

# Ultrasound in assisted reproduction: a call to fill the endometrial gap

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Ultrasound offers essential details and an overall view of the anatomic features of the reproductive organs, as well as physiologic assessment. There is still a great gap, however, in our understanding and interpretation of endometrial sonographic findings. Endometrial thickness, growth, and sonographic patterns have been repeatedly tested and compared with pregnancy rates in IVF cycles, yielding conflicting results. Generally, the data accrued so far suggest refraining from clinical decisions based solely on endometrial thickness. The three-layer ultrasound pattern reflects normal follicular/proliferative dynamics, and its presence in the pre-hCG period was reported to carry a better outcome: Significantly higher clinical pregnancy rates were found in patients with this pattern on the day of hCG administration among IVF cohorts. Subendometrial contractility (endometrial “waves”) offers a tool that can be used in cases of repeated implantation failure in patients reporting cramps around the planned time of embryo transfer, or as a reassuring modality to assess uterine quiescence during preparations for embryo transfer. We support the creation of an integrated endometrial score incorporating conservative endometrial measurements, endometrial-myometrial junction studies, and endometrial contractility, as well as new concepts that remain to be tested, such as endometrial surface area. Such scores may enable us to improve the effectiveness of endometrial ultrasound imaging in the clinical setting. (Fertil Steril® 2016; ■:■-■. ©2016 by American Society for Reproductive Medicine.)

**Key Words:** Endometrium, ultrasonography, ovarian follicle, artificial reproductive technologies

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It is hard to imagine reproductive medicine and management of various artificial reproductive technology (ART) protocols without the vast information and guidance provided by ultrasound imaging. Ultrasound offers essential details and comprehensive overall anatomic features of the reproductive organs as well as information for physiologic assessment. However, although we think that ultrasound application to follicular characterization and reproductive procedures is well established, there is still a great gap in the understanding and interpretation of endometrial sonographic findings. Therefore, here we focus our attention on endometrial evaluation while also reviewing the role of ultrasound in monitoring

follicular development and its use in clinical procedures related to ART.

## ENDOMETRIAL ASSESSMENT

When evaluating the endometrium in the context of assisted reproduction, we would ideally like to identify a receptive endometrium and predict the chances of successful implantation. We know that endometrial thickness is a biomarker for serum estrogen thickening as a response to increasing circulating estrogen levels. Yet, we must acknowledge that its function is more than its mere thickness. Many groups (1–5) have investigated molecular, proteomic, and genetic aspects of the endometrium in an effort to provide a defined profile that reflects the

implantation window, so far yielding interesting but not necessarily applicable findings. We think that sonographic patterns should be associated with molecular as well as microarchitectural characteristics of receptive endometrium and suggest an endometrial scoring system based on the following studied parameters.

## Endometrial Thickness and Patterns

Endometrial thickening and sonographic patterns have been repeatedly tested and compared with pregnancy rates in IVF cycles, yielding conflicting results either supporting (6–9) or dismissing (10–12) the ability of ultrasound. Intuitively, most clinicians would feel more comfortable and reassured by a thick endometrium accompanying ART treatment, and most authors would agree that thin endometrium, usually defined as endometrial thickness (EMT) <7 mm,

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is correlated with lower implantation rates; on the other hand, this does not imply a linear correlation between EMT and implantation rates, or a clear threshold for embryo implantation (9). A systematic review and meta-analysis was published in 2014 (13) supporting the limited capacity of endometrial measurement to predict conception in ART cycles (receiver operating characteristic curve analysis gave an area under the curve of 0.56). As a result, the authors suggested refraining from clinical decisions based solely on EMT measurement. At the same time, the meta-analysis presented significantly lower clinical pregnancy rates among women with EMT  $\leq 7$  mm (odds ratio 0.42, 95% confidence interval 0.27–0.67;  $P=.0003$ ). Another insight that should be emphasized from these data is the overall low incidence of  $<7$  mm endometrial thickness compared with the rate of failed implantation, so thin endometrium may explain implantation failure in a only a subset of patients. Integrating the specificity and sensitivity of the test with the prevalence of pregnancy/nonpregnancy status yielded the following positive and negative predictive values for clinical pregnancy: 77% and 48%, respectively. The clinical relevance is that once a sonogram detects an EMT of  $<7$  mm, the chances not to conceive were 77% (although confusing, a “positive” result in this context means a thin lining). This rate may seem high, but not compared with the baseline rate of non-conception of 50%–60%. Therefore, the thin endometrium increases the chance to end the cycle with no conception, but by no means eliminates it. As for the negative predictive value, when EMT  $>7$  mm (again, a “negative” result in this context), chances to conceive were 48%, somewhat increased compared with the background population. Different cutoff values of endometrial thickness were tested, demonstrating somewhat improved pregnancy rates up to a measured thickness of 10 mm.

Despite multiple studies and the recent meta-analysis, the issue of endometrial thickness remains unresolved, probably reflecting the need to reassess the clinician’s “gut feeling” that thicker is better (Fig. 1). As evidence, well established journals keep publishing studies dealing with the effect of endometrial thickness and supporting better pregnancy rates in a subgroup analysis of growing endometrial measurements during IVF cycles (9, 14). Other important support for the poor association between endometrial thickness and pregnancy prediction arises from acceptable pregnancy rates reported even with EMT  $<6$  mm: 28.5% (9) and 28.1%–31.5% (14). Another study supporting lack of association between EMT and implantation rates was published in 2015. In that study, only normal blastocyst transfers were included in the analysis (15) and EMT had no impact on implantation rates.

Data on endometrial patterns are equally contradictory. Endometrial patterns have been classified as an early follicular triple-line pattern consisting of a central hyperechoic line surrounded by two hypoechoic layers, an intermediate isoechogenic pattern with the same echogenicity as the surrounding myometrium and a central echogenic line in the periovulatory period, or homogeneous hyperechogenic endometrium in the luteal phase. The three-layer ultrasound pattern reflects normal follicular/proliferative dynamics (16): Its presence in the pre-hCG period was reported to pre-

FIGURE 1



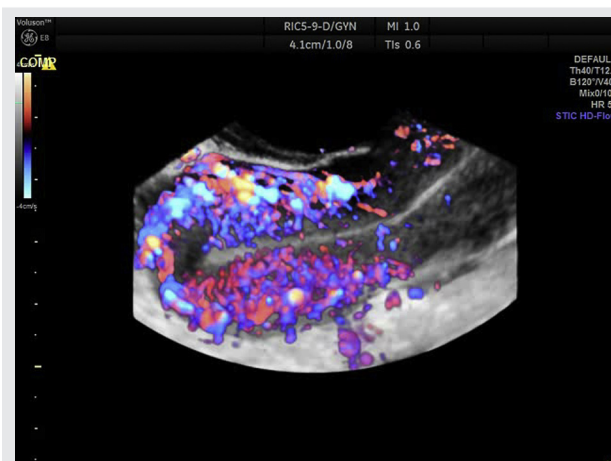
Sagittal plane of a late follicular three-layer-thick endometrium.

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dict a better outcome, but not consistently. Significantly higher clinical pregnancy rates were found in patients with three-layer pattern on the day of hCG administration among IVF cohorts, but not necessarily throughout all of the endometrial thickness range (6, 7). Gingold et al (15), in the aforementioned study, reported a negative correlation between a mid-late secretory (homogeneous, hyperechoic) endometrium and pregnancy outcome.

In addition to the pixel description, current ultrasound devices also provide tools for evaluation of blood supply with the use of Doppler studies (Figs. 2 and 3). Though some of the indices tested showed some value in predicting implantation (17), receiver operating characteristic curves failed to show a true value (18).

FIGURE 2



Uterine sagittal plane demonstrating myometrial vascular network acquired by four-dimensional ultrasound Doppler flow.

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