Case Report
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# Inconsistencies between endometrial receptivity assay and Adhesio-RT test for the window of implantation in women with repetitive failed donor oocyte embryo transfers

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Two commercially available second-generation endometrial receptivity assays using microarray analysis or next-generation sequencing are available in the market: endometrial receptivity assay (ERA) (Igenomix Laboratories) and Adhesio RT (OVO laboratories, Montreal, Canada). Little is known about how the results of these tests compare. We present a case of a subject with repetitive failed donor oocyte embryo transfer, who underwent evaluation of endometrial receptivity using both the Adhesio and ERA tests. These two tests did not provide consistent results, with ERA suggesting receptivity on day 5 of progesterone treatment and Adhesio suggesting receptivity on the eighth day. An ERA test subsequently performed on the eighth day of progesterone treatment was suggestive of post-receptive endometrium during the same time frame that Adhesio was suggestive of receptive endometrium. In conclusion, it is important to note that these two tests may not provide consistent results in at least some subjects. Therefore, intertest validity studies are recommended.

**Keywords:** Endometrium; Embryo implantation; Reproducibility of results

## Introduction

Commercially available endometrial receptivity tests offer detection of treatable and previously undiagnosed causes of implantation failure when a shifted window of implantation (WOI) is present. Evaluation of endometrial receptivity may be helpful in women with recurrent implantation failure [1,2], which is the current indication of the ERA test.

Several tests are available for endometrial receptivity testing and include 1st generation tests that test for the presence of a single protein including β2-integrin, and second generation tests that use microarray analysis or next generation sequencing. At least three second-generation tests exist, including the ERA tests (Igenomix Corporation, Valencia, Spain), which test for the expression of 248 genes, and the Adhesio-RT (OVO laboratories, Montréal, Canada), which tests for the expression of 10 genes. A third second-generation test, the WOI (WIN-test [Samir Hammamah], France) is also commercially available. However, in patients who present recently, the question of inter-test validity of these two second-generation endometrial receptivity analyses is raised.

## Case report

A 29-year-old woman who had undergone surgical removal

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of the ovaries at the age of three years for malignancy presented after failing four egg donor transfer cycles. She believed that the malignancy was lymphoma of the ovaries but was not entirely sure, and pathology reports were unavailable since this had occurred in Lebanon. The male partner was 41 years old without medical issues and had a semen analysis of 3.2 mL, with 49.2 million sperm per mL, 72% forward motility, and 1% normal forms, according to strict morphology. After the third failed transfer, she underwent an estrogen and progesterone mock cycle and two biopsies for Adhesio. As per the Adhesio protocol, biopsies were performed at six and eight days of progesterone administration. This test determined a delayed WOI, which was receptive after eight days of progesterone treatment. Adhesio presented the levels of messenger RNA expression at the time of each biopsy, which was about 90% of the control level on day 8 and less than 40% of the control level on day 6, in this patient's case. She underwent embryo transfer subsequent to the biopsy, with transfer on the 8th day of progesterone, and it failed. The patient was then transferred to our clinic. Upon presentation, she was recommended to undergo her first ERA test. This test was performed at 100 hours of progesterone in an estrogen-primed mock cycle, giving a WOI of 124±3 hours. Not feeling comfortable transferring at 124-hours of progesterone, given the conflicting results between the two tests, she requested that we repeat the ERA test with biopsies at both 124±3 hours and 192 hours (8 days×24-hours) to coincide with the WOI timing suggested by both the previous ERA and Adhesio tests. Performing the ERA tests at the time of the suggested WOI and not at 120 hours, as suggested by the company, should confirm the previously recommended WOI. This second ERA included a biopsy performed at 126 hours of progesterone treatment and demonstrated a WOI of 126±3 hours in July 2018. The third ERA biopsy performed in the same mock cycles as the second ERA was read as post-receptive based on a biopsy at 195 hours of progesterone. For the three ERA tests and Adhesio, the patient received the same dose and type of progesterone. Blastocyst transfer was subsequently performed at 126 hours of progesterone and it also failed.

## Discussion

Clearly, these two tests did not yield congruent results relative to the WOI. The WOI may vary in some women from cycle to cycle. Two articles published the results of ERA testing in 2 patients, which demonstrated significant inter-cycle variability [3,4]. Nevertheless, it is likely that many women show consistent results when tested, given the experience with pregnancy rates after embryo transfer timed to ERA. However, the rate of consistency is unknown and requires a large study with several biopsies performed in the same women in different cycles. One case report recently suggested that the response to progesterone in women undergoing evaluation of endometrial receptivity may be more complex than duration alone [5]. A woman who had a didelphic uterus demonstrated both a right hemi uterus that was receptive, and a left hemi uterus that was unreceptive, on evaluation in the same time period with two concurrent biopsies by the ERA test [5]. It is therefore possible that the proximity of vaginal progesterone to the organ in question may play a role in endometrial receptivity.

It is possible that the patient's WOI shifted in the case of the 29-year-old discussed in the case highlighted in our report. However, this is unlikely since the second ERA test gave results consistent with the first, suggesting that this patient's WOI was stable. The error could lie with either ERA or Adhesio-RT. However, given the many pregnancies reported at a high rate with the ERA test in the literature and 8 days being an exaggerated WOI, we question the results of Adhesio in this case. Being unfamiliar with Adhesio, it is possible that the Adhesio biopsy should have been performed on the 8th day of progesterone treatment (equivalent to 7.5 days or 180 hours) or about 12 hours earlier than it was performed. Clearly, moving the biopsy 12 hours earlier would not have generated receptive results with the given WOI of 126 hours, as determined by the ERA test, in the same mock cycle. Without a doubt, it would be better to investigate this finding as part of a large study and not as a single case. Such a study would demonstrate non-consistent rates; however, with this report, we can only document that irregularities between tests occur. It is unlikely that such a study would be undertaken by either Igenomix or OVO labs, since results may interfere with their interests. For a non-affiliated researcher to perform such a study, approximately 100 patients and significant expenses would be required (about 200,000.00 CND); therefore, it is unlikely to occur. As such, a report is the only option to discuss this issue. There are multiple reasons why these two tests yield conflicting results. A review

by Messaoudi et al. [6] suggested that multiple factors can result in discrepancies between different commercial and experimental evaluations of endometrial receptivity, which have been used to determine those endometrial gene expressions that are important for implantation. These reasons included evaluation in natural cycles or stimulated cycles (with human chorionic gonadotropin trigger), size of the patient cohort studied, age of the patients, geographic location or ethnicity of the patients, type of DNA microarray used particularly if they contained different genomic information, statistical and bioinformatic methodologies applied, and whether the samples were obtained serially in the same patient or compared from different patients at different stages of the luteal phase [6]. In conclusion, it is important to note that ERA and Adhesio-RT may not provide consistent results in at least some subjects.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

## Ethical approval

This study require approval of the Institutional Review Board because no patient data is contained in this article. The study was performed in accordance with the principles of the Declaration of Helsinki.

## Patient consent

The patient consented to this publication.

## Funding information

None.

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