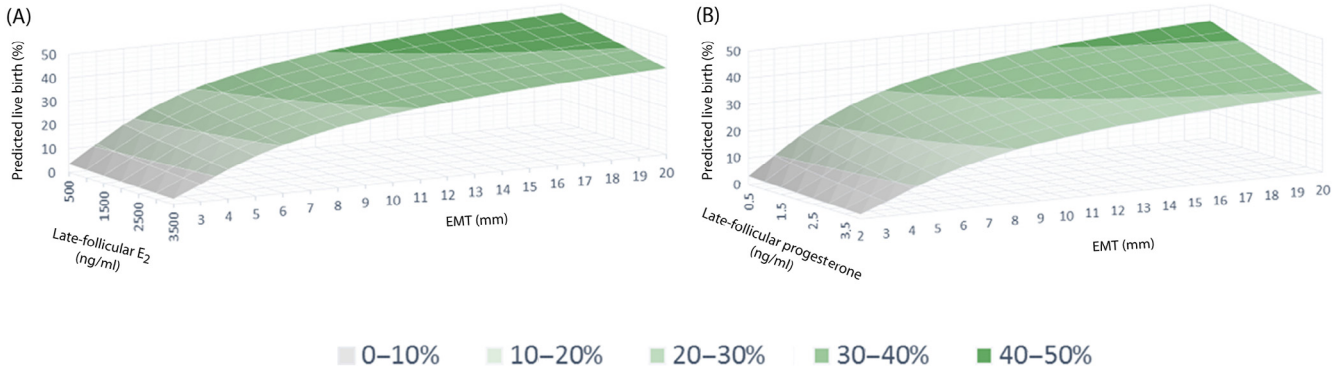

Figure 3 – Surface plots of the relationship between the effects of (A) endometrial thickness (EMT) and late-follicular oestradiol and (B) progesterone on live birth. Predicted live birth probabilities derived from the regression model detailed in Supplementary Table S2 (model 1).

we also found that BMI was linearly associated with EMT (**Supplementary Table S1**). This discrete effect of BMI on EMT did not seem to translate into an increase in live birth rates. In fact, BMI was not associated with live birth rates in this sample of GnRH antagonist suppressed cycles, an observation that was also confirmed by a recent randomized controlled trial (Toftager et al., 2017).

Late-follicular phase oestradiol levels were also shown to have an independent effect on EMT in our study. Although previous researchers have also established a positive linear correlation between oestradiol levels and EMT (Zhang et al., 2005), this finding was contradicted by a study including 2339 cycles using various stimulation protocols, which mentioned that oestradiol levels above 1000 pg/ml had no effect on EMT (Amir et al., 2007). We report a similar finding to this latter study, but in a larger sample set. In addition, late-follicular oestradiol over 3000 pg/ml seemed also to result in a discrete but statistically significant negative effect on live birth (**Supplementary Table S2** and **Figure 3A**), which is also in accordance with previous research (Kolibianakis and Devroey, 2002; Marchini et al., 1991). Specifically, these investigators have speculated that high oestradiol levels may alter the expression of progesterone receptors, potentially triggering an advancement in endometrial maturation despite the presence of otherwise normal pre-ovulatory circulating progesterone levels.

A longstanding debate on the importance of progesterone in fresh embryo transfer cycles has taken place. According to studies in women undergoing oocyte donation, progesterone plays a crucial role in endometrial receptivity, but not in oocyte quality (Check et al., 1994, 2010; Hofmann et al., 1993; Legro et al., 1993; Melo et al., 2006; Shulman et al., 1996). To the best of our knowledge, this is the first study relating circulating late-follicular levels of progesterone with EMT. Elevated progesterone (mostly defined as a HCG-day progesterone >1.5 ng/ml) may decrease the thickness of the endometrium by inducing early secretory endometrial transformation, which may anticipate the window of implantation and have a negative effect on live birth rates (Bosch et al., 2010; Healy et al., 2017; Hill et al., 2017; Santos-Ribeiro et al., 2014; Venetis et al., 2016).

Endometrial thickness was associated with a statistically significant decrease in birthweight z-scores, albeit not clinically translatable to an increase in cases of LBW. This contradictory finding may potentially be caused by the limited size of the singleton live birth sample subset (**Table 3**). As z-scores account for the differences in gestational age and new-born gender, this more robust statistical approach

Table 3 – Endometrial thickness regression estimates for neonatal outcomes in singleton pregnancies (n = 939).[a]

Model[b]		Model 2				
Best-fit FP	Coefficient (95% CI)	<7.0 mm	7.0–8.9 mm	9.0–10.9 mm	11.0–12.9 mm	≥13.0 mm
Gestational age (days)						
Linear	0.32 (−0.08 to 0.73)	−0.96 (−4.76 to 2.84)	0.13 (−2.12 to 2.39)	Reference	0.69 (−1.71 to 3.10)	2.26 (−1.02 to 5.55)
Preterm birth (<37 weeks, n = 91)						
Linear	−0.09 (−0.07 to 0.03)	0.06 (−0.82 to 0.93)	−0.09 (−0.62 to 0.45)	Reference	−0.46 (−1.10 to 0.19)	−0.91 (−1.98 to 0.16)
Birth weight z-score[c]						
FP1 (−2)	−0.11 (−020 to −0.02)[d]	−0.40 (−0.69 to −0.12)[e]	−0.13 (−0.30 to 0.03)	Reference	−0.08 (−0.27 to 0.10)	−0.18 (−0.42 to 0.05)
Low birth weight (<2500 g, n = 74)						
Linear	−0.07 (−0.19 to 0.04)	−0.11 (−1.22 to 0.99)	0.26 (−0.33 to 0.86)	Reference	0.24 (−0.40 to 0.88)	−0.74 (−1.98 to 0.49)

[a] Multivariable generalized estimating equation regression analyses (adjusted for female age, body mass index, parity and late-follicular oestradiol and progesterone) with endometrial thickness (EMT) and other continuous variables added either as best-fitting fractional polynomials (FPs) (model 1, in which the best-fit FP and regression coefficients (95% CI) for EMT are presented here) or ordinal categories (model 2, presenting here the regression coefficients [95% CI] for EMT).

[b] The FP of the variable EMT was scaled at $\frac{x}{10}$.

[c] Plotted in **Figure 4**.

[d] P = 0.017.

[e] P = 0.006.

FP1, first-degree fractional polynomial (power).

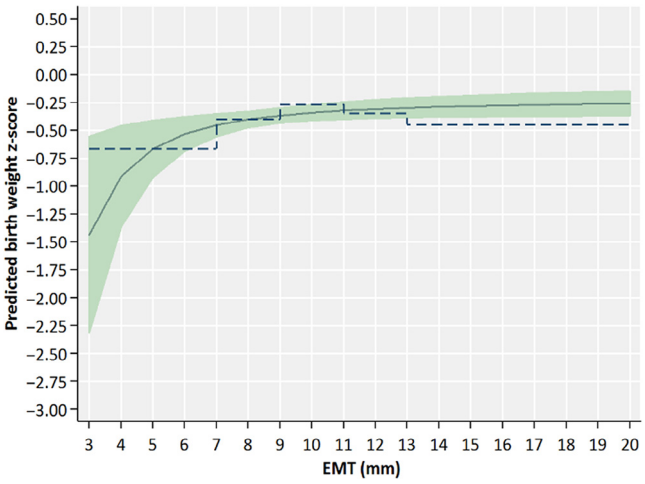

Figure 4 – Predicted birth weight z-scores according to endometrial thickness. The figure depicts the predicted birth weight z-scores after multivariable generalized estimating equation regression adding endometrial thickness (EMT) as either a continuous (model 1, teal solid line and area for predicted z-score and 95% CI) or categorical-ordinal (model 2, blue dashed line) variable; the regression models are described in Table 3. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

results in a more accurate assessment of the association between EMT and birthweight. This finding is also relatively unexplored, with Chung et al. (2006) also concluding in their small subgroup analysis of singletons that an EMT less than 10 mm had an almost threefold increased risk of LBW. Both studies highlight the potential effect of a thin endometrium beyond live birth rates, with birth weight being hindered by possible abnormal trophoblastic invasion (Chung et al., 2006). These results, however, require further confirmation in larger studies.

Strengths and limitations

The main strengths of our study are the large sample size and the inclusion of information on late-follicular endocrine profile to better understand the relationship between EMT, live birth and neonatal outcomes. This allowed for a better estimation of the potential value of EMT in modern-day medicine, in which combined transvaginal ultrasound and serum hormonal monitoring during ovarian stimulation have prevailed in most centres. This study also has limitations beyond its retrospective nature that need to be addressed. First, given the previous evidence of a potential hindering effect of thin EMT, we can assume that, in some patients, deferring their embryo transfer may have been proposed to ensue further investigation. In a previous study from our centre, an EMT below 7 mm was the indication for the use of the 'freeze-all' strategy in about 10% of all cases (Santos-Ribeiro et al., 2016). This presents a risk for selection bias, which may have potentially underestimated the incidence of thin EMT and the effect of thin EMT on the studied outcomes. Furthermore, although we excluded all women with intrauterine abnormalities visible on either ultrasound or hysteroscopy, one could argue that some patients could still have undiagnosed endometrial disease, given that we do not routinely carry out hysteroscopies before IVF. Nonetheless, we would argue that the likelihood that this could play a major role is minimal, given that two recent randomized controlled trials showed that routine hysteroscopy before IVF does not affect pregnancy outcome (El-Toukhy et al., 2016; Smit et al., 2016).

In **Supplementary Table S2**, the clinical usefulness of the cut-offs in model 2 are presented; however, we would still advise caution in the application of these limits in all instances given the risks of residual confounding after ordinal categorization of a continuous variable. Given the relatively large size (over 200 patients) of all our study subgroups, one would except this risk to be relatively small.

In the neonatal outcomes analysis, the relatively small subset of cases included resulted in large confidence intervals. Furthermore, as we could not adjust for other potential confounders for preterm delivery (such as history of preterm delivery) or LBW (namely, female smoking), our results should be interpreted with caution and require confirmation in future studies.

Implications for clinical practice and conclusion

The present study adds information on the value of EMT as a non-invasive parameter to infer on endometrial receptivity, a matter that is not yet universally acknowledged. Taken together, our findings suggest that the prognostic value of EMT should still be considered in clinical practice for both live birth and neonatal birthweight. Tailoring the ideal timing of embryo transfer, i.e., in the same fresh cycle or in a subsequent frozen embryo transfer cycle according to EMT, could be further optimized when the late follicular hormonal profile is also considered.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2017.12.016.

ARTICLE INFO

Article history:
Received 16 July 2017
Received in revised form 14 December 2017
Accepted 19 December 2017
Declaration: The authors report no financial or commercial conflicts of interest.

Keywords:
Endometrial receptivity
Endometrial thickness
Endometrium
Female infertility
IVF–ICSI outcome
Neonatal birthweight

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