

Letter to the Editor

Re-thinking the window of implantation

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Shoham, Weissman and Gleicher¹ proposed an alternative conceptual framework for implantation, based on evidence from extrauterine pregnancies. They argue that implantation consists of two distinct stages: an initial phase of trophoblastic attachment requiring only minimal biological conditions, followed by a second phase in which decidualization becomes essential for sustained placentation and fetal development.

We propose a few modifications that may help in testing this view and its validity.

PROBABILISTIC WOI

Embryos transferred at different developmental stages may all implant successfully, despite variations in embryo–endometrial synchrony due to mismatch between the standard and the actual endometrial developmental stage.

We therefore propose that implantation should be described as a continuous probability function rather than binary. Its minimal description requires a functional form and at least two parameters: a central value and a variance. These may vary from cycle to cycle.

Such a model naturally explains:

- repeated implantation failure followed by spontaneous success
- differences in receptivity between women
- cycle-to-cycle variability within the same woman
- rising cumulative pregnancy rates with repeated euploid embryo transfer

Rather than searching for a single implantation day, research should quote implantation probability for each day.

SUFFICIENT OR NECESSARY?

Shoham et al.¹ proposed sufficient conditions for attachment: vascularity and mid-luteal progesterone exposure. We question whether these are *necessary* conditions that attachment fails in their absence. Both can be measured using virtual histology.

Measurable evidence for vascularity suggests optical identification of the vessels' plexus² and its evolution. Progesterone exposure can be measured through the glandular component, the first exposure-induced morphological evolution.³

ENDOMETRIOSIS AND LIMITED EVIDENCE

A central pillar of the two-stage model is the finding that the fallopian tube constitutively expresses integrin receptors without cyclical mid-luteal change. However, ectopic pregnancy is known to be linked to endometriosis while the constitutive-expression data is derived from fertile women with regular cycles rather than from women who went on to have an ectopic pregnancy.

The possibility that endometriosis-related changes alter extrauterine sites and generate cycle-dependency in some patient, cannot be excluded by the existing data.

VASCULARITY, PROGESTERONE, AND VASCULAR ARCHITECTURE AS A BOUNDARY CONDITION

Trophoblastic invasion remodels the maternal spiral arteries. We suggest that the initial vascular network functions as boundary conditions on which the trophoblast builds. Such pre-attachment architecture may shape the attachment probability, placental development and pregnancy course.

The pre-existing arterial plexus, may constrain how the trophoblast remodels maternal spiral arteries. Vascular parameters should therefore be measured before, during, and after the presumptive window.

FUTURE DIRECTIONS

Future studies should pay particular attention to:

- vascular architecture, measured longitudinally
- necessity of vascularity and luteal progesterone exposure for attachment

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- possible cycle-dependence of extrauterine biology in women with endometriosis
- immune microenvironment and its responsiveness to progesterone
- virtual histopathology predictive models, prospectively validated before clinical adoption

CONCLUSIONS

Measurements of physiological characteristics rather than molecular signatures may be an attractive solution. Virtual histopathology allows quantitative characterization of vascular and glandular change without relying exclusively on transcriptomic biomarkers.

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DATA AVAILABILITY STATEMENT

Data available upon reasonable request from tsafir@iyar.org.il.

CONFLICT OF INTEREST STATEMENT

Yuval Or is the Medical Director of Fertigo Medical where Tsafir Kolatt serves as the Chief Executive Officer. The company is developing quantitative image-based (“virtual

histology”) real-time assessment of endometrial features referenced in this opinion piece as a potential future research and clinical tool. This financial and professional relationship is disclosed in accordance with journal policy. The clinical and research directions discussed above, particularly regarding quantitative endometrial assessment, should be evaluated independently of the authors’ institutional interest in this technology.

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES

No Generative AI or AI-Assisted Technologies were utilized to write this contribution

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