



Precise Assessment of Endometrial Receptivity: Microengineered Endometrial Chip Model Combined With The Endometrial Receptivity Scoring System*

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Abstract The establishment of endometrial receptivity is a critical prerequisite for successful embryo implantation and early pregnancy. However, current clinical methods for assessing receptivity are insufficiently validated, and their reliability is inadequate for guiding precision medicine. Although microfluidic organ-on-a-chip models have emerged as promising *in vitro* platforms garnering significant academic interest, their practical clinical translation has been hindered by challenges in accurately replicating patient-specific microenvironments and the lack of standardized quantitative evaluation systems. Recently, Lee *et al.* published a groundbreaking study in *Nature Communications*, which effectively addresses these critical limitations by integrating a patient-derived vascularized endometrium-on-a-chip (EoC) with a newly developed endometrial receptivity scoring system (ERS²). This commentary offers a comprehensive analysis of the key findings from this work, systematically examining the design, construction, dynamic simulation validation, and translational potential of the EoC-ERS² platform. This innovative approach successfully transforms conventional subjective assessments of endometrial receptivity into a digitized, objective, and quantitative evaluation framework. As a result, it establishes a robust foundation for a paradigm shift toward personalized infertility management and precision medicine in reproductive health.

Key words endometrial receptivity, embryo implantation, 3D microfluidics, precision medicine

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Embryo implantation is a key event in establishing a successful pregnancy, relying on three core factors: a receptive endometrium^[1], a developmentally competent blastocyst-stage embryo, and precisely synchronized interactions between maternal and embryonic tissues^[2]. However, successfully achieving normal embryo implantation remains challenging due to various genetic and environmental influences^[3], making assisted reproductive technology (ART) essential for overcoming these obstacles^[4]. Through ART, a high-quality embryo can be transferred into a receptive endometrium, which requires strict temporal alignment between the embryo and maternal endometrium during the “window of implantation (WOI)”^[5]. The success of ART is fundamentally dependent on endometrial homeostasis^[6]. Currently, clinical evaluations of the endometrial state often rely on methods such as endometrial thickness measurement^[7], endometrial pattern assessment^[8],

endometrial receptivity array (ERA) testing^[9], endometrial blood flow measurement, and uterine artery Doppler ultrasound assessment^[10]. However, these methods heavily depend on clinicians' subjective judgment and fail to fully capture the dynamic, real-time changes within the endometrial environment, as well as the phenotypic interactions between blood vessels and endometrial epithelial and stromal cells. Consequently, accurately identifying a receptive endometrium remains a significant challenge in ART.

Recently, a study by Lee *et al.*^[11] marked a breakthrough in personalized translational treatment

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for infertility. By obtaining real patient biopsy samples and integrating them with three dimensional (3D) microfluidic technology, the team developed a microengineered endometrium-on-a-chip (EoC) model combined with an endometrial receptivity scoring system (ERS²). This innovative model faithfully recreates the endometrial microenvironment and effectively captures the spatiotemporal dynamic changes necessary for *in vivo* endometrial function, providing a novel approach for personalized endometrial receptivity testing.

1 Endometrium-on-a-chip

3D organoids and co-culture platforms have emerged as groundbreaking tools for studying human placentation, implantation, and endometrial activity, effectively addressing the limitations of animal models and two-dimensional (2D) *in vitro* experiments^[12-13]. Despite these advancements, existing models are limited by inadequate cellular heterogeneity, aberrant tissue polarity, and an inability to faithfully recapitulate vascular and immune dynamics^[14]. To accurately reconstruct the multi-layered and highly vascularized natural structure of the endometrium, researchers developed a microfluidic organ-on-a-chip containing three parallel microchannels. These channels were precisely populated with endometrial stromal cells, endothelial cells, and endometrial epithelial organoids derived directly from patient biopsy tissues, as shown in Figure 1. This design not only replicates the patient-specific microenvironment at the time of biopsy but also preserves the expression profiles of key native adhesion molecules, such as integrin $\alpha\beta3$ and osteopontin (OPN), at the molecular level^[15].

The natural endometrium is a dynamic organ that undergoes cyclical remodeling in response to fluctuations in female reproductive hormones. This

remodeling process encompasses the proliferative phase, the secretory phase, and menstrual shedding in non-pregnant states^[16]. To verify whether the chip could accurately reflect this hormone-regulated dynamic physiological process, Lee *et al.* performed model validation. The results demonstrated that the model effectively simulated the complex dynamic changes of endometrial tissue during the mouse estrous cycle. For example, in the endometrial chip simulating the “estrus phase”, extensive blood vessel formation and development were observed, aligning closely with the angiogenesis patterns found in natural tissue. Furthermore, chips constructed from cells harvested at different stages of the estrous cycle displayed expression patterns of key markers that closely mirrored levels found *in vivo*. After successfully replicating the cyclical physiological microenvironment of the endometrium, Lee *et al.* utilized this platform to explore key stages in the reproductive process. The chip effectively simulated core events occurring at the maternal-fetal interface, wherein the embryo (trophoblast cells) initially establishes stable adhesion with the endometrial epithelial cells through a network of signaling molecules, followed by its invasion of the epithelial barrier into the deeper stroma. By monitoring the area and volume of trophoblast invasion in real time, as well as tracking the morphological dynamics of surrounding stromal cells aggregating toward the embryo, the entire embryonic invasion process was documented. However, in simulating the human patient microenvironment, this model utilized biopsy samples collected on post-ovulation day 5, which did not replicate the dynamic fluctuations of estrogen and progesterone concentrations throughout the menstrual cycle. Additionally, the human umbilical vein endothelial cells (HUVECs) used in the model do not fully mimic the physiological characteristics of endometrial microvessels.

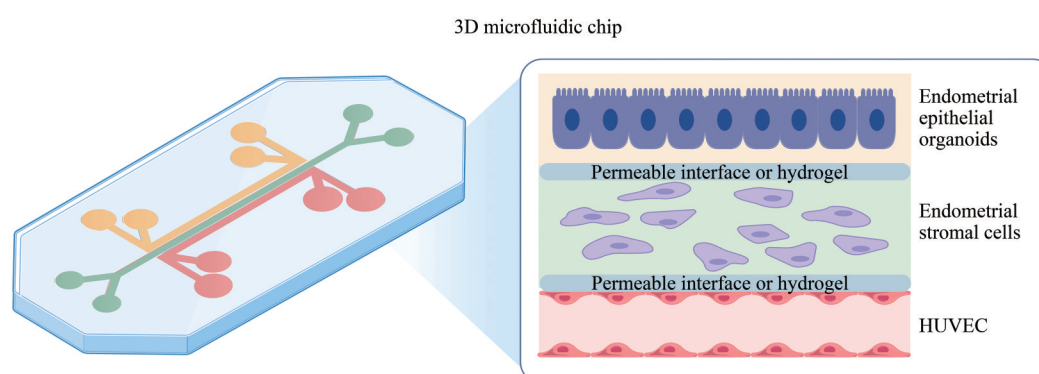


Fig. 1 3D microfluidic chip structure

HUVEC: human umbilical vein endothelial cell. Created with BioGDP.com^[17].

2 Endometrial receptivity scoring system

In recent years, multiple emerging technologies have been developed to enhance the accuracy of endometrial receptivity assessment. Within the realm of molecular diagnostics, beyond the well-established ERA, the novel rsERT—a WOI prediction tool composed of endometrial receptivity-specific marker genes screened *via* a combination of RNA sequencing and machine learning—has demonstrated improved accuracy in detecting subtle WOI shifts^[18]. In terms of non-invasive imaging, *in vivo* high-resolution photoacoustic endometrial imaging (PAE) can non-invasively capture the comprehensive microvascular network of the endometrium^[19]. Additionally, the combination of high-definition hysteroscopy with image recognition technology offers a promising non-invasive alternative for evaluating endometrial receptivity^[20]. However, these technologies still exhibit inherent blind spots in comprehensively analyzing the endometrial microenvironment. For instance, molecular testing tools like ERA and rsERT are unable to directly observe the spatial distribution of proteins and physiological functions such as angiogenesis^[21], while imaging technologies like PAE and high-definition hysteroscopy fall short of quantifying the expression of key receptivity-related molecular markers. To address these limitations, Lee *et al.* proposed a unique evaluation framework known as ERS², utilizing the EoC model for integrated qualitative and physiological assessment.

The ERS² framework is established on four core parameters: the expression intensity of integrin $\alpha\beta3$, the expression intensity of OPN, the total blood vessel area, and the angiogenic sprout area. Rather than defining a strict maximum score of 5 for each parameter, this system initially employs a calibration cohort of six patients with clinically normal endometrium, mapping the physiological expression range of healthy individuals to scores of 3–5, where a score of 5 corresponds to the upper physiological expression limit in healthy subjects. Raw quantitative values are not artificially capped; instead, scores are adjusted according to deviations from the normal range. The scoring criteria are as follows: a score of 1–2 indicates insufficient endometrial receptivity, a score of 3–5 indicates normal endometrial receptivity, and a score greater than 5 indicates an over-receptive state. The cumulative total score at the physiological upper limit for all four parameters is 20. A cumulative score ranging from 12 to 20 classifies the endometrium as being in the “receptive” window,

indicating a high probability of readiness for embryo implantation during IVF-ET procedures. Regarding clinical utility and economic cost, the process from biopsy cell extraction to the completion of the ERS² assessment typically requires approximately seven days. Furthermore, the system relies heavily on customized microfluidic chips, expensive Matrigel, multiple recombinant growth factors, and high-end confocal microscopes. Consequently, at its current stage, this platform is more suitable as a second-line precision screening tool for patients experiencing recurrent implantation failure (RIF) rather than as a first-line routine test. Retrospective clinical validation indicated that patients clinically diagnosed with a normal endometrium consistently scored between 13 and 15 on the chip and successfully achieved pregnancies. In contrast, patients with RIF or recurrent pregnancy loss (RPL) typically scored between 5 and 9, placing them in the “non-receptive” range and resulting in failures to achieve pregnancies in subsequent *in vitro* fertilization cycles. This scoring system effectively bridges macroscopic physiological manifestations with microscopic cellular and molecular mechanisms, significantly enhancing the accuracy of clinical outcome predictions (Figure 2). At present, the prediction of clinical outcomes using this scoring system primarily focuses on “clinical pregnancy outcome” and “IVF-ET outcome prediction”, with no follow-up data provided regarding “live birth” outcomes.

3 Specific therapeutic agents and efficacy monitoring

In addition to its precise evaluation of endometrial receptivity, the ERS² system based on the EoC model shows considerable potential for enhancing the diagnostic accuracy of various endometrial diseases. In an *in vitro* disease model utilizing cells from a patient with intrauterine adhesion (synechia), the research team assessed the therapeutic efficacy of three medications: C-X-C motif chemokine ligand 12 (CXCL12), human chorionic gonadotropin (hCG), and vitamin D3 (VitD3). The results indicated that CXCL12 achieved the highest ERS² score of 16, demonstrating optimal recovery of both angiogenesis and receptivity markers. hCG primarily improved integrin $\alpha\beta3$ expression, resulting in a score of 12, while VitD3 displayed a mild overall effect with a score of 15. The efficacy of CXCL12 was further validated in a murine model, where it significantly increased endometrial thickness and microvessel density, which were

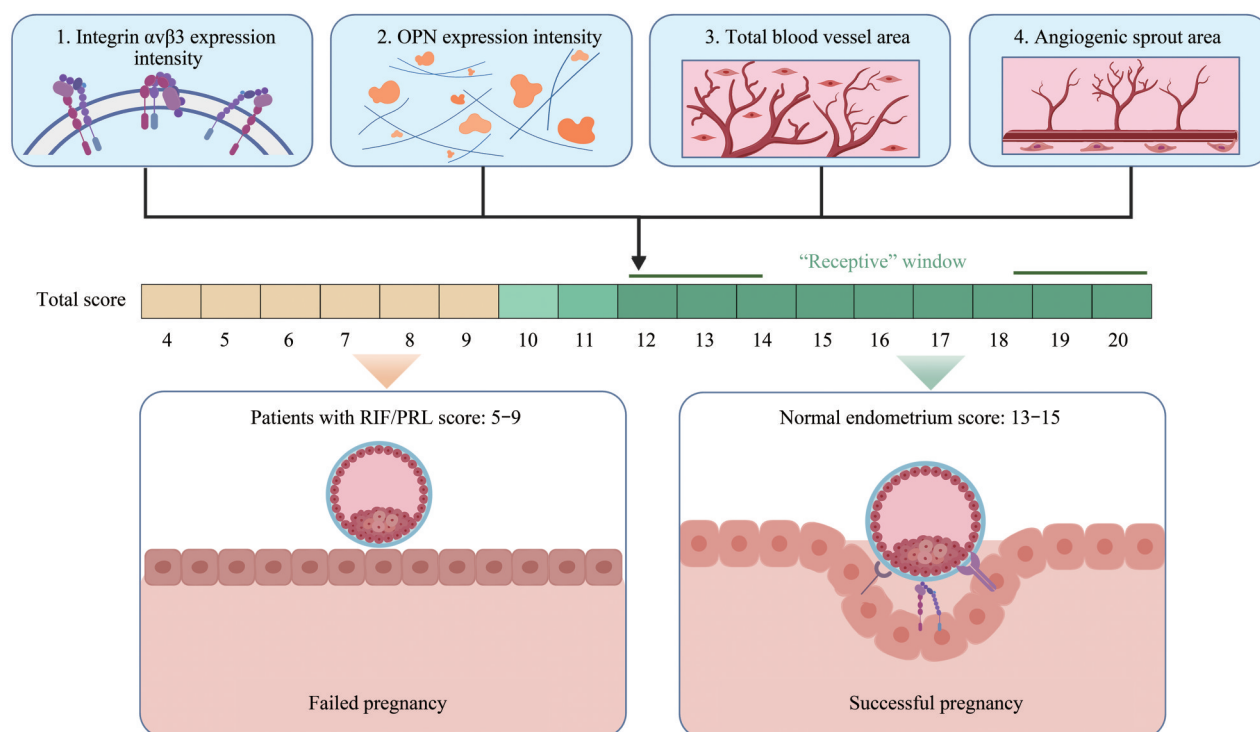


Fig. 2 Endometrial receptivity scoring system

OPN: osteopontin; RIF: recurrent implantation failure; RPL: recurrent pregnancy loss. Created with BioGDP.com^[17].

positively correlated with ERS² scores. Additionally, CXCL12 treatment notably enhanced embryo attachment and invasion depth in *in vitro* assays. Regarding drug dosages and administration routes, the EoC-ERS² system revealed that responses to each drug were dose-dependent and that therapeutic efficacy varied according to the route of administration.

For patients experiencing RPL, platelet-rich plasma (PRP) therapy is a common clinical intervention aimed at improving the endometrial microenvironment^[22]. In a case study involving a patient with RIF/RPL who received three consecutive PRP treatments, routine clinical ultrasound examinations consistently failed to detect any significant abnormalities in endometrial thickness or morphology. However, the EoC-ERS² system adeptly captured qualitative changes in the microenvironment, showing that, as the number of PRP treatments increased, the expression of integrin $\alpha v \beta 3$ and OPN, as well as the angiogenic area in the endometrium, steadily rose. Consequently, the ERS² score increased from an initial 6 to 16 following the third treatment. Notably, while this study demonstrated a correlation between improvements in ERS² scores and repairs to the endometrial microenvironment, it did not establish

a direct causal relationship between ERS² scores and the ultimate clinical endpoint—live birth rates. In this context, the term “successful pregnancy” refers to clinical pregnancies confirmed by the presence of an intrauterine gestational sac, while biochemical pregnancies, clinical pregnancies, and live births represent different stages, each with distinct clinical implications. Moreover, as a simplified *in vitro* model, the EoC system lacks a complete *in vivo* regulatory network, encompassing systemic circulation, immune cell infiltration, and neural innervation. Therefore, improvements in *in vitro* microenvironment scores cannot be directly equated with guaranteed success in achieving pregnancy *in vivo*, as highlighted by the patient’s subsequent clinical outcome being marked as “N/A”. Despite these limitations, the EoC-ERS² system remains a valuable complementary tool to conventional ultrasound. For patients with “ultrasound-normal” unexplained RIF/RPL, it can uncover hidden endometrial microenvironmental defects and dynamically monitor treatment responses at cellular and molecular levels. By providing quantified and visualized results, the system allows for an accurate assessment of the current endometrial microenvironment, thereby aiding clinicians in determining the optimal timing for embryo

implantation during *in vitro* fertilization and embryo transfer. This enhanced precision in timing is expected to significantly improve pregnancy outcomes while also instilling greater confidence in patients regarding the treatment process and the likelihood of successful embryo implantation.

4 Limitations and future perspectives

The EoC-ERS² platform demonstrates significant potential for clinical translation; however, its application is currently limited by several factors. First, the scoring system remains in the preliminary phase and requires extensive validation with data from larger, diverse cohorts of healthy individuals to establish standardized baselines. Second, reliance on specific biomarkers, including integrin $\alpha\beta 3$, OPN, and angiogenic features, may inadequately capture the complex nature of endometrial physiology. Future advancements should involve integrating real-time, non-invasive macroscopic imaging with the microscopic pathological profiling enabled by this microfluidic platform, alongside multidimensional biomarker assessments. This integration promises to foster a more robust and comprehensive closed-loop system for precision reproductive medicine.

5 Conclusion

The study by Lee *et al.* provides a critical conceptual and technical link between ART and the bioengineered endometrial microenvironment. This research developed a vascularized EoC that offers enhanced physiological biomimicry through HUVECs and introduced the quantitative evaluation framework, ERS². Future enhancements can be realized by substituting HUVECs with endometrium-derived endothelial cells. Transitioning from traditional subjective, morphology-based assessments to an objective, function-oriented approach addresses significant shortcomings of existing ultrasound and gene expression profiling methods in capturing microscale tissue dynamics. Moreover, this platform uniquely excels in accurately defining endometrial receptivity, identifying latent functional defects, and guiding patient-specific therapeutic strategies. Consequently, it establishes a new paradigm for personalized infertility treatment and precision medicine in reproductive health.

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子宫内膜容受性的精准评估: 微工程化子宫内膜 芯片模型联合子宫内膜容受性评分系统*

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摘要 子宫内膜容受性的建立是胚胎成功着床与早期妊娠的关键条件。然而, 目前评估接受度的临床方法尚未得到充分验证, 其可靠性尚不足以精准指导个体化医疗。尽管微流控器官芯片模型已成为具有前景的体外平台并获得学术界广泛关注, 但其临床实际转化因准确复制患者特定微环境的挑战以及缺乏标准化的定量评估系统而受阻。近期, Lee 等在 *Nature Communications* 发表了一项开创性研究, 通过将患者来源的血管化子宫内膜芯片 (EoC) 与新研发的子宫内膜容受性评分系统 (ERS²) 相结合, 有效解决了这些关键局限。本评论对该研究中的关键发现进行了全面剖析, 系统审视了 EoC-ERS² 平台的设计构建、动态模拟验证及其临床转化潜力。这一创新方法成功将传统上对子宫内膜容受性的主观评估转化为数字化、客观且量化的评价框架。因此, 它为向个性化不孕症管理和生殖健康精准医疗的范式转变奠定了坚实基础。

关键词 子宫内膜容受性, 胚胎着床, 3D微流控, 精准医疗

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