Endometrial receptivity: miRNAs signing in?

Embryo implantation is complex and dependent on various factors in order to be successful. These factors include female age, embryo quality and chromosome constitution, endometrial receptivity, the female immune system status, and the embryo transfer method. Repeated implantation failure (RIF) generally is defined as the failure of a couple to conceive after the transfer of ≥ 10 good-quality embryos or after three in vitro fertilization (IVF) cycles. The interaction between the blastocyst and endometrium is critical for a pregnancy to be established and maintained. This interaction occurs during what is known as the window of implantation (WOI), which is a narrow time frame of maximal endometrial receptivity (reviewed by Craciunas et al. [1]). In recent years, several approaches have been developed and used clinically as biomarkers of endometrial receptivity and the WOI. Examples include endometrial thickness and pattern, Doppler indices, and the identification of patterns of endometrial gene expression considered to be representative of its receptive status (1). Another such group of potentially clinically useful biomarkers are microRNAs (miRNAs) which have been shown to be involved in the regulation of the genes responsible for the WOI timing (reviewed by Chen et al. [2]).

In their investigation, Chen et al. (2) used a novel custom-designed multigene expression profiling platform called PanelChip to assess the potential usefulness of miRNAs as biomarkers of endometrial receptivity and the WOI. The platform was based on the use of quantitative real-time polymerase chain reaction. Endometrial biopsies were collected from a relatively small (n = 36) group of infertile women. Most samples from these biopsies underwent analysis to determine endometrial receptivity via a commercially available test (Endometrial Receptivity Analysis [ERA]; Igenomix, Miami, FL). What the investigators characterized as "residual endometrial tissues" underwent analysis using the PanelChip platform. Of the women included in the study, only very few (13/36, 36%) were undergoing IVF treatment because of RIF, while most (23/36, 64%) were classified as the control group. The control group of women had been able to establish implantation after their first embryo transfer cycle. It also should be noted that the investigators determined RIF differently from the conventional definition and included women who had had two previous failed IVF attempts, instead of three, in the RIF study group.

The use of the PanelChip assay identified six miRNAs, namely hsa-miR-155-5p, hsa-miR-20b-5p, hsa-miR-330-5p, hsa200 miR-718, hsa-miR-940, and hsa-miR-144-3p, expressed differentially between the RIF (n = 8) and control (n = 17) groups of women. These results were in agreement with those obtained via the ERA test. In other words, both tests showed a distinct endometrial expression pattern between the RIF and control groups of women. Further data analysis and method validation on a new group of control (n = 6) and RIF (n = 5) women reduced the number of identified miRNAs to three. Therefore, the investigators concluded that hsa-miR-155-5p, hsa-20b-5p, and hsa-miR-718 miRNAs could most accurately provide a molecular signature to describe RIF. These findings are, indeed, intriguing and potentially demonstrate an active role of miRNAs in regulating the WOI timing. However, the number of analyzed RIF biopsies was small, and the study itself examined patients undergoing treatment in a single IVF clinic, rather than in multiple clinics. The usefulness of the identified miRNAs would have been more evident if they were found to be common among larger groups of women being treated for RIF in several IVF clinics.

Studies that aspire to develop clinically useful biomarkers for prognostic and diagnostic purposes require highly selected and targeted patient cohorts that can act as training sets for algorithmic selection and as validation in either the control or test cohorts. Deciphering these appropriate cohorts in human reproductive studies usually is very difficult as there are several factors or variables to be considered. With this in mind, future directions could include establishing standardized training and validation datasets that can be applied to multiple research projects relating to biomarkers of RIF, as individual patient variability and small patient cohorts risk leading to transient and not reproducible conclusions (3). Standardization is especially crucial in the study of miRNAs, as their transient and regulatory nature implies that variability in their levels will exist in the same patient depending on the timing of sample collection, and within patient cohorts as their hormone responses and genomes will vary significantly. The function of miRNAs in reproduction is complex. This probably is the reason why Chen et al. (2) were not able to establish many common miRNAs with other studies as they point out in their investigation.

Currently, the ERA test is the one that has been used most widely to predict endometrial receptivity (4, 5). Studies using this test and performing a personalized embryo transfer (pET), according to its results generally have reported positive clinical outcomes. One of these studies determined that women with RIF have a higher rate of nonreceptive endometrium (26%) when compared with women without RIF (12%). These findings are echoed in the study of Chen et al. (2). Moreover, a recently published multicenter randomized controlled trial (RCT) examining the clinical effectiveness of pET after the ERA test, reported a statistically significant improvement in outcomes, such as pregnancy, implantation, and cumulative live birth rates, when pET took place, compared with frozen and fresh embryo transfers. These results are encouraging and further illustrate the value of predicting endometrial receptivity during IVF. It is of note, however, that the patient dropout rate for this RCT was higher than what was expected initially.

It is evident from published studies that one of the main causes of RIF is issues with endometrial receptivity and the timing of the WOI. These findings were confirmed further in the investigation performed by Chen et al. (2), who identified three miRNAs that could provide an endometrial signature for RIF with an accuracy of approximately 91%. MicroRNAs have been identified previously as potentially useful biomarkers of, for example, embryo viability, but there was a lack of consensus in the identified miRNA molecules among different studies. The results in the investigation by Chen et al. (2) are

fascinating. However, the three miRNAs determined to be possible RIF endometrial biomarkers will need to be verified further in larger groups of patients, having treatment in multiple IVF clinics, and in an RCT setting to clearly determine their clinical value and ability to predict RIF and endometrial receptivity.

Elpida Fragouli, Ph.D.[a]
Anna Mantzouratou, Ph.D.[b]

[a] Nuffield Department of Women's and Reproductive Health, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom; and [b] Department of Life and Environmental Sciences, Bournemouth University, Bournemouth, United Kingdom

https://doi.org/10.1016/j.fertnstert.2021.05.070

You can discuss this article with its authors and other readers at
https://www.fertstertdialog.com/posts/32991

REFERENCES

1. Craciunas L, Gallos I, Chu J, Bourne T, Quenby S, Brosens JJ, et al. Conventional and modern markers of endometrial receptivity: a systematic review and meta-analysis. Hum Reprod Update 2019;25:202–23.
2. Chen CH, Lu F, Yang WJ, Yang PE, Chen WM, Kang ST, et al. A novel platform for discovery of differentially expressed microRNAs in patients with repeated implantation failure. Fertil Steril. 2021;116:181–8.
3. Cozzolino M, Díaz-Gimeno P, Pellicer A, Garrido N. Evaluation of the endometrial receptivity assay and the preimplantation genetic test for aneuploidy in overcoming recurrent implantation failure. J Assist Reprod Genet 2020;37:2989–97.
4. Ruiz-Alonso M, Blesa D, Díaz-Gimeno P, Gomez E, Fernandez-Sanchez M, Carranza F, et al. The endometrial receptivity array for diagnosis and personalized embryo transfer as a treatment for patients with repeated implantation failure. Fertil Steril 2013;100:818–24.
5. Simón C, Gómez C, Cabanillas S, Vladimirov I, Castillón G, Giles J, et al. A 5-year multicentre randomized controlled trial comparing personalized, frozen and fresh blastocyst transfer in IVF. Reprod Biomed Online 2020;41:402–15.