Variations in the endometrial receptivity assay (ERA) may actually represent test error

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We previously presented a case of a patient who had significant variations in the results of the ERA test. On multiple biopsies performed over several months, her results demonstrated receptivity at 154 ± 3 h, 170 ± 3 h, 146 ± 3 h, and 148 ± 3 h, in that order [1]. This case raised the question if some patients have variations in their results with the ERA month to month. In response to this case, Stankewicz et al. from Igenomix wrote a response [2]. They stated that the finding in our first case represents issues with compliance and actually demonstrated the consistency of the ERA test. They argued that issues came up because the first biopsy was performed after only 106 h of progesterone exposure (among others issues) when “It is recommended to all clinicians that the first endometrial biopsy should be obtained after 120 h of progesterone administration” [2]. They go on to argue that “It should be noted that the WOI duration varies from 12 to 48 h, depending on each patient. An ERA result indicates that the endometrium is receptive at a specific moment of the cycle (with a time frame of ± 3 h), but it does not define the total length of the WOI” [2]. This would suggest that the variations seen in our previous patient results were due to a subject with around a 48-h window of implantation (WOI). This could be true, although we do not actually know the duration of the WOI of the patient in the first case, and it equally may not be true. However, a recent second case has come to our attention which has us questioning the conclusions by Stankewicz et al. A 38-year-old woman with 6 years of primary infertility who had undergone two embryo transfers of euploid blastocysts with a chemical pregnancy and a blighted ovum as the result underwent an ERA test. The first ERA was performed after 121 h of progesterone. The result was pre-receptive, with

receptivity or re-biopsy suggested at 145 ± 3 h. A second biopsy was then performed after 146 h of the same dose and type of progesterone. This ERA resulted in a diagnosis of early receptive endometrium and to perform a “transfer 12 h later than the time at which the endometrial biopsy was performed.” Clearly, these two results are inconsistent. They were performed as the test recommended. Anyone who does an ERA test realizes that, occasionally, early receptive results occur. Given the recommendation of transferring 12 h later, it is clear that an early receptive and a mid-receptive endometrium demonstrate significant difference and may even impact outcomes. Igenomix argues that “the implantation window does not vary within an individual once it has been identified, lasting this way for up to at least 40 months” [3]. However, it is possible that some women have variation in the WOI, particularly because the reproducibility evidence in citation [3] was based on seven women.

When reading the letter by Stankewicz et al., they characterized the WOI with a figure. They represented early, middle, and late pre- and post-receptive periods. However, for the receptive (WOI) period, they failed to include the early and late phases of this window, which clearly exist. These are important diagnoses since when occurring Igenomix request that you transfer 12 h distant from these phases. It was slightly deceiving in citation [2] to not include these periods (early and late) of the WOI in the figure, representing it as equal for the entire duration. As for the 38-year-old patient, she underwent two more embryo transfers after 158 h of progesterone with euploid blastocysts, both resulted in miscarriages.

We do not believe that the ERA is a bad test. We have used it in about 20 women where they had unexplained failed embryo transfers, and a WOI that was distant from the period we were transferring the embryo: on correcting the duration of progesterone most conceived and at a much higher rate than reported in the literature, which was written by the IVI group. However, when combined, both cases we have written suggest it is possible that, in some women, the ERA test delivers an erroneous result, possibly due to variation in the WOI. In the

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case of the 38-year-old, the expectation of a receptive endometrium at 145 h based on a biopsy done on the duration of progesterone recommended is inconsistent with the finding of an early receptive endometrium.

We wish to address several questions or issues related to this second case. It may be argued that a second biopsy was recommended after the first to be performed at 145 h due to uncertainty in the results. However, as of the last 6 months, Igenomix has stated that one biopsy is sufficient to perform embryo transfer after the ERA test, which has been sufficiently validated given data submitted over time. Therefore, the 145 ± 3 h recommendation should have returned as receptive, which it did not. Please note: these ERA tests were performed more than 8 months ago, and recently came to our attention. The lack of need for a second biopsy can also be determined by what was written in the Stankewicz article where they stated “Instead of performing the personalized ET based on this recommendation, the authors performed” another biopsy [2]. Again implying a repeat biopsy is not necessarily needed. It could be argued that an early receptive and a mid-receptive endometrium are equal. However, if this was the case, the

difference in the genetic profiles would not be able to be detected by the ERA test. In addition, it is unlikely that embryo transfer would be recommended 12 h later since pregnancy outcomes would be the same, which in reality is unlikely. In conclusion, this case clearly demonstrates inconsistencies in two ERA results in the same patient performed 4 months apart, both in 2017.

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