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Non-Invasive Methodologies for Endometrial Evaluation in Medically Assisted Reproduction

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ABSTRACT

A conceptual synopsis of the state of non-invasive image-based endometrial receptivity assessment methods utilized within in vitro fertilization (IVF) cycles is presented in narrative review format. Many methods for assessing the endometrial contribution to cycle outcome have been posited over the decades since IVF became a mainstream approach for treatment of infertility. Yet, understanding of the endometrial component remains incomplete and most methods for assessing endometrium in the context of IVF are subject to significant divides within the literature. The need for non-invasive, per-cycle approaches to assess endometrial receptivity is being addressed with innovative methods; and, incremental progress is laying a foundation for quantitative assessment of the many factors that contribute to endometrial receptivity. Non-invasive image-based assessments of the endometrium align on two key factors: 1) they make quantifiable assessments of specific endpoints; and, 2) they are conducted on a per-cycle basis which enables real-time clinical decision making. Herein we summarize endometrial thickness, endometrial pattern, uterine biophysical profiles, endometrial scoring, Doppler approaches, uterine contractility, endometrial length and volume, endometrial compaction, the ultrasound-based endometrial receptivity test, and artificial intelligence and machine learning approaches to assessment of endometrium. We also note and discuss the importance of accounting for embryo quality when making decisions focused on endometrial assessment methods since the two factors are intimately intertwined in successful establishment of pregnancy.

KEYWORDS

Ultrasound, Endometrium, usER, Matris™, ER, IVF, MAR.

LIST OF ABBREVIATIONS

MAR	Medically assisted reproduction	**3D**	Three-dimensional
IVF	In vitro fertilization	**2D**	Two-dimensional
ART	Assisted reproductive technology	**ICSI**	Intercytoplasmic sperm injection
AI	Artificial intelligence	**usER**	Ultrasound based ER
FET	Frozen embryo transfer	**ET**	ET
PI	Pulsatility index	**ML**	Machine learning
RI	Resistance index	**NEQsi**	Numeric embryo quality scoring index
S/D ratio	Systolic to diastolic ratio		

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Introduction

The endometrium, and its ability to recognize, receive and implant a competent embryo, is a critical component to the success of in vitro fertilization (IVF) cycles. However, it is not clear which endometrial characteristics best predict implantation. Numerous approaches have been taken to better understand the endometrium and its contribution to IVF outcomes. Progress has been incremental and the literature is divided. Our objective in the present review is to provide a conceptual synopsis of the collection of non-invasive imaging-based approaches that have been proposed over time to assess endometrial receptivity (ER) in the context of IVF and guide those thought processes to the current state of the art.

The term 'endometrial receptivity' has multiple definitions within the literature. For example, ER has at times been defined as the thickness of the endometrium, circulating estrogen/progesterone levels, or as the goodness of fit of a particular gene profile. In contrast, poor or enhanced ER has been mentioned as the responsible factor for differences in pregnancy rates among various patient populations when no quantifiable metric was identified. The term ER also has been seemingly applied to several measurable and immeasurable factors. Herein, we have defined 'ER' as the state of readiness of the endometrium to support implantation of an embryo. We view ER as a continuum and expect ER in each patient cycle will fall at a unique point on the continuum. Importantly, we do not believe it reasonable to attribute ER to a single quantifiable factor. No single quantifiable metric of the endometrium has been conclusively demonstrated to predict cycle outcome.

The question then arises, is it possible to measure ER? Historically, there have been two types of approaches to assess the endometrium during IVF cycles: laboratory-based methods that rely on biopsies or tissue excisions, and non-invasive image-based approaches. Biopsy and image-based approaches each produce quantifiable metrics and provide data for guiding clinical decision-making. Histological examinations of endometrial tissues and RNA-sequencing based methods of determining gene expression profiles require surgical retrieval of tissues and cannot be conducted on live cycles in which embryo transfers are contemplated (mock cycles are required). These approaches are founded on the assumption that data acquired in one cycle will be representative of what will occur in future cycles for any given patient. However, inter-cycle variability is significant, even when medication protocols are equalized[1, 2]. In addition, tissue analysis methods are invasive, expensive, and time consuming. Non-invasive image-based approaches to assessing the endometrium may be utilized in each cycle for which embryo transfer is contemplated. Different image-based ER assessment methods have been proposed over time as developments in technologies arise. The methodologies reviewed here include measurement of endometrial thickness (ET); endometrial pattern; endometrial volume; endometrial compaction; uterine contractility; sub-endometrial blood flow quantitation; ultrasound based ER scoring systems; and, machine learning (ML) / artificial intelligence (AI) methods.

The need for non-invasive, per-cycle approaches to assess ER is driving innovation and laying a foundation for quantitative assessment of the many factors contributing to the ER continuum. In assessing ER, two key features are important: quantifiability and the ability to use the assessment in the cycle during which embryo transfer is contemplated. Patient-to-patient variability must be accounted for and intra-cycle variability within individual patients must be recognized. For brevity, topics which have been recently critically appraised are discussed succinctly and review articles have been referenced.

Methods

A literature search was conducted on July 13, 2023, for the years 1990-2023: search terms were (Endometrium or Endometrial or Uterus or Uterine) and (non-invasive or "non invasive"; or, noninvasive, diagnostic, test, assessment, evaluation, AI, artificial intelligence, usER, Matris, compaction, ultrasound or sonography or imaging) and (Infertility or IVF or reproductive or reproduction). Databases searched included: Academic search complete, Academic search elite, Alt Health Watch, CAB abstracts, Canadian Reference Centre, CINAHL Plus with full text, Health source – Nursing/Academic Edition, Pub Med. A total of 16,763 articles were identified. After duplicates were removed 15,780 articles remained. Articles eliminated at the title level, 14,669, left 1111 articles. A further 952 were eliminated at the abstract level, leaving 159. At the full text level, 17 articles were eliminated, leaving 142. An additional 12 articles were added through review of citations in the accepted articles. Criteria for elimination at title level included opinion pieces, conference abstracts, case studies, non-human focus, cancer focus, pathology not related to infertility, reviews, related to hysterectomy, post-partum and articles concerning technical advances for ultrasound equipment. Abstract exclusion criteria included fetal environment, drug preparations, uterine contractions at time of transfer, invasive tests such as biopsy, review or meta-analysis, uterine transplant technology, assessment of pathology. Abstract inclusion criteria were must be a non-invasive procedure and must have some measure of pregnancy as an outcome.

Endometrial Thickness and Pattern

ET and pattern assessments have been broadly adopted as the standard of care assessment of ER. The thickness of the endometrium is frequently measured at the day of oocyte pick up in fresh embryo transfer cycles or just prior to beginning progesterone supplementation in frozen embryo transfers (FET). Endometrial pattern refers to the relative echotextures of the stratum functionalis compared to the stratum basalis. Most often, endometrial patterns are described as “triple-line” or homogenous. Triple line patterns have discernible echotextural differences between stratum basalis and stratum functionalis and a well demarcated lumenal echo. Homogenous patterns do not demonstrate visually appreciable differences between the endometrial tissue layers. Endometrial pattern assessment have been interpreted broadly.

The focus of most imaging studies which measure ET has been to predict implantation; however, a clear understanding of the expected changes in the endometrial echoes during the ovarian cycle is critical to understanding the measures that would be expected at the time of implantation. One highly variable endpoint in measuring ET appears to be the locations at which the measurement were taken. To clarify, for consistency ET measurements should be taken using a line drawn from the endometrial–myometrial interface at the visually thickest superior and inferior aspects of the endometrial cavity, within 5 to 10 mm of the fundal aspect of the endometrium. Using this clearly defined location, ET changes over the ovarian cycle in a clinically typical population are demonstrable[3]. Current thinking is that implantation is more likely to occur when ET is greater than 7 mm; however, pregnancies are observed with significantly lower thicknesses[4]. An analysis of 96,000 embryo transfer cycles showed that in cycles with a fresh embryo transfer, live birth rates were higher until ET was 10-12 mm; in frozen embryo transfer cycles live birth rates plateaued after 7-10 mm[5]. ET less than 6 mm were associated with a reduction in live birth rates in fresh and frozen embryo transfer cycles; however, there did not appear to have been a focus on interpretation of the effects of confounding variables especially the quality of the embryos being transferred.

A recent critical appraisal of studies on ET and embryo transfer outcomes was performed with the intent of assessing the predictive of ET measurements in individual IVF cycles[6]. The extensive volume of contradictory reports and the apparent lack of correlation between ET and clinical outcomes in patients undergoing IVF was highlighted. The absence of consensus can be interpreted to mean that simple thickness measures are not sensitive enough to predict ER and the probability of implantation. The authors argued that patients should not be denied embryo transfer when their ET is below an arbitrary thickness threshold and found no evidence that ET played a clinically significant role. As such, ET would likely better be incorporated into a larger model to build analytic systems capable of identifying the mechanisms and confounding variables that collectively effect establishment of pregnancy.

The patterns displayed by the endometrium undergo predictable, quantifiable changes throughout the menstrual cycle under the influence of estradiol and progesterone[3]. However, the literature is equally divided on whether endometrial pattern, generally defined as triple-line versus homogenous, is a significant predictor of outcome. We located 17 articles that examined endometrial pattern as an outcome predictor. Approximately half found that endometrial pattern was not a significant predictor of outcome, while the others identified pattern as a significant predictor. Although the patterns associated with endometrial development during the ovarian cycle are well documented, there is considerable biological variability in the endometrial responses of individuals. It has become increasingly important that imaging technologies for evaluation of the endometrium not be limited to simple measurements of endometrial thickness and pattern, but include the full range of endometrial expression and reaction to reproductively active hormones.

Endometrial Biophysical Profile and Endometrial Scoring

A uterine biophysical profile system has been proposed[7]. The system was designed by assigning “points” for several noted criteria (including ET, pattern, PI, RI, contractility, and color Doppler) and then taking the sum as a result. Limited information was found concerning the biophysical profile system; however, one small study (n = 35) supported its use in assessing ER and a second study involving intrauterine insemination cycles (n = 85) reported contradictory results[8].

A recent study proposed a three-point grading system for endometrium on the day of □hCG and progesterone initiation[9]. The proposed method incorporated endometrial pattern, thickness and the proportion of the endometrium represented by the outermost tissue layer to create a collection of eight endometrial categorical grades. Higher pregnancy rates were reported when ET exceeded 7 mm and the external layer of the endometrium was greater than 50% of the total thickness.

Spectral Doppler and Color Flow Doppler Ultrasonography

Color flow Doppler and power flow Doppler imaging are means of turning motion, either toward or

away from the transducer (color flow Doppler) or motion in any direction (power flow Doppler) into a visually detectable color overlay on the two-dimensional ultrasound image[10-12]. Studies tend to be based upon color Doppler examinations which allow easy identification of uterine vessels and calculation of blood flow indices using pulsatility index (PI), resistance index (RI), Vmax, or the systolic to diastolic ratio (S/D ratio). Doppler assessments of vessels supplying the uterus are presumed to reflect downstream impedance of the blood flow towards the endometrium and thus endometrial perfusion[10, 11].

No differences were found between pregnant versus not-pregnant groups when uterine artery RI was investigated as a tool to assess ER. Data for PI grouped into low, medium, and high categories for evaluation of the predictive value of pregnancy showed no differences in pregnancy rates in the low and medium categories; however, no pregnancies were established in the women with high PI values[13]. Therefore, elevated PI was associated with a lower pregnancy rate leading to the conclusion of a high negative predictive value. A single recent study demonstrated differences in PI between pregnant and non-pregnant groups post-hoc and was interpreted to mean that PI may have positive predictive value, however, this observation stands in contrast with most reports[14]. Assessments of uterine artery RI have shown no positive predictive value, except that absent or low diastolic flow was associated with failure to conceive: reviewed in[10].

Measurements of uterine vascularity appear to have little relation to the probability of conception in ART cycles. It is important to note that it remains unlikely that measures of uterine vessels reflect the state of blood flow to the endometrium as most of the draw on vascular resources would be taken by myometrial tissues and there is significant collateral circulation among uterine and ovarian vasculature[10]. While some ultrasonographically detectable criteria have been observed to be associated with negative pregnancy outcomes; no prognostic value has been observed in any measurement of vascular perfusion. Power flow and 3D power Doppler assessments have not been able to provide a positive predictive index of pregnancy[10-12]. While it might be logical to infer that a high degree of endometrial perfusion would indicate a more favorable endometrium, we were unable to locate detailed studies supporting this hypothesis.

Sub-endometrial Contractility

Motion analysis, or direct measurement of sub-endometrial contractions, is a method of evaluating the endometrium based on the observation that the uterus and endometrium are in constant motion. Patients with higher frequency uterine contractions were found to have lower pregnancy rates[15]. The effects of progesterone on uterine contractions have been demonstrated by the observation that higher progesterone concentrations correlated with lower amplitude and frequency uterine contractions. Low amplitude and frequency of contractions is hypothesized to facilitate implantation. However, administration of a selective oxytocin antagonist to reduce the frequency and power of endometrial contractions did not affect pregnancy rates in a clinical trial[16, 17]. A single article using non-invasive imaging identified junctional zone thickness as a significant predictor of implantation in ICSI cycles[18]. No further exploration of junctional zone was conducted.

Endometrial Volume and Length

Evidence for 3D volumes as predictors of ER and implantation has been contradictory. When endometrial volumes were compared among patients who conceived and those who did not, pregnancy and implantation rates were significantly lower when volume was less than 2 mL, and no pregnancies were established when endometrial volume was less than 1 mL[11, 19]. We identified eight studies which evaluated the correlation between endometrial volume and pregnancy. Seven were prospective cohort studies and used similar stimulation protocols and embryo quality cutoffs. One study reported on endometrial volume as a stand-alone assessment[20], however, most also included either ET and pattern, or a various blood flow indices. In some, endometrial volume was significantly correlated with a positive pregnancy outcome[20-25]. However, others have found no relationship between 3D volume of the endometrium and conception[19, 26]. No correlations were found among estradiol levels, ET, or endometrial volume leading the authors to conclude that there was no positive predictive value in assessing endometrial volume.

Two small prospective cohort studies using a single stimulation protocol were identified and evaluated the relationship between ET, endometrial length and cycle outcome. Correlations between endometrial length and pregnancy outcomes were observed[27, 28]; however, neither found a significant relationship between outcome and ET. No data were presented regarding the biophysical height or torso length of the patients which could be correlated to organ dimensions. In addition, the relationships between endometrial length and endometrial volume were not explored.

Endometrial Compaction

Endometrial compaction as a method of assessing ER was originally proposed in 2019. The definition of compaction was noted as a decrease ". . . in ET between the end of the estrogen phase and the day of

embryo transfer"[29]. Ten additional publications focused on compaction were identified in our search of the literature and represent a mix of retrospective and prospective observational cohort analyses. All studies eliminated cycles in which the endometrium did not reach a minimum thickness of 7 millimeters. Some studies included multiple categories for the definition of compaction[29-31], while some studies assigned a single category of compaction. In most cases, the categories were defined by a decrease in thickness between 5% and 20%. Patient exclusion/inclusion criteria, cycle stimulation protocol, and number of embryos transferred varied among studies. Outcome measures ranged from ongoing pregnancy rate to live birth. Some studies reported multiple outcomes[32, 33]. The reports were conflicting in their conclusions. Significant correlation between compaction and the outcome was reported[29, 30, 32-34]; however, no connection between endometrial compaction and cycle outcome was also demonstrated[31, 35-39]. Studies with a significant correlation ranged in N from 71[32] to 1420[34] with a mean N of 454, and those that reported no significant correlation ranged in N from 107[36] to 3091[37] with a mean N of 1496. Limitations in the studies which identified a positive relationship between endometrial compaction and outcome[31, 33, 34] included that the first endometrial measurement was taken by transvaginal ultrasound and the second measurement was taken transabdominally. The difference in measurement methods has the potential to introduce significant variability and error into the assessment.

The Ultrasound-Based Endometrial Receptivity Test

Ultrasound-based Endometrial Receptivity (usER) testing was developed to provide a non-invasive method for assessing ER on a per-cycle basis (usER, Matris™, Synergyne Imaging Technology, Inc, Saskatoon, SK). Early clinical trials with the precursor to the usER test (40) and field trials with the commercialized usER test (41) demonstrated the proof of concept that an ultrasound based ER scoring system could correlate endometrial image attributes with IVF cycle outcomes.

The usER test is founded on a proprietary software system designed to quantify the state of glandular differentiation, glandular coiling, numerous typical and atypical anatomic features that have been demonstrated to effect IVF outcomes. usER testing evaluates the effects of reproductively active hormones on the endometrium using a virtual histology approach to extract image-based metrics and condense them into an ER score. The usER test is a 'real time' ER assessment implemented on each cycle in which embryo transfer is contemplated. Standardized transverse and mid-sagittal images of the endometrium are acquired ~48 hours prior to an anticipated day-5/day-6 embryo transfer. The image series are communicated to a secure central server, processed, scored, and the receptivity score is reported to the clinic. usER scores range from 0 – 10 (0 – poorest ER; 10 – optimal ER). Although the score is a numeric scale, the relationship between usER score and pregnancy rate is non-linear, leading to a threshold interpretation model. Endometria with scores >=7 or above are considered well – to – optimally prepared and ET is recommended. Scores of <= 6.5 or are recommended for deferral of embryo transfer[42].

Routine implementation of usER testing was demonstrated to improve pregnancy rates by 12% (when fresh and frozen ET cycles were considered in aggregate; N = 1521) and conserve embryo potential[42]. The improvements in pregnancy rates have been attributed to accurate identification of poorly prepared endometria and deferral of embryo transfer to a subsequent cycle with better ER[43]. An approximate 10% increase in pregnancy rate was observed in patients who proceeded with usER-based cycle selection during a frozen ET cycle. Accurate identification of poorly prepared endometria was particularly apparent when fresh ET cycles were considered, as ovarian stimulation protocols may have higher variability effects on the growth and development of the endometrium. The pregnancy rate for patients who had fresh ET cycles was 20% higher in the usER-based cycle selection group than standard of care ET group. We identified one report (N = 224) that conflicts with these findings[44] in which the authors stated that they failed to control for many of the factors which impact outcome. Inclusion and exclusion criteria for the patient case information included in the retrospective analysis comparing outcomes based on usER versus ET cut-off was not described. Negligible correlation between usER score and ET on a given IVF cycle has been demonstrated[45]. A pilot study has also provided proof of concept that usER testing may be implemented to optimize endometrial preparations over time by providing a standardized approach to quantifying overall quality of endometrial preparations as medication protocols are adjusted / standardized within the clinic[46].

Linking ER and Embryo Quality

The relative contributions of the embryo and the endometrial environment to IVF cycle outcome are not well understood. However, we cannot assess if a non-invasive approach to determining ER is truly competent if we do not consider the effect of embryo quality on the probability of conception. New tools like the numeric embryo quality scoring index (NEQsi) provide an opportunity to begin untangling the contribution of the embryo from that of the endometrium in a straightforward statistically driven way[47].

As a proof-of-concept, we integrated usER score and NEQsi score to determine how ER and embryo quality interact. We conducted a retrospective analysis of 1720 IVF cycles in which both usER scoring and Gardner embryo grading were utilized. The analysis was an assessment of all patients presenting for embryo transfer to approximate real world clinical practice. Inclusion into this analysis was based solely on the availability of data within the patient charts (patient demographics and date range for data collection for this cohort are published[47]). Multivariate statistical modelling was used to determine how embryo quality affected cycle outcome in both receptive and poor-receptivity endometrial environments, as assessed by the usER test (**Figure 1**). We made two key observations:

1) When the endometrium was identified as receptive (usER score of 7 to 10) and we applied the full range of NEQsi scores associated with the receptive endometria (n = 1574, NEQsi range 3-12), embryo quality was the outcome predictor ($p < 0.0001$); and,

2) When the endometrial environment was identified as poor-receptivity (usER score of 0 to 6.5) and the full range of NEQsi scores associated with the poor receptivity endometrial environments (n = 146, NEQsi range 4-12) was applied, the usER score was the primary outcome predictor ($p = 0.038$).

Figure 1: **Linking Embryo quality and ER**. The green circle (upper left) represents receptive endometria and red circle (lower left) represents poor-receptivity endometria, as assessed by usER. The range and distribution of NEQsi scores were comparable between the two groups. The outcome predictor for each subanalysis is shown on the right.

This initial analysis that merges embryo quality and usER scores provides evidence that receptive endometria would not be expected to offset low-quality embryos and that high-quality embryos are unlikely to overcome the effects of poor-receptivity endometria. A larger multi-center observational study to validate this proof-of-concept analysis is currently underway.

Artificial Intelligence and Machine Learning Approaches to Quantification of ER

Artificial intelligence (AI) and machine learning (ML) approaches are being integrated into many aspects of reproductive medicine. An AI/ML approach to understanding probability of pregnancy before an embryo transfer takes place would be desirable and have potential for significant improvement in clinical outcomes. New approaches utilizing AI/ML have been constructed to better assess and understand oocytes and embryos. Computational approaches to automatic identification and segmentation of endometrium on 2D ultrasound images have been developed[48-50] and describe automated methods for ET measurement with accuracy up to 90% with an error range of 4 mm (± 2mm when compared to human measurements). It is important to note however that these methods presuppose that ET measurements predict cycle outcome.

An AI algorithm was produced with the aim of predicting cycle outcomes by combining ultrasound image features and clinical case notes[51]. Like the other AI approaches, the authors implemented an automated approach to segmentation of the endometrium within 2D ultrasound images. Ultrasound based measurements of endometrial volume, blood flow, and contractility were assessed and entered the model in combination with clinical case information to produce an AI model with ~ 72% accuracy in outcome prediction. It is noted that many key reasons for infertility were excluded from development of this model and that further validation of the approach is needed to determine its utility.

Discussion

There is a high degree of variability in the results reported with most of the image-based approaches identified for assessing ER. It is probable that the conclusions of studies with contradictory findings are heavily influenced by the study designs, methodologies, patient cohorts examined, medication protocols, sample sizes, and statistical error levels. We also noted that there was significant variability in the timing of the various assessments within a given IVF treatment cycle. The contribution of embryo quality (whether morphologically or genetically assessed) has been approached with great variability across the studies that have evaluated ER. Due to this variability, a combined approach that simultaneously assesses multiple metrics is likely to be more successful than any one factor on its own.

Of the methodologies noted, few have been broadly adopted. The exception is the broad acceptance of ET measurement and pattern assessment. Each of these variables is subject to interpretation and clinical decisions are based upon the experience of individual practitioners, introducing considerable variability in interpretation. Although ET and pattern are widely utilized in clinical decision making, the literature is divided regarding their utility in predicting patient outcomes. In fact, there are concerns

that cancellation of an embryo transfer based solely on an arbitrary ET cut-off is unwarranted[6].

The present narrative review was intended to provide a synopsis of the state of the field of non-invasive ER assessment. We acknowledge that it is not a comprehensive critical appraisal of each method identified. Although we took a systematic approach to our literature search and followed a systematic method for inclusion of original research articles, other review articles have been cited due to restrictions to the number of references. Additionally, we acknowledge that methods of ER testing which involve swabs, aspirates, metabolites, or microbiome analysis may be considered non-invasive but have not been addressed.

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CONFLICT OF INTEREST

HP and JI are employees of Synergyne ART Analytics. RAP is Distinguished Professor of Obstetrics and Gynaecology at the University of Saskatchewan and President and CSO at Synergyne ART Technologies.

DISCLOSURES

HP and JI are employees of Synergyne ART Analytics. RAP is Distinguished Professor of Obstetrics and Gynecology at the University of Saskatchewan and President and CSO at Synergyne ART Technologies.

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