The Refractory Endometrium is Still Refractory

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INTRODUCTION

Achieving pregnancy using assisted reproductive technology relies on successful implantation of transferred embryos into a receptive endometrium. Despite the burgeoning use of ART to address infertility, the overall success measured in terms of live-birth deliveries per entire treatment course is less than 50%.[1] Endometrial thinness is a common cause of infertility that is often refractory to hormonal therapy, a condition referred to as refractory endometrium, and it frequently leads to repeated implantation failure.[2] The RE is characterized by a lack of proliferative growth response and an increase in endometrial thickness normally elicited by endogenous or exogenous sex hormones that render it incompetent for implantation. Embryo implantation and especially pregnancy rates are compromised with endometrial thickness less than 6 to 8 mm as measured by transvaginal ultrasound,[3,4] Although the precise threshold values are unknown in any given patient, endometrial thickness is considered a biomarker for endometrial receptivity and is widely used as an indicator of the success of treatments directed to the RE. This Commentary summarizes current treatment options in RE and, in so doing, highlights the critical unmet need to identify new therapeutic targets that are based on a better molecular understanding of the normal and dysregulated endometrium.

Key Words: Refractory endometrium (RE), assisted reproductive technology (ART), progesterone receptors, estrogen receptors, IVF

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PATIENT WORKUP

The initial approach to any patient with infertility requires a complete assessment of ovulation, ovarian reserve, tubal patency, and uterine anatomy, as well as a semen analysis. Diagnosis of a thin endometrium is made by transvaginal ultrasound, with a measurement of <7 mm commonly used as a cut-off value predictive of low implantation success. Importantly, a trilaminar pattern on ultrasound during the ovulatory phase is a favourable sign and may be more predictive of receptivity than endometrial thickness per se, whereas a hyperechoic appearance signals likely implantation failure.[4] Several potential etiologies should be considered in the thin endometrium, including the following: infectious; iatrogenic, consequent to either previous curettage or medications; and idiopathic. The first step in confirming the diagnosis of an intrinsically thin endometrium is the exclusion of endocrine abnormalities affecting hypothalamic-pituitary-ovarian axis; this is the subject of extensive literature and is not addressed here.

NORMAL REPRODUCTIVE CYCLE

During the normal reproductive cycle, estrogen stimulates endometrial proliferation (follicular phase) and induces upregulation of progesterone receptors.[5] Exposure of the endometrium to P after ovulation initiates the change from a proliferative to a secretory endometrium that confers receptivity to implantation.[6] The molecular events that determine normal uterine receptivity are orchestrated by timed changes in E and P signalling; however, the precise defects in the normal proliferative-secretory cycle in patients with infertility in association with endometrial hypoplasia remain elusive.

PERFUSION DEFECTS IMPLICATED IN INFERTILITY

Several putative mechanisms that may underlie EH have been proposed. Subendometrial perfusion as measured by contrast-enhanced ultrasound was shown to discriminate between normal and unexplained infertility during natural cycles.[5] The investigators concluded that a failure of uterine blood flow in the late proliferative phase may lead to impaired development of the endometrium and consequent infertility. The optimal oxygen concentration for embryo preservation in IVF technology is considered relatively hypoxic (in the range of ~5%).[7] This finding leads to the contrary speculation that oxygen levels are abnormally high in the absence of an adequate epithelial layer in patients with EH because oxygen diffusion from the spiral artery layer is increased, thereby possibly increasing redox stress to the implanting embryo. Thus, the putative effects of alterations in uterine blood flow in EH are unclear.

CURRENT TREATMENT OPTIONS

A small pilot trial concluded that human chorionic gonadotropin administration (150 IU subcutaneously daily for 7 days) in the follicular phase preceding frozen embryo transfer both increased endometrial thickness and improved clinical outcomes in patients with E-refractory thin endometrium (<6 mm).[8] The human GnRH-GnRH receptor system may work through transactivation of the E receptor-α (ERα). E signalling by ERα was shown to stimulate the proliferation of uterine luminal epithelial cells, a process that then requires suppression by timed P exposure to optimize receptivity during the window of implantation.[1]

Extended E treatment may increase the success rates of IVF-FET protocols, although the risk of abnormal placentation may be increased with this approach.[6] The reported adverse effect of controlled ovarian hyperstimulation on endometrial receptivity may be mitigated by using FET supported by hormone replacement therapy, even in patients with thin endometrium.[4]

Several different regimens have been the subjects of trials to prepare the endometrium, including vaginal sildenafil, as well as intrauterine infusion of granulocyte colony-stimulating factor, human growth hormone, and autologous platelet-rich plasma, as reviewed elsewhere.[3]

The use of granulocyte colony-stimulating factor is predicated on its capacity to activate endogenous or bone marrow–derived endometrial progenitor cells, but to date it is of unproven efficacy.[4] The general rationale for using growth factors to stimulate endometrial thickness is supported by gene expression analysis demonstrating evidence of deficient cellular proliferation in patients with RE.[9] Nevertheless, the results with these approaches are not yet supported by sufficiently powered randomized controlled trials.

FUTURE PERSPECTIVES

Gene Expression Analysis

Pathway analyses of genes that are differentially regulated in women with RIF suggest that the balance of endometrial E and P levels is critical during the window of implantation.[10] The determination of uterine receptivity by using endometrial biopsy and transcriptomic microarray-based receptivity assays may help guide the optimal timing of FET.[9] Gene transcript analyses have identified a number of gene pathways that may serve as biomarkers for uterine receptivity. The endometrial receptivity array test, in which 238 genes serve as an endometrial receptivity biomarker cluster, has proved accurate in the identification of personalized timing of the window of implantation among various patient groups.[11] The validity of gene expression analysis implicating dysregulation of E and P signalling is supported by a study demonstrating that too high or too low midluteal serum P concentrations (<50 and >99 nmol/L) were associated with decreased implantation rates in cryopreserved embryo transfers conducted during artificial cycles.[12] However, the utility of gene expression analysis in guiding the timing and success of FET requires further validation in larger prospective trials.

The Balance of Estrogen and Progesterone Levels is Critical

Even using this type of personalized approach to guide the timing of FET, successful implantation ultimately depends on appropriate endometrial function.[7] Transcriptomic analysis has provided a deeper understanding of the complex interacting pathways involved in the regulation of

ABBREVIATIONS

ART	assisted reproductive technology
E	estrogen
EH	endometrial hypoplasia
FET	frozen embryo transfer
P	progesterone
RE	refractory endometrium
RIF	repeated implantation failure