Endometrial receptivity in the eutopic endometrium of women with endometriosis—it is affected: let me show you why

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The endometrium maintains complex controls on proliferation and apoptosis as part of repetitive menstrual cycles that prepare the endometrium for the window of implantation and pregnancy. The reliance on inflammatory mechanisms for both implantation and menstruation creates the opportunity in the setting of endometriosis for establishment of chronic inflammation that is disruptive to endometrial receptivity, causing both infertility and abnormal bleeding. Clinically, there can be little doubt that the endometrium of women with endometriosis is less receptive to embryo implantation, and strong evidence exists to suggest that endometrial changes are associated with decreased cycle fecundity as a result of this disease. Here we provide unifying concepts regarding those changes and how they are coordinated to promote progesterone resistance and estrogen dominance through aberrant cell signaling pathways and reduced expression of key homeostatic proteins in eutopic endometrium of women with endometriosis. (Fertil Steril® 2017;■: ■–■. ©2017 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, endometrium, progesterone resistance, implantation, endometrial receptivity

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The endometrium maintains complex autocrine, paracrine and endocrine signaling involving sex steroids, cytokines and chemokines and intracellular signaling, culminating in receptivity to embryo implantation (1). In lieu of a successful pregnancy, the endometrium undergoes complex inflammatory changes that, in a non-scarring fashion, sloughs the lining so that it can be replaced following menstruation (2). While acute inflammation is required for both implantation and menstruation (3), chronic inflammation is disruptive and a major cause of infertility and menstrual bleeding disorders (4–6). Endometriosis affects millions of women, and a major cause of infertility and pelvic pain (7). Women with endometriosis are twice as likely to have infertility (8,9) and pregnancy loss (10,11). Changes in endometrial receptivity due to endometriosis has been well studied and several key studies support our argument that endometriosis affects the endometrium and reduces fertility. How these changes affect fertility is equally important, as a thorough understanding of the physiological mechanism will provide opportunities for both diagnosis and therapy for this common condition.

ENDOMETRIOSIS AND INFERTILITY—WHAT IS THE EVIDENCE?

Inflammation is centrally associated with the pathophysiology of endometriosis, contributing to progesterone resistance and estrogen dominance (12). Endometriosis is a systemic and reversible inflammatory condition that alters endometrial function (13,14). Clinical and nonhuman animal studies support this association between endometriosis and infertility, including: 1) early prospective studies showing that endometriosis patients are infertile (15,16); 2) a recent large retrospective study demonstrating that increased risk of infertility was associated with endometriosis (8); 3) repeated demonstration of reduced success rates in women with endometriosis in the setting of intrauterine insemination (IUI) (17–19); 4) IUI results, in general, that find decreased fecundity when comparing

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endometriosis to other diagnoses (20); and 5) a high prevalence of endometriosis in women who have otherwise unexplained infertility (21).

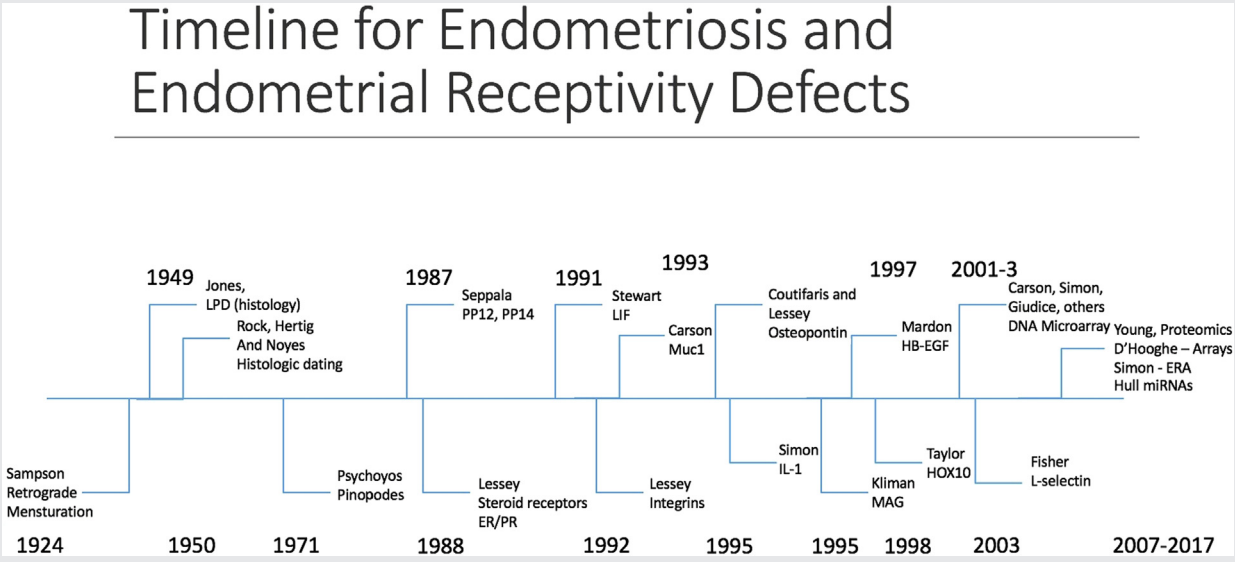
Treatment of endometriosis has been shown to be beneficial for future fertility and improved pregnancy outcomes (22,23). Studies from in vitro fertilization (IVF) cycles have documented decreased pregnancy rates (24,25) which can be improved with GnRH agonist (GnRHa) suppression (26), surgery (27), or aromatase inhibitor therapy (28). Although early studies on donor oocytes have suggested that the primary defect associated with endometriosis may reside in the ovary and oocyte quality (29), larger and more recent studies have documented that defective implantation is also likely involved (30). Prapas et al. studied the result of 240 cycles, placing sibling oocytes from the same donor into women with or without endometriosis. Adjusted odds ratios (95% confidence intervals) showed reduced implantation (0.78 [0.67–0.91]), clinical pregnancy rate (0.22 [0.08–0.57]), ongoing pregnancy (0.11 [0.03–0.35]), and live birth rate (0.19 [0.09–0.38]) for women with endometriosis (30).

Nonhuman animal studies support clinical data suggesting that endometriosis leads to implantation defects, again implicating the endometrium. Induction of endometriosis in animals demonstrates similar phenotypes to human disease (31–34). The failure to implant embryos associated with endometriosis was transferable in the peritoneal fluid (PF) in rabbits (35), as well as in mice who received human endometriotic PF (36). Induction of endometriosis in baboons has been shown to be associated with gradual but profound alterations in the endometrium over time (37), suggesting that inflammation and the immune system may be involved in these changes.

Endometrial biomarkers are differentially expressed in the endometrium of women with endometriosis compared with normal women (38,39), and studies over the years have refined and expanded these approaches to include microRNA arrays, proteomics, and selected molecules, including BCL6 (Fig. 1). Early studies on endometrial proteins that participate in embryo attachment and invasion reported an endometriosis-associated decrease in expression of key proteins (5,40). Endometrial integrins are cell-surface receptors for extracellular matrix proteins that were first described in early 1990 (41,42). We and others reported on specific key integrins with a role in implantation (41,43,44), and the $\alpha v\beta 3$ integrin was decreased in women with infertility and endometriosis (45) and unexplained infertility (46). L-Selectin ligand, another extracellular ligand thought to be an attachment receptor on the endometrium for embryo-derived selectin, is decreased in the endometrium of women with endometriosis and unexplained infertility (47–49).

The changes in endometrial gene expression associated with defective endometrial receptivity reflect a shift away from normal progesterone action (39) and toward excessive estrogen activity. Such alterations in the balance between estrogen and progesterone likely affect fertility and implantation while also promoting the pathogenesis of endometriosis as a disease (50). Progesterone receptor changes and downstream effects of progesterone (51,52) are noted in women with endometriosis (53). Park et al. suggested that the endometrium of women with endometriosis is more proliferative as a result of endometriosis (54), and we demonstrated the endometrium displays an inappropriate elevation in secretory-phase estrogen receptor (ESR1) levels

FIGURE 1



Timeline for major discoveries in endometriosis and related defects in endometrial receptivity. Pivotal research on endometriosis commenced with the work of Sampson, and changes in endometrium have been noted by representative investigators up to the present day. There are many other important contributions that are not indicated here (140–163).

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