Intra-patient variability in the endometrial receptivity assay (ERA) test

Kristy Cho¹ · SeangLin Tan^{2,3} · William Buckett² · Michael H. Dahan^{2,3}

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Many correctable factors have been attributed to repeated implantation failure (RIF). These include endometrial polyps, submucosal fibroids, intrauterine synechiae, endometriosis, and embryo aneuploidy [1, 2]. However, unexplained RIF can be a significant challenge for the clinician and couple. The use of endometrial genomic expression to identify a personalized transfer timeframe and optimize embryo-endometrial synchrony has significant appeal as a possible management of RIF [3]. One such test is the endometrial receptivity assay (ERA), performed by Igenomix.

An endometrial biopsy is performed at the expectant time of embryo transfer as part of an estrogen and progesterone supported cycle or natural cycle. The ERA analyses the endometrial biopsy sample using next-generation sequencing to identify the expression of 238 genes [1]. Then, a computed prediction model uses this information to estimate the receptivity of the endometrium [1]. An embryo transfer synchronized with a “receptive” endometrium is said to be associated with a pregnancy rate of 50% and implantation rate of 38.5% [1]. In 2013, a model was developed initially with a training set of 79 endometrial samples collected from oocyte donors, then 49 of which were redated with the trained ERA algorithm; ERA dating was

found to more closely predict cycle dates based on serum LH peaks compared to histologic features [4]. Furthermore, seven of these samples were compared to repeat endometrial biopsies, collected on average 3 years later, from the respective patients on the same cycle day [4]. These samples were found to have identical endometrial receptivity classifications compared to the earlier samples [4]. Despite the initially promising results, the sample size is small and it is also unclear whether the results from oocyte donors are applicable to the RIF population, as the genomic expression in RIF patients may be downregulated compared to the fertile counterparts [5]. For a test to be of clinical value, ideally, it should be reproducible in the same patient. Therefore, the following small study presents evidence highlighting an issue noted with the ERA.

A 44-year-old healthy post-menopausal woman failed the transfer of two high-quality donor oocyte blastocysts. When all standard causes of failure were ruled out, an ERA test was performed. After 10 days of oral estradiol valerate (Duchesnay, Canada) 2 mg three times daily, she commenced endometrin (Ferring, Canada) 100 mg vaginally three times daily until the biopsy time. In total, she underwent 4 ERA tests within a 4-month period (Table 1). It should be noted that significant variability in the window of implantation occurred with the first three ERA tests, none of which had overlapped in the window of implantation timeframe. This lack of consistency is present even when the 3-hour error of the test was taken into consideration. During this period, she did not experience weight loss or gain. All biopsies were performed with the same model of pipet. The patient signed consent for publication of this data.

Several questions arise in light of this result. Can the implantation window vary month to month in an individual, even when uniform doses of exogenous hormones are taken? Does the ERA test reliably predict the window of implantation? Are certain populations more amenable to accurate results with the

✉ Michael H. Dahan
dahanhaim@hotmail.com

¹ Department of Obstetrics and Gynecology, University of British Columbia, Suite 930-1125 Howe Street, Vancouver, British Columbia V6Z 2K8, Canada

² Department of Obstetrics and Gynecology, MUHC Reproductive Centre, 888 Boul de Maisonneuve E #200, Montreal, Quebec H2L 4S8, Canada

³ OriginElle Fertility Clinic, 2110 Decarie Blvd, Montreal, Quebec H4A 3J2, Canada

Table 1 Summary of ERA results

ERA	Interval since last assay (days)	Interval since first assay (days)	Duration of P ₄ supplementation (hours) when biopsy was performed	Endometrial receptivity classification	ERA recommendation	ERA recommendation for subsequent timing of biopsy/transfer (hours of P ₄)
#1	N/A	N/A	106	Pre-receptive	Repeat endometrial biopsy	154 ± 3
#2	42	42	194	Post-receptive	Repeat endometrial biopsy	170 ± 3
#3	38	80	170	Post-receptive	Perform embryo transfer	146 ± 3
#4	33	113	148	Receptive	Perform embryo transfer	148 ± 3

N/A not applicable, P₄ progesterone

ERA test than others? Some of the issues with the ERA include that it is expensive and there is limited ability for independent centers to study outcomes. Therefore, there may be a bias in the ERA literature presently available.

Perhaps independent groups should be able to perform studies on the ERA test. Although this study is based on a single patient, the lack of consistency is intriguing. Hopefully, this report may lead to more researchers without a direct financial benefit to publish their experience with the ERA test.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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