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# Commentary on a recent published study on endometrial receptivity assessment

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**Abstract**

The application of virtual histology in determining endometrial receptivity has been effectively demonstrated in a recent publication. This commentary aims to elucidate previous research in this area and highlight the essential conditions for optimizing this technology.

On April 28, 2025, an interesting study by Min-bo Zhu et al. was published in *Reproductive Biology and Endocrinology* [1]. We commend Zhu et al. for their significant contribution to understanding endometrial receptivity (ER) as evidenced by images collected via hysteroscopy.

The success of assisted reproductive technology (ART) treatments is largely dependent on the quality of embryos and the ER, and their specific interaction. Traditionally, endometrial dating (ED) and ER have been assessed through methods such as patient's reports, hormonal levels, ultrasound examination, endometrial biopsy, and more recently, endometrial transcriptomics and proteomics [2]. However, these methods often lack accuracy and remain subjects of debate.

Zhu et al. referenced a prior study by Yang S. et al. [3], which utilized high-definition hysteroscopy to capture images of endometrial glands and employed an image recognition algorithm to analyze gland density and opening size in order to predict endometrial receptivity. They integrated two complementary methodologies by comparing the effectiveness of image recognition technology and pinopode detection in predicting implantation success. Given that pinopodes cannot be identified in vivo, our focus here will be on their analysis of gland images. The study involved identifying and counting the number of endometrial glands, as well as calculating the total number of pixels occupied by all glandular openings to determine their mean size, expressed in pixels, at an approximate constant tissue distance. The density of endometrial glands and the average size of the gland openings were greater in the pregnancy group compared to the non-pregnancy group [3]. The authors highlighted their quantitative methodology, contrasting it with previous studies that relied on subjective evaluations of endometrial morphology through visual assessments of vessel distribution and glandular opening size. Their research employed image recognition technology, providing an objective alternative.

We wish to highlight several limitations of this study, which do not diminish its significance. Zhu et al. divided their cohort into only two groups. This broad categorization limits the ability to: (a) further investigate whether the statistical parameters they used have a cutoff or are continuous, specifically regarding the parameter *distribution* within each group, and (b) trace the evolutionary trajectory of the two parameters throughout the cycle. The latter limitation hinders the determination of the

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optimal timing for embryo transfer based on endometrial course prediction.

Furthermore, the real-time application of this method on the actual transfer day inherently limits the ability to compare it with the gold standard of histology or other non-real-time techniques such as transcriptomics.

These constraints likely stem from the authors' decision to focus on only two features, despite the availability of numerous additional options. It is well recognized that additional tissue elements and gland features undergo changes during the cycle. Furthermore, it is crucial to consider the homogeneity of the two-parameter distribution across the endometrial tissue. As the authors correctly note, the study has so far concentrated on the fundus. Identifying inhomogeneities could reveal pathological regions that may alter the statistics of these two parameters, yet could also aid in different diagnoses. Addressing this issue may involve incorporating a broader range of tissue elements and features.

Fortunately, since the image recognition algorithm was consistently applied across all cases, the lack of a detailed description does not compromise the study's results.

In 2019–2021, we addressed the issue of ED and conducted two studies demonstrating how the advent of computerized virtual histology introduces a novel ED method. Magnified images of ex-vivo endometrial tissue samples, collected at various cycle days, were analyzed using computerized image analysis with statistical representation of tissue features, enabled the mathematical calculation of the cycle day [4, 5]. During this study approximately one thousand images were captured from all participants and days. Computer vision algorithm was employed to identify pores (gland outlets) and blood vessels (BVs) on the captured images of the ex-vivo tissue that originally faced the lumen. Various attributes of these features, such as diameter, shape, and rim contour, were calculated. For each feature, we compiled its complete probability distribution, in which the average represents only a single moment. Additionally, we calculated densities and filling factors. We then compared histology-based ED, serum hormone levels on the collection day, and patient reports with our novel method of ED during the endometrial secretory phase.

In the study concerning endometrial gland pores [4], the correlation coefficient between traditional histology ED and the new method was high and statistically significant. In the study regarding the uterine vessel network [5], we observed a systematic and consistent trend in vessel diameter distribution at different tissue depths, demonstrating that the magnitude of this trend evolves throughout the endometrial cycle.

By the end of 2023, we concluded an in-vivo trial using a newly designed mini-hysteroscope, specifically developed to capture high-resolution images and video clips that can provide an in-vivo morphological view of the endometrium. Following the analysis of several hundred images that were captured from all participants and days, we successfully traced the endometrial evolution throughout its cycle. The results from our ED algorithms again demonstrated a highly significant correlation with other, more traditional ED markers. For a single patient on a specific calendar day, we could accurately determine the cycle day of the uterus (e.g., ED). Clinically, performing hysteroscopy using our new system calls for only a few captured images with a less than 5 min procedure.

Zhu et al. concluded that the integration of high-definition hysteroscopy with image recognition technology provides a promising, non-invasive alternative for the evaluation of ER. However, those results were based on only two gland-related parameters. Conversely, we retain that new technologies should use multiple parameters of ER, related not only to the gland pores but to the BVs as well, allowing for a more nuanced analysis beyond a simple binary distinction.

We totally support the authors' conclusion about the virtual ER assessment through hysteroscopic approach. This new technology is a safe and potentially effective method for studying in real-time and in-vivo the ER. Moreover, the technique needs to be standardized and the algorithms should be custom-designed, considering the characteristics of image acquisition and the features of the hysteroscope. In the next future, its use in the clinical setting could predict the optimal timing for embryo transfer in IVF treatments reducing medical costs and enhancing the success rates of the ARTs.

#### Authors' contributions

Y.O. ; I.TK and T.K. contributed to the manuscript preparation and final review.

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#### Data availability

No datasets were generated or analysed during the current study.

## Declarations

#### Ethics approval and consent to participate

Not applicable.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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