Inter-cycle consistency versus test compliance in endometrial receptivity analysis test

Tiffany Stankewicz¹ · Diana Valbuena² · Maria Ruiz-Alonso²

Received: 7 March 2018 / Accepted: 16 May 2018 / Published online: 26 May 2018
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We have reviewed, with interest, the letter by Cho et al. [1]. In this letter, the authors questioned the consistency of the diagnosis of the window of implantation (WOI) using the endometrial receptivity analysis (ERA) test in one patient through four different biopsies over four different months. After careful examination of the data provided by the authors in their letter, we feel the need to thank them for actually showing the consistency of ERA testing outcomes and prediction. In this case, the authors performed an ERA test in one patient and, after receiving the report with explicit instructions on how to proceed, instead performed the subsequent endometrial biopsy at a moment completely discordant from the original recommendation. Cho and co-authors conclude that the ERA test shows variability from month to month following various biopsies in one patient. Our conclusion, which we aim to set forth in this letter, is quite the contrary. According to our review of this case and the ERA concept, it illustrates how consistent ERA results are between different cycles within this patient and between different cycles as originally described [2].

It is recommended to all clinicians that the first endometrial biopsy should be obtained after 120 h of progesterone administration, because this is the optimal time frame where any displaced WOI will be identified. As any other sampling test requires special conditions (i.e., glucemia analysis requires a fasting period), ERA requires analysis to be performed in this time frame in order to interpret the results appropriately. In this case, the authors performed the first biopsy after 106 h of progesterone exposure, the ERA predictor recognized a pre-receptive endometrium, and the resultant report indicated that the personalized WOI for this patient was estimated to lie at

154 ± 3 h of progesterone administration (Fig. 1(A)). For this cycle, the report clearly suggested a confirmatory endometrial biopsy at the stated progesterone exposure timing to confirm receptivity as measured by the ERA test. Instead of obtaining the second biopsy following the recommendations, the second endometrial biopsy was performed after 194 h of progesterone exposure, a full 40 h later than suggested and outside the normal WOI in humans (Fig. 1(B)). The ERA predictor identified this second biopsy as post-receptive; however, as it was taken after so many hours of progesterone exposure, the report recommended another biopsy 24 h earlier because it was out of the normal range established to have an endometrial biopsy for ERA (P+3 to P+7). It is not a surprise that a pre-receptive endometrium became post-receptive during this time frame, as the duration of time between the first and second biopsies was 88 h (3 days and 16 h).

A third biopsy was then performed on this same patient after 170 h of progesterone exposure. Here, the ERA results again showed a post-receptive uterine lining; however, for this biopsy, the predictor recommended a personalized ET at 146 ± 3 h (Fig. 1(B)). Instead of performing the personalized ET based on this recommendation, the authors performed a fourth endometrial biopsy following 148 h of progesterone exposure. Here, the results of the third and fourth biopsies were consistent and, interestingly, match up quite nicely with the initial recommendation (Fig. 1(A)). During this particular ERA diagnostic case, we established a direct line of communication with the doctor leading the case.

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. Therefore, it is highly probable that if the recommendation given for the first ERA were followed, receptivity would have been confirmed following the second biopsy. Furthermore, it has been documented 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

✉ Maria Ruiz-Alonso
Maria.ruiz@igenomix.com

¹ ERA Department, Igenomix, Miami, USA

² ERA Department, Igenomix, Valencia, Spain

Fig. 1 Endometrial profiling based on ERA results. A) Igenomix initial prediction. B) Biopsies performed by Cho et al.

[2]. In addition, there are several cases in which patients have achieved a second pregnancy up to 3 years apart by following the same initial ERA recommendation used for the first pregnancy, again showing consistency of the detected WOI.

Independent publications by Hashimoto et al. [3], Mahajan [4], and Tan et al. [5] have demonstrated the clinical value of the ERA test in patients with implantation failure of endometrial origin.

Here, we present our case to suggest that Cho et al. have misinterpreted their own data and suggested that the ERA test is not accurate nor is it reproducible. We have pointed out a number of questionable clinical decisions made by the Cho team which led them to perform four different endometrial biopsies in one patient after receiving a recommendation for the best way forward in this case. Biopsies two, three, and four all corroborate our initial finding that the patient was receptive with approximately 150 h of progesterone exposure. The most important question that remains to be answered is whether this 44-year-old patient, presented in the Cho et al. letter, went on to achieve pregnancy following transfer of embryos in the predicted WOI.

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