What exactly is endometrial receptivity?

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Endometrial receptivity is a complex process that provides the embryo with the opportunity to attach, invade, and develop, culminating in a new individual and continuation of the species. The window of implantation extends 3–6 days within the secretory phase in most normal women. In certain inflammatory or anatomic conditions, this window is narrowed or shifted to preclude normal implantation, leading to infertility or pregnancy loss. Of the factors that prevent normal implantation and pregnancy, embryo and endometrial quality share responsibility. In this review, we highlight the advances in the study of implantation from the perspective of the endometrium, normally a barrier to implantation. New advances will allow the early identification of defects in endometrial receptivity and provide new avenues for treatment that promote successful establishment of pregnancy. (Fertil Steril® 2019;111:611–7. ©2019 by American Society for Reproductive Medicine.)

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Embryo implantation is a complex process involving both the embryo and the maternal endometrium, whose initial steps occur over approximately a 4- to 6-day interval during the mid-luteal phase. The ability of the endometrium to allow normal implantation is termed *receptivity*, and optimal receptivity leads to normal implantation processes that serve as a foundation for a healthy pregnancy. Robert Edwards once wrote that the endometrium is the last barrier to progress in assisted reproductive technology (ART) (1). Indeed, embryos readily implant in many tissue locations (2–4), whereas the endometrium is unique in its ability to block embryos from implanting, except during this narrow window of receptivity (5). Most women attain normal receptivity during the mid-luteal phase, driven solely by the sequential actions of the steroid hormones, E_2 and P. The downstream molecular responses have now been well characterized (6) and include critical shifts in expression of receptors for these sex steroids (7). Down-regulation of estrogen (E) receptor-α seems to be one crucial event on which receptivity depends (8–10) and is a common to other species (11).

By definition, endometrial receptivity is "that period of endometrial maturation during which the trophectoderm of the blastocyst can attach to the endometrial epithelial cells and subsequently proceed to invade the endometrial stroma and vasculature" (12). Attainment of endometrial receptivity is not an "all or none," binary event, nor does the analogy of a window suffice to account for clinical observations associated with endometrial-related subfertility. Rather, degrees and types of abnormal receptivity lead to a range of reproductive problems, from complete implantation failure (infertility) to severely deficient implantation (miscarriage) and mildly abnormal implantation and invasion (e.g., pre-eclampsia). Indeed, the contributing factors that disturb receptivity may not all have been recognized, but they include endocrine causes, inflammatory events, thin endometria, fibroids, polyps, septa, and immunologically mediated disturbances. In this review, we examine mechanisms governing normal receptivity but focus on inflammation as a primary cause of unexplained endometrial receptivity defects. How subclinical inflammation is established and then recognized by the eutopic endometrium remains a puzzle. However, inflammatory pathways seem to be pivotal to the phenomenon of P resistance, a rapidly expanding field of study. Understanding the mechanisms of P resistance

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holds promise for better diagnostics and new directed therapies that may entirely alter how we manage unexplained infertility.

ENDOMETRIAL RECEPTIVITY AND EARLY STUDIES

One of the earliest concepts related to endometrial receptivity defects was the identification of patients with a shortened luteal phase and delayed development of the secretory endometrium (13). The idea of a luteal-phase endometrial differentiation abnormality as a cause of infertility was based on foundational work by Georgeanna Seegar Jones (14) and establishment of histologic criteria for endometrial dating by Noyes et al. (15). However, there remains no gold standard definition of delayed or accelerated endometrial development, because histology, P levels, and other measures remain largely unreliable (16–18). The diagnosis of luteal phase defect (LPD) was nonetheless extensively studied in the context of infertility.

Early studies suggested the incidence of LPD ranged from 3% to 15% of infertile women (15, 19, 20). This diagnosis was also associated with early fetal wastage (21, 22). Luteal phase defect was more common in older women, women taking clomiphene citrate, and those with recurrent pregnancy loss (19), but it became apparent that LPD was not due to a single factor. As reviewed by Jones in *Fertility and Sterility* (23), LPD was associated with hyperandrogenism, hypothyroidism, and hyperprolactinemia. Although endometriosis was thought by some to be associated with LPD (24), others found no increased incidence (25, 26).

Despite the shortcomings of histologic dating, there is consensus that P is essential for establishment and maintenance of early pregnancy. Progesterone is anti-inflammatory and is thought to induce immuno-tolerance at implantation and during early pregnancy. On the basis of classic studies of early lutectomy, we know that P is an essential element to maintenance of early pregnancy (27). The timing of implantation has been examined from many vantage points but occurs at the peak of luteal P secretion. In the 1950s hysterectomy specimens from pregnant subjects showed that embryos did not attach until day 20 of a 28-day cycle (28). Later, Navot et al. (29) studied success during ART cycles using fertilized donor oocytes transferred into hormonally prepared recipients and reported a broad window of transfer that occurred between cycle days 15 and 20. Wilcox et al. (5) validated that implantation normally occurred between 7 and 10 days after ovulation (days 21–24) in fertile women trying to conceive. In that study, a delay in implantation beyond postovulatory day 10 was associated with a heightened risk of miscarriage, probably due to a loss of synchrony between endometrium and embryo and failure to rescue the corpus luteum (5).

Interference with P action using antiprogestins interferes with endometrial function (30, 31) and can cause pregnancy loss or infertility (32, 33). Furthermore, an early rise in P during ovarian stimulation reduces the success of ET in that cycle, though the embryos are normally competent in a subsequent frozen transfer (34, 35). Additionally, there is a 2 or 3-day temporal window of P exposure that promotes optimal receptivity (5, 36). These data strongly suggest that abnormal length of P exposure leads to embryonic–endometrial dyssynchrony due to impaired endometrial receptivity.

PROGESTERONE ACTION AND IMPLANTATION

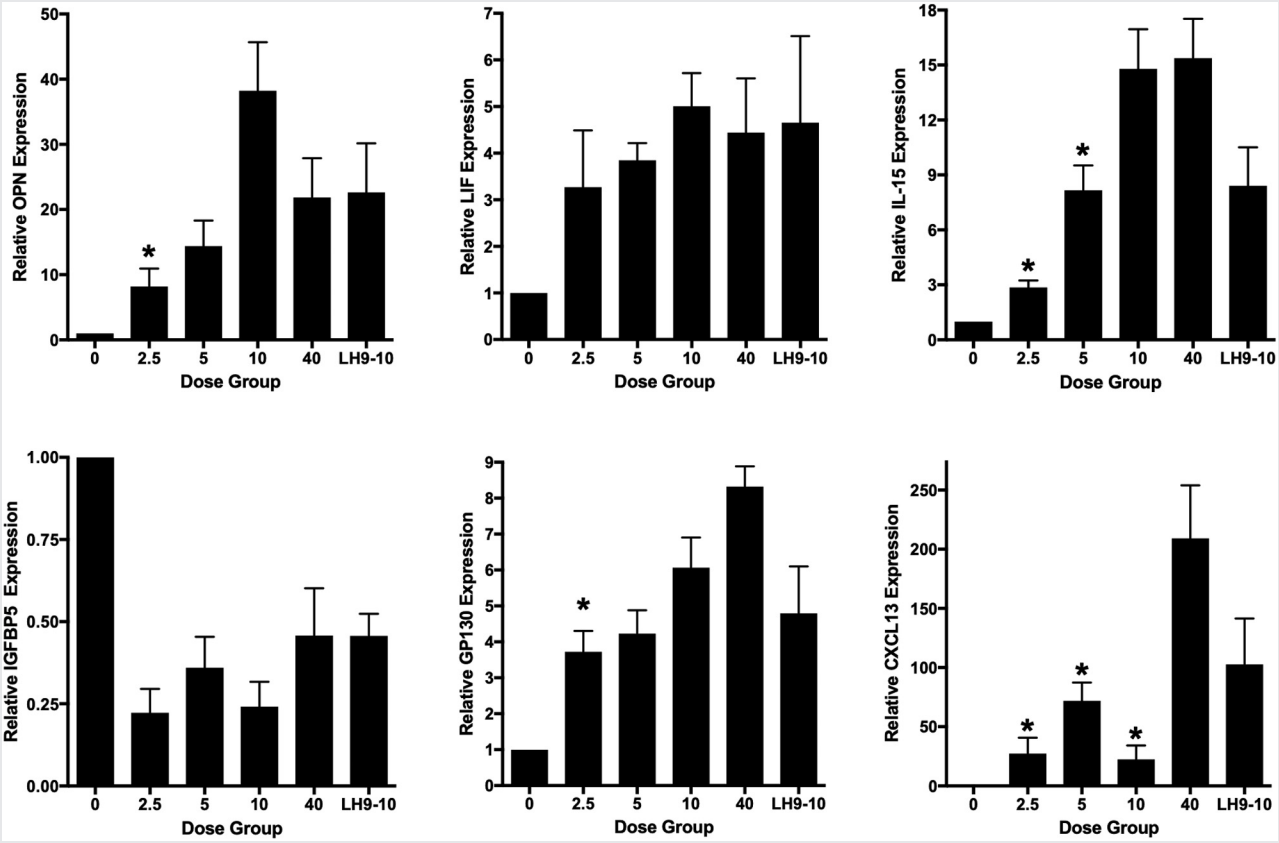
The first and most enduringly recognized endometrial protein shown to be essential for implantation was endometrial leukemia inhibitory factor (37, 38). Leukemia inhibitory factor expression is induced by nidatory E in the mouse but regulated by P in the human (39–41). Down-regulation of epithelial progesterone receptor A (PR-A) receptor may be required for its appearance (42, 43), suggesting a role of P inhibiting its own receptor. The action of P in the endometrium is essential for embryo implantation, and eventual decidualization has been recently well characterized (41).

Progesterone is also responsible for the timely down-regulation of E receptors. The COUP-TFII–driven Indian Hedgehog pathway promotes down-regulation of ER in the endometrial epithelium (41, 44). One P-regulated gene essential for normal uterine development and fertility is the repressor of estrogen activity (REA) (45). Interestingly, the timing of endometrial receptivity may be regulated by this gene (46). One biomarker sensitive to E suppression is the alpha v/beta 3 integrin ($\alpha v\beta 3$) (47). This implantation-related protein appears at the time of implantation on cycle day 20 and is thought to be involved in attachment and embryo function during implantation (48–51). This biomarker is absent in the presence of histologic delay, which is characterized by elevated E (9, 52) and P receptors (53). Because blocking P action is associated with subfertility and increased endometrial P receptor (30) and E receptor (54), it again confirms the importance of P in the timely down-regulation of these two receptors. In addition, the argument can be made that down-regulation of epithelial E receptor is also central to endometrial receptivity and fertility.

Progesterone resistance (see recent review (55)), as with treatment with RU-486 or other antiprogestins, results in an interference of P action. One of the major contributors to P resistance is the presence of endometriosis (56, 57). This disturbance in endometrial receptivity seems to be graded in response to the immunologic characteristics of the individual, as well as the amount, activity, and location of disease. Unlike antiprogestin treatment, P resistance is less predictable and often paradoxical (58). Thus, it seems that P resistance is not the same as P deficiency. Normal endometrium seems so robust in its ability to respond to P that endometrial histology was unchanged across a wide range of concentrations, with delayed histologic changes only seen with P concentrations below those seen in ovulatory women—although only a small number of genes showed a significant dose-response (59) (Fig. 1).

Progesterone resistance represents an organic and systemic disruption of the actions of P and defines a defective and graded responsiveness to P. Using the $\alpha v\beta 3$ biomarker as an endpoint for P resistance, we reported that outcomes in

FIGURE 1



Relative expression of selected genes by reverse transcription–polymerase chain reaction. Samples from women in modeled cycles (leuprolide down regulated with identical E_2 dosing and randomized daily doses of IM P) compared with a single subject with placebo injection (labeled 0) and a natural cycle group at 9–10 days after LH surge. Samples are taken from subjects previously described (60). *Difference between dose groups at $P<.05$, excluding placebo and natural cycle samples, using analysis of variance and Newman-Keuls post hoc testing. Numbers along the x-axis represent daily doses of IM-administered P.

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IVF were poor in women that were in phase histologically but lacked the β3 integrin (60). This type of defect in implantation was correctable by administration of letrozole to block aromatase activity, restoring both integrin expression and fertility.

The proposed mechanisms of P resistance have been reviewed elsewhere (58, 61). Our current model includes alterations in the phosphatidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway that regulates growth and proliferation, as seen in uterine fibroids (62) and endometriosis (55, 63). Activation of this pathway seems to be central to the defects observed in the eutopic endometrium of women with endometriosis (64). Downstream events include activation of E receptor-α and hypoxia-induced factor 1-α/vascular endothelial growth factor pathways. Suppression of the COUP-TFII pathway as seen in P resistance also activates angiogenesis (65). We postulate that PI3K/AKT activation occurs in part via KRAS (55) and is associated with loss of ARID1A (66), which we reported is reduced in endometriosis and essential for normal fertility (67). Central to these aberrant pathways are inflammatory changes in women with endometriosis, including elevations in interleukin (IL)-6 and IL-17 (68, 69). These inflammatory signals contribute to KRAS elevation (70) and lead to prolonged phosphorylation of STAT3 (71) and reduction of proteins that normally inactivate STAT3 (72). STAT3 stabilizes hypoxia-induced factor 1-α, normally expressed only at menstruation, and vascular endothelial growth factor pathways. Interleukin-6 and IL-17 also contribute to prostaglandin pathways and cyclo-oxygenase 2 activation, commonly associated with endometriosis, contributing to aromatase expression, which may further shift the balance between E and P actions. Inflammatory-mediated KRAS expression and phosphorylated STAT3 promote and activate Sirtuin-1 (SIRT1) and BCL6, respectively, which have been shown to be key mediators of P resistance (72). BCL6 and SIRT1 are thought to target the COUP-TFII/Indian Hedgehog pathway used by P. SIRT1, as a histone deacetylase, has been reported to inactivate many signaling pathways downstream of P receptor, including those containing peroxisome proliferator-activated receptor-γ, retinoic acid receptor, and Gli1 (70). With P signaling impaired and E action enhanced, the endometrium is unable to support implantation and maintain pregnancy.

ENDOMETRIAL ASSESSMENT

Historically, endometrial histology was used as the primary indicator of endometrial receptivity (14, 15). Histology alone is a blunt tool, however, and critical reanalysis of the Noyes endometrial dating criteria demonstrates its shortcomings (73). Further, essentially all early studies involving endometrial dating were performed in infertile women, many of whom may have endometriosis and therefore aberrant responses to P. Clearly, better methods are needed.

The use of integrin testing allowed a multi-dimensional assessment of histology and biochemical integrity (74, 75). Of three integrins that were hormonally regulated and occupied the window of implantation, the $\beta 3$ integrin subunit of $\alpha v \beta 3$ was shown to have the greatest utility in defining defects in endometrial receptivity. It was shown to be reduced when histology was delayed, but more importantly, when histology was "in phase" with $\beta 3$ integrin expression expected, this integrin was lacking in clinical conditions associated with infertility, including endometriosis (76) and hydrosalpinges (77), and aberrantly expressed in a significant subset of women with unexplained infertility (78) and unexplained recurrent pregnancy loss (79). The return of normal fertility and integrin expression was demonstrated using salpingectomy (80) or treatment with an aromatase inhibitor (59). Interestingly, $\alpha v \beta 3$ integrin expression is tied to the down-regulation of E receptor-α, which is seen in both LPD and endometriosis. This persistence of a more proliferative phenotype is likely implicated in abnormal expression of other endometrial biomarkers used for the Endometrial Function Test developed at Yale (81).

The endometrial receptivity array (ERA) is an attempt to clinically improve on histologic detection of embryonic–endometrial dyssynchrony due to accelerated or delayed endometrial luteal-phase differentiation (82). The published data supporting the ERA, to date, are limited and await the results of an international, randomized, multicenter trial. Features of the ERA test necessary for it to be highly useful include the following: [1] the frequency of abnormal ERA results should be different between patients with and without implantation problems; [2] abnormal findings should predict a poor probability of normal embryo implantation; [3] because embryo transfer must be done in a nonbiopsy cycle, ERA findings must be consistent from cycle to cycle; and [4] alteration of transfer timing based on the ERA should improve outcome. Below, we briefly examine the published data for each of these necessary features.

There is approximately a 25% and 14% incidence of an abnormal ERA test in women with recurrent implantation failure (RIF) vs. control subjects undergoing IVF, respectively (83–86). Assuming that true endometrial receptivity problems in the control group are approximately 5%, then ERA correctly identifies implantation problems in approximately $25\% - (14\% - 5\%) = 16\%$ of those with true implantation problems and misidentifies problems in $14\% - 5\% = 9\%$ of patients. These calculations suggest that ERA only identifies a minority of patients with recurrent implantation failure and likely misidentifies a small percentage.

Cycle to cycle consistency of the ERA, to our knowledge, has only been examined in one publication (87), which described a comparison of seven women, each of whom had duplicate endometrial sampling performed 29–40 months apart. Only five of these were luteal phase, and only four were in the receptive phase, none of which were abnormal. The ERA results were highly similar across the samples, demonstrating reproducibility. It must be acknowledged, however, that assessment of reproducibility is limited by the small numbers, the lack of abnormal mid-luteal test results, and use of a natural cycle. Interestingly, the concept of reproducibility of gene expression has been recently tested in six subjects with normal receptivity, comparing gene expression across multiple cycles using a whole-genome microarray (88), though the direct application of these data to the ERA remains uncertain.

To correct embryo–endometrial dyssynchrony identified by the ERA, a shift in the timing of frozen embryo transfer must be used. Demonstration of the benefit of this approach in women with a history of implantation failure is limited to a small number of poorly powered observational studies (84, 86). These studies fail to show a statistically robust benefit, but all show a definitive trend toward benefit. In contrast, a retrospective cohort study of good-prognosis patients could detect no benefit of ERA in the general infertility population (89). Preliminary data of a multicenter, randomized, open-label trial presented during the 2016 American Society for Reproductive Medicine meeting suggested a possible benefit of ERA in women not selected for RIF. These data suggested that among women with frozen transfer, there was a higher pregnancy rate per transfer in the women having ERA-guided transfer timing (85.7% vs. 60.8%), though the advantage was counterbalanced by an increased combined rate of miscarriage, biochemical loss, and ectopic pregnancy, resulting in similar ongoing pregnancy rates. We await definitive data from the large, multicenter, randomized trial. It should also be noted that the ERA test does not demonstrate an abnormality in 75% of patients with RIF (75%). Because 40%–50% of euploid embryos fail to implant, it is extremely likely that there are other implantation-related abnormalities not measured by the ERA test.

A newer test for endometrial receptivity is the ReceptivaDx test, based on the finding of overexpression of endometrial BCL6 in women with endometriosis (90). Unlike ERA, ReceptivaDx identifies endometrial receptivity defects associated with P resistance, usually due to endometriosis. The BCL6 protein (vide supra) pairs with the histone deacetylase, SIRT1, to interfere with P signaling (70). A clinical study suggests that a positive test for BCL6 (high expression) is strongly predictive of poor reproductive outcomes in IVF (91), and another suggests that these women can be effectively treated using either GnRH agonist suppression or surgery for endometriosis before IVF (92). These findings also support the idea that some women with such defects could be treated without ART. Further randomized prospective studies are underway to confirm these initial observations.

In summary, endometrial receptivity seems to be multidimensional, though a majority of unexplained defects seem to

be related to endometriosis. Testing for timing of ET using some approaches, such as ERA, does not test for endometriosis per se and confines the patient to ART. Approaches aimed at diagnosis of inflammatory-based defects in endometrial receptivity may be more directed and could provide avenues for pregnancy to women outside of ART. Within ET cycles, new approaches, including ERA and ReceptivaDx, seem to provide guidance for improving pregnancy outcomes. In particular, treatment of women with BCL6 defects was shown to significantly reduce the prevalence of miscarriage after treatment for endometriosis. More prospective studies, using pregnancy outcome endpoints, are certainly needed before we can overcome Edward's "last barrier" to ART success.

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