Human Reproduction Open, pp. 1–1, 2020
doi:10.1093/hropen/hoaa015

human reproduction open

LETTER TO THE EDITOR

Reply: Endometrial thickness performs poorly as a predictor of IVF outcome, but does the endometrial receptivity array perform any better?

Sir,

We thank Dr Robert for his interest in our work on the association of the endometrial thickness (EMT) with the pregnancy likelihood in fresh IVF cycles (Griesinger *et al*., 2018). We note that Dr Robert agrees that the EMT is, in clinical practice, not a good prognostic factor for ongoing pregnancy or live birth in fresh IVF cycles among other well-established confounders, such as female age, despite the fact that in most univariate analyses, a statistical significant association of the EMT with pregnancy likelihood has been observed. This understanding of the available evidence is also reflected in the ovarian stimulation guideline of the European Society of Human Reproduction and Embryology 2019, in which it is stated that 'Routine monitoring of endometrial thickness during ovarian stimulation is probably not recommended' (ESHRE guideline on ovarian stimulation). Furthermore, this guideline states, but only as a good practice point, that 'The guideline group suggests performing a single measurement of the endometrium during ultrasound assessment on the day of triggering or oocyte pick-up to counsel patients on potential lower pregnancy chance'. So it appears as if some degree of consensus has been reached on the limitations of endometrial thickness measurements by 2D transvaginal sonography in clinical practice.

Dr Robert expresses his enthusiasm for what is called the endometrial receptivity array (ERA), a commercially available test of endometrial receptivity based on the expression of 238 genes in an endometrial tissue sample taken at a pre-defined time point within the menstrual cycle. More specifically, the author claims that the ERA is 'an excellent diagnostic test because it has good sensitivity and specificity'. All that the cited paper (Díaz-Gimeno *et al*., 2013) demonstrates in support of this claim is, however, that an endometrial gene expression array can identify time points of sampling across the menstrual cycle and this to a better degree than the reference pathologists using conventional histology. So the 'gold standard' for establishing the diagnostic test performance of the ERA has been the menstrual cycle phase, and not endometrial receptivity. However, there is a 'gold standard' for endometrial receptivity, and this is implantation of an embryo. Of note, it is inferred from oocyte donation treatment in recurrent implantation failure patients that most non-implantations are embryonic in origin (Budak *et al*. 2007), e.g. a patient can well be receptive but still not pregnant after embryo transfer. The setting of IVF would still allow determining the specificity and false-positive rate of the ERA (e.g. how often does the ERA test diagnose a non-receptive endometrium on LH+7 in women who later get pregnant after embryo transfer on that day), an information currently not available.

Dr Robert also suggests that what is called a 'personalized embryo transfer' would 'probably hold the key to effectively treating a significant number of cases of infertility'. In short, personalized embryo transfer means changing the conventional timing when to replace an embryo into the womb based on an ERA estimated best time point. This practice is, however, based on a number of assumptions, such as that there are no alternative pathogenic mechanisms frequently occurring in the endometrium leading to non-implantation other than displacement of the window of implantation, that embryonic cleavage speed is not a relevant factor in the interplay between embryo and the endometrium and that the window of implantation is indeed restricted to a relatively short time period in the human. All these assumptions should be corroborated before widespread implementation of the ERA in routine practice.

Conflict of interest

S.T. is an employee of IBSA Institut Biochimique SA; B.C. is an employee of IBSA Institut Biochimique SA.

References

Budak E, Garrido N, Soares SR, Melo MA, Meseguer M, Pellicer A, Remohí J. Improvements achieved in an oocyte donation program over a 10-year period: sequential increase in implantation and pregnancy rates and decrease in high-order multiple pregnancies. *Fertil Steril* 2007;**88**:342–349.

Díaz-Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martínez-Conejero JA, Alamá P *et al*. The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. *Fertil Steril* 2013;**99**:508–517.

Griesinger G, Trevisan S, Cometti B. Endometrial thickness on the day of embryo transfer is a poor predictor of IVF treatment outcome. *Hum Reprod Open* 2018. doi: 10.1093/hropen/hox031.

Georg Griesinger [1,*], Barbara Cometti[2], and Silvia Trevisan[2]

[1] *Department of Reproductive Medicine and Gynecological Endocrinology, University Hospital of Schleswig-Holstein, Campus Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany*

[2] *R&D Scientific Affairs, IBSA Institut Biochimique SA, Lugano, Switzerland*

*Correspondence address. Tel: +49 451 505778-212; Fax: +49 451 505778-213; E-mail: georg.griesinger@uni-luebeck.de

orcid.org/0000-0002-0606-5804

doi:10.1093/hropen/hoaa015