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ARTICLE

Endometrial thickness of less than 7.5 mm is associated with obstetric complications in fresh IVF cycles: a retrospective cohort study

BIOGRAPHY

Galia Oron, MD, completed her Obstetrics and Gynaecology residency in 2010, and postgraduate training in reproductive endocrinology and infertility, with excellence, at McGill University, Canada, in 2014. Her special research interests are the effect of growth differentiation factors on maturation of human ovarian follicles and IVF pregnancy outcomes.

Galia Oron[1,2,*,†], Liran Hiersch[1,2,†], Shiran Rona[1,2], Roni Prag-Rosenberg[1,2], Onit Sapir[1,2], Maya Tuttnauer-Hamburger[1,2], Yoel Shufaro[1,2], Benjamin Fisch[1,2], Avi Ben-Haroush[1,2]

KEY MESSAGE

In IVF pregnancies with fresh embryo transfer, thin endometrial lining on the day of HCG triggering was found to be associated with small for gestational age neonates and obstetric complications that might be related to poor placentation.

ABSTRACT

Research question: Does endometrial thickness affect the occurrence of obstetric complications in fresh IVF cycles?

Design: We conducted a retrospective cohort study that included all singleton deliveries resulting from fresh embryo transfers in a single centre between 2008 and 2014. Obstetric complications, i.e. preeclampsia, placental abruption, placenta previa, small for gestational age and preterm delivery, in singleton live births were compared among patients with an endometrial thickness of less than 7.5 mm and 7.5 mm or over on day of HCG triggering. We adjusted for confounders, including maternal age, body mass index, smoking, peak oestradiol, parity, chronic hypertension, pre-gestational diabetes, gestational diabetes, vanishing twin, inherited or acquired thrombophilia, and past pregnancy complications.

Results: A total of 5546 fresh embryo transfer cycles were carried out during the study period, of which 864 singleton deliveries met inclusion criteria. After adjusting for potential confounders, an endometrial thickness of less than 7.5 mm was found to be associated with increased risk for adverse obstetric outcome (adjusted OR 1.53; 95% CI 1.03 to 2.42; $P = 0.04$) even after excluding patients with prior pregnancy complications (adjusted OR 2.2; 95% CI 1.05 to 4.59; $P = 0.035$).

Conclusions: Our results demonstrated that a thin endometrial lining was associated with obstetric complications that might be related to poor placentation. These findings should be validated in large prospective cohort studies.

[1] Infertility and IVF Unit, Helen Schneider Hospital for Women, Rabin Medical Center, Beilinson Hospital, Petach Tikva 4941492, Israel
[2] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[†]Joint first authors.

*Corresponding author. E-mail address: orongalia@gmail.com (G Oron). https://doi.org/10.1016/j.rbmo.2018.05.013
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KEYWORDS

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Fresh embryos
In vitro fertilization
Obstetric complication
Singleton live birth

INTRODUCTION

It has been widely accepted that IVF pregnancies are at increased risk for adverse pregnancy outcome. Although this increased risk has been attributed to the higher frequency of multiple gestations associated with IVF treatment (*Practice Committee ASRM, 2013*), numerous studies have shown that singleton IVF pregnancies are also at increased risk for adverse outcome compared with spontaneously achieved pregnancies (*Olivennes et al., 1993; Jackson et al., 2004; Romundstad et al., 2006; Reddy et al., 2007; McDonald et al., 2009; Cooper et al., 2011; Pinborg et al., 2013*). Whether these outcomes are related to the infertility itself or the IVF technology is yet to be determined (*Schieve et al., 2004*; *Bower and Hansen, 2006*; *Hayashi et al., 2012*).

A series of systematic reviews and meta-analyses have shown that IVF-conceived singletons are associated with higher risk of pregnancy complications, including preterm delivery, low birth weight (*Jackson et al., 2004; McGovern et al., 2004; McDonald et al., 2009; Grady et al., 2012*), preeclampsia and placental abruption (*Schieve et al., 2004; Healy et al., 2010*) compared with spontaneously conceived singletons. Whether this is due to the IVF treatment or rather the maternal underlying infertility itself is under debate (*Basso and Baird, 2003*; *Thomson et al., 2005*). A few studies of treatment parameters during IVF that might adversely affect implantation or placentation, thereby resulting in placenta-related obstetric complications have been published. A study by *Kalra et al. (2011)* showed that supra-physiologic levels of sex steroid hormones during treatment seem to contribute to the increased risk of low birth weight and other disorders of abnormal placentation when comparing fresh versus frozen transfers. In addition, a previous study by our group reported that elevated peak oestradiol levels during IVF treatment, even in singleton pregnancies, is associated with increased risk of placenta-related pregnancy complications without adversely affecting embryo implantation or pregnancy rates (*Farhi et al., 2010*). These findings were confirmed in additional studies reported recently (*Imudia et al., 2012; Royster et al., 2016*).

One of the important factors found to influence IVF outcomes is endometrial thickness on the day of HCG administration in fresh cycles (*Al-Ghamdi et al., 2008*). Thin endometrial lining was associated with decreased pregnancy rate, advanced maternal age and poor ovarian reserve (*Kasius et al., 2014; Yuan et al., 2016; Moffat et al., 2017*) and higher rate of ectopic pregnancies (*Rombauts et al., 2015*). Risk of ectopic pregnancy was linked to endometrial thickness in a retrospective cohort study of 8120 assisted reproduction technology cycles. In addition, endometrial thickness was also associated with the risk for placenta previa in a retrospective cohort study of 4537 singleton deliveries resulting from IVF treatment (*Rombauts, et al., 2014*).

Placenta-related pregnancy complications comprise a group of diseases with a similar pathophysiologic mechanism attributable to inadequate utero-placental circulation and abnormal placentation (*Toal et al., 2007; Sun et al., 2009*). The junctional zone represents the inner third of the myometrium that, together with the overlying endometrium, is involved in placentation. It is presumed that impaired remodelling of the uteroplacental spiral arteries during pregnancy may predispose to subsequent defective deep placentation and eventually to diminished uteroplacental blood initiating obstetric complications, such as fetal growth restriction, placental abruption, preeclampsia and preterm delivery (*Brosens et al., 1972*; *Dommisse and Tiltman, 1992*; *Meekins et al., 1994; Odegard et al., 2000; Kim et al., 2002; Kim et al., 2003; Ball et al., 2006*; *Norwitz, 2006*; *Brosens et al., 2011*; *Maynard and Karumanchi, 2011*).

Little is known about the association between endometrial thickness and adverse pregnancy outcome; specifically, pregnancy complications that might be related to poor placentation, including preeclampsia, preterm delivery, placental abruption and intrauterine growth restriction (*Pardi et al., 1997*; *Ventolini, 2011*; *Holden et al., 2017*).

Therefore, the purpose of our study was to evaluate the association of endometrial thickness on the day of HCG trigger in fresh IVF cycles with obstetric pregnancy complications.

MATERIALS AND METHODS

Study design

We conducted a retrospective cohort study evaluating the outcome of singleton deliveries in women aged 42 years or younger, resulting from fresh IVF cycles carried out between January 2008 and December 2014, at a single centre in a tertiary university-affiliated hospital. The study was approved on 1 December 2014 by the local Institutional Review Board (Study code 0587-14-RMC). Following standard practice, pregnancy outcome and obstetrical complications of the patients were continuously updated in the hospital's obstetric and neonatal computerized database. Trained physicians and nurses at the clinic, who were routinely involved in conducting standardized detailed surveys to gather missing information on obstetric and neonatal outcome, used telephone and postal surveys to obtain missing data for the study. To avoid potential bias, loss of follow-up was defined only after numerous failed attempts to reach the patients by telephone or post.

We used one of four IVF protocols: flexible antagonist protocol (gonadotrophin on days 2–3 of the cycle and gonadotrophin releasing hormone [GnRH] antagonist once the leading follicle reached 14 mm), a short agonist flare protocol (initiation of GnRH agonist on days 2–3 of the cycle and gonadotrophin on the third day of the GnRH agonist), a mid-luteal long agonist protocol (GnRH agonist in the mid-luteal phase and gonadotrophin after 2 weeks of down-regulation) or a natural cycle (triggering the natural leading follicle when it reached >17 mm).

Causes of infertility included polycystic ovarian syndrome, male infertility, tubal factor infertility, endometriosis (diagnosis by laparoscopy or ultrasound diagnosis of ovarian endometrioma), poor ovarian reserve according to the Bologna criteria (*Ferraretti et al., 2011*) and unexplained infertility.

On the basis of semen quality on the day of oocyte retrieval, the oocytes were inseminated 3–6 h after oocyte retrieval with either intracytoplasmic sperm injection or conventional insemination. Fertilization was indicated by the