Endometrial receptivity screening in the general assisted reproductive technology population

The article by Riestenberg et al. (1) details a prospective cohort study assessing the value of the endometrial receptivity assay (ERA) in screening a general assisted reproductive technology (ART) population. This is an important contemporary question as clinicians seek to optimize every aspect of the ART process to enhance their patient's outcomes.

The ERA was originally studied in the setting of patients with recurrent Implantation failure (RIF). The test evaluated the profiles of the endometrial transcriptome and concluded that with the use of a limited number of transcripts ($n = 248$), it is possible to define a unique profile for each day, and now possibly half-days surrounding the window of implantation. The investigators who developed this diagnostic tool applied the test to women with RIF and demonstrated that the endometrial transcriptomic profile was either significantly advanced or delayed in these women (2). They suggested that the timing of transfer could be "personalized" in these individuals to assure that the embryo transfer occurred while the endometrium was optimally receptive.

The prospective cohort study by Riestenberg et al. (1) evaluated a much broader population. This was done by offering all ART patients the opportunity to perform the ERA before their first euploid transfer cycle. This nonrandomized design limits the interpretation of the study because of potential selection bias when determining who gets screened, but the investigators did a good job of controlling for many variables that impact clinical outcomes. For example, the ERA group was 2 years older, but at these ages the addition of aneuploidy screening effectively negates the impact of reproductive aging.

In the end, a detailed and thoughtful analysis reaches a very simple and direct conclusion. The ERA has no value in screening the general ART population. Such a finding is not a surprise. The reality is that using any diagnostic screening tests in populations where the prevalence of the actual disorder is low is prone to error.

A recent seminal contribution by Pirtea et al. (3) demonstrates that RIF occurs in approximately 7% of women. If 30% of these were to have abnormal advancement or delay in the window of transfer, that would mean a prevalence of approximately 2% in the general population. Even if the sensitivity and specificity were 90%, the very substantial majority of abnormal results would be false positives.

In theory, it could be argued that a patient would not need to be adversely impacted severely enough to result in RIF, and that there still might be a difference in sustained implantation rates. Stated otherwise, implantation rates could be reduced, but not so severely that women would have ≥ 3 consecutive failures. In fact, that is really the question addressed in this manuscript and the answer is quite clear – the test has no clinical value in screening the general ART population.

The data from this study are important in several other ways. The prevalence of abnormal was astoundingly high at 59%. While that included some whose window of receptivity may have shifted as little as 12 hours (24% of screened population), that still was a basis for altering the timing of transfer relative to progesterone exposure to provided "personalized" care. Given the implantation rates enjoyed by many groups without employing the test, it is exceedingly improbable that 59% of the population could be meaningfully impaired. The prevalence of abnormal was higher in the study cohort than in some prior publications, but the diagnostic test was performed by the same group that developed the ERA and should represent the gold standard for testing at this time. That means that the results are unlikely to be a result of technical problems with the assay and leads the reader to conclude that the prevalence of abnormal test results is genuinely high. The question then becomes whether or not those test results actually prognosticate an adverse outcome in the general ART population. The results of Riestenberg et al. (1) clearly show that ERA results are not meaningful in that setting.

The investigators have been very careful in interpreting their data. They did not assert findings that were not directly part of their study. However, as professionals performing ART, it is important to consider how these findings might alter our understanding of the physiology of the endometrial transcriptome (as gauged by the ERA) and receptivity.

The ERA is an interesting diagnostic test as it presumes to provide insight to the mechanism of impaired receptivity – a literal shift in the time when the endometrium is receptive. The data reported by Riestenberg et al. (1) challenge that assumption. If the window of receptivity were abnormal and went uncorrected, as would have been the case in approximately 59% of the women in the unstudied (control) group, the resulting embryonic endometrial dyssynchrony would inevitably lower implantation rates. It would not matter if the patient has a diagnosis of RIF; the reality is that if the timing of endometrial receptivity and the ability of the embryo to implant are misaligned, then an increased risk for implantation failure would occur. No decrease was observed. Thus, the premise that the ERA provides insight into the mechanism and that such information should direct personalized clinical care is in doubt.

These findings do not mean that an abnormal ERA result could not be a valid marker in women with RIF. It simply means that at best it is a marker of impaired receptivity in that population. However, even within the RIF population there is considerable debate as to the predictive value of the test. The company-sponsored study had marginal results with abandonment of the original research plan and sample size (4). The final study found no benefit to personalized transfer as directed by ERA results after the first transfer. A small difference was identified cumulatively through a year of care. Even those results have been criticized (5). Clearly, this important topic merits additional investigation. Among the studies needed would be a prospective blinded study where the results are withheld until after the treatment cycle. This would demonstrate the actual sustained implantation

rates for patients with varying degrees of prereceptivity or postreceptivity. Such a nonselection study would be most powerful and essential to determine if the test predicts anything.

For now, the study by Riestenberg et al. (1) provides a high level of confidence that the test should not be applied to the general population. Well-intended clinicians always seeking to find better ways to enhance outcomes for their patients should resist the temptation to apply this or similar diagnostic tests until well-done validation studies demonstrate how best to use them and the magnitude of improved outcomes that should be expected are available.

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