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).

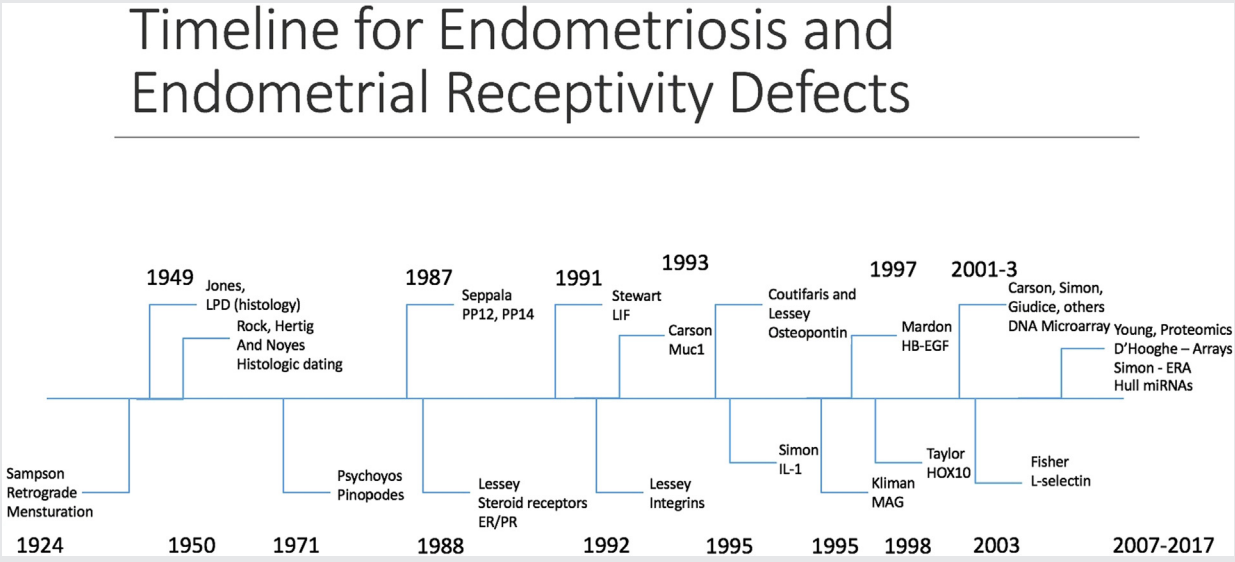
Treatment of endometriosis has been shown to be beneficial for future fertility and improved pregnancy outcomes (22,23). Studies from in vitro fertilization (IVF) cycles have documented decreased pregnancy rates (24,25) which can be improved with GnRH agonist (GnRHa) suppression (26), surgery (27), or 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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at the time of implantation (55). Because ESR1 levels are down-regulated at implantation in almost all mammalian species studied and the primary role of progesterone (56), this failure to down-regulate ESR1 is a single primary end point that may predict implantation failure.

ENDOMETRIOSIS AND INFLAMMATION

Why would the endometrium and endometrial receptivity be altered in endometriosis? Inflammation is known to alter endometrial receptivity and has been associated specifically with endometriosis (57,58). Endometriosis results in systemic and local cytokine expression changes that disrupt normal endometrial function (59–62) and is reversible by surgical removal of endometriomas (63). One of the hallmark changes seen in the endometrium of women with endometriosis is an induction of p450 aromatase expression (64,65). Though usually restricted to certain cell types, including the ovary, placenta, and brain (66), overexpression of p450 aromatase in endometrium changes the dynamic of progesterone-to-estrogen activity, and favors development and growth of endometriosis (67). Furthermore, inflammation has been shown to influence aromatase and steroid receptor expression (68). Brosens et al. demonstrated that elevated aromatase expression is associated with poor IVF outcomes (69). Estrogen, perhaps locally produced, has been shown to inhibit key molecules in attachment of embryos, including the $\alpha v\beta 3$ integrin (70). Reduced integrin expression is associated with reduced IVF outcomes that can be overcome with aromatase inhibitors given in the stimulation cycle (28). Thus, $\alpha v\beta 3$ integrin is a one example of a single biomarker that has been shown to predict IVF outcome and be amenable to therapy.

The proimplantation cytokine leukemia inhibitory factor (LIF) is essential for normal implantation (71). LIF was shown to peak at the time of implantation in mice. In mice with targeted LIF mutations, embryos would float within the uterus but not implant, and exogenous LIF would result in implantation, suggesting an important role of this cytokine. Studies in humans have shown that LIF is present at the time of implantation (72) and that its expression is reduced in women with endometriosis (73). Other key molecules that are required for normal endometrial receptivity, such as HOXA10 (74), are reduced in endometriosis but restored after surgical resection of disease tissue (75). Reduction in HOXA10 has been reported to be due to epigenetic changes associated with aberrant methylation of the HOXA10 promoter (76).

The inflammatory response seen in endometriosis is unusual and may be related to intrinsic programmatic endometrial responses to progesterone withdrawal (2). During the late phases of the menstrual cycle, progesterone levels fall and inflammatory responses ensue in an orchestrated response required for menstruation (2,77). Because progesterone action is impaired in the setting of endometriosis (78), this may mimic progesterone withdrawal and thereby stimulate a premature inflammatory (premenstrual) response (79). Rel-A (p65) is a subunit of nuclear factor κB that is central to the inflammatory response. Rel-A inhibits progesterone receptor (PR) via the PR promoter (80) and therefore further contributes to progesterone resistance. ARID1A, an antiinflammatory protein that is often mutated in ovarian and breast cancers (81,82), is down-regulated in endometriosis (83) and appears to be a key regulator of the inflammatory response seen in this disease by blocking Rel-A action on cytokine expression (82). Inflammatory responses are also exaggerated by the loss of other regulatory proteins, including protein inhibitor of STAT3 (PIAS3), which we recently reported was reduced in the endometrium of women with endometriosis (84).

These inflammatory responses of the endometrium in endometriosis has important downstream effects that affect fertility (85–90) and have been recently reviewed (5,91). Interleukin (IL)-17 is central to many of the changes in endometriosis, including the stimulating effect on cyclooxygenase-2 (COX-2) activity and IL-8 and aromatase expression (92). IL-17 is specifically elevated in the blood and endometrium of women with endometriosis (61). COX-2 (93) and prostaglandins (94,95) are central to eutopic endometrial changes associated with endometriosis. The shift toward estrogen dominance induces these factors that promote inflammation, angiogenesis, cell proliferation, and immunosuppression. IL-17–induced IL-8 has been shown to target the PTEN/protein kinase B (AKT) signaling pathway, which is aberrantly activated in endometriosis (96). IL-17 also induces the inflammatory cytokine IL-6 (61), which is elevated in the endometrium of endometriosis patients (97,98). IL-17 expression is reduced after treatment of endometriosis (61).

We have reported that endometriosis is associated with sustained activation of STAT3 in eutopic endometrium, which is driven by IL-6 (13) and exacerbated by down-regulation of its primary inhibitor, PIAS3, in women with endometriosis (84). STAT3 phosphorylation stabilizes hypoxia-induced factor 1-alpha (HIF1A) (13) and stimulates BCL6 expression (99). STAT3 activation appears to contribute to progesterone resistance and is central to inflammatory responses, including stimulation of these downstream effectors leading to the hallmark changes seen in endometriosis: proliferation, cell survival, and angiogenesis. HIF1A, which normally appears at menstruation, is responsible for many downstream effects, including angiogenesis. Inflammation associated with endometriosis has been implicated in epigenetic change (100) as well as aberrant activation of signaling pathways.

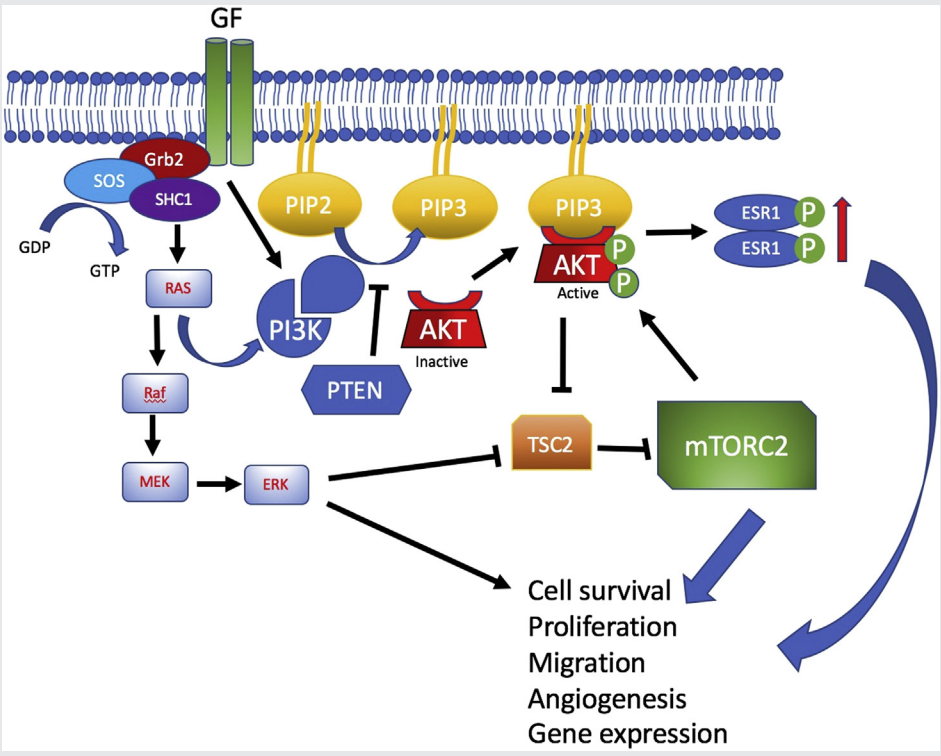
ENDOMETRIOSIS AND INFERTILITY: ROLE OF EUTOPIC ENDOMETRIUM

Endometriosis has been described as a progesterone-resistant disease owing to the blunted or inadequate response to progesterone of both eutopic and ectopic endometrial cells and tissue (101–103). This is demonstrated by low expression of PR (104), blunted expression of progesterone target genes (47,105,106), and an inadequate decidualization response (47,103,106). Progesterone resistance associated with endometriosis contributes to increased cell proliferation and survival (54) and elevated levels of estrogen receptor (55). Because progesterone plays a role in decreasing inflammation in the endometrium, the insensitivity to progesterone signaling results in a proinflammatory condition (107,108). The

consequences of this is far reaching, affecting estrogen-driven mechanisms and differentiation capacity of the tissue.

A role for eutopic endometrium in endometriosis-related infertility has been focused also on the defects in decidualization, a change in endometrial morphology that is essential for pregnancy success (109–111). There are multiple pathways by which decidualization defects might arise, and many have been identified as aberrant in endometriosis, with defects in decidual responses having been widely reported (103,112,113). The decidua is an important component of the maternal/embryo interface that provides nutrients to the embryo, protects the developing embryo from stress pathways and immune rejection, and regulates the invasion of the trophoblast. Therefore, aberrant decidualization would lead to unfavorable effects on embryo implantation and pregnancy. Although progesterone is a key hormone involved in initiating and prolonging the decidualization process, signaling pathways have been demonstrated to amplify this response, including the PKA pathway (114–118), whereas the AKT and mitogen-activated protein kinase (MAPK) pathways have been demonstrated to blunt decidualization. Impaired decidualization has been reported in both eutopic and ectopic tissues in endometriosis (103,109,119). Human endometrial stromal cells suppress AKT during decidualization (120), and increased activation of PI3K/AKT impedes decidualization (103). FOXO1, required for decidualization, is inactivated by the AKT pathway (121), whereas inhibition of PI3K and AKT increases nuclear FOXO1 and IGFBP1 expression in response to progestin and dibutyryl cyclic AMP treatment (103). PI3K/AKT also activates estrogen receptor alpha (ESR1) (Fig. 2) (122). In addition, AKT has been shown to down-regulate ESR2 (123), with the net effect of enhancing estrogen action. The AKT pathway may also affect progesterone action; AKT can down-regulate PR expression in breast cancer and endometrial cancer cells, as well as in stromal cells derived from endometriosis (124–126). AKT has been shown to attenuate PR action in endometrial cancer cells by affecting recruitment of coregulators to PR on chromatin (127). AKT inhibitors increased cellular PR, decreased cell survival, and increased apoptosis in endometriosis (126). NOTCH1 is another gene that is critical for decidualization of both mouse and human uterine stromal cells (128). Decreased Notch signaling is associated with endometriosis and contributes to impaired decidualization through the down-regulation of FOXO1 (128). Interestingly, NOTCH1 may be a target of SIRT1 (129).

FIGURE 2



The phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (AKT) pathway is triggered when receptor tyrosine kinases are activated by ligand binding (GF) subsequently activating PI3K and adapter proteins (Grb2, SOS, and SHC1). PI3K converts intracellular phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3). In the absence of PTEN, which antagonizes PI3K, PIP3 activates AKT as a primary kinase downstream of PI3K. AKT moves to the plasma membrane and is phosphorylated and activated by mammalian target of rapamycin complex 2 (mTORC2). PTEN antagonizes PI3K activity by dephosphorylating PIP3, leading to its conversion back to PIP2. Kras also contributes to PI3K activation and triggers generation of extracellular signal-regulated kinase (ERK) pathway.

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Studies have also demonstrated that the MAPK pathway is overactive in the eutopic endometrium of women with endometriosis (130). Microarray analysis in eutopic endometrium from endometriosis patients identified members of the MAPK and PI3K signaling pathways to be significantly regulated (131,132). These genes included RON, SOS, 14-3-3 protein eta, and uPAR in epithelial cells and KSR and PI3K p85 regulatory subunit alpha in stromal cells. A recent genome-wide association study of stage A endometriosis revealed that a total of 14 pathways were enriched, including the Grb2-Sos, Wnt-signaling p130Cas, and extracellular signal-regulated kinase (ERK) 1/ERK2/MAPK pathways (133). Wu et al. (134) conducted comprehensive profiling of gene expression differences between ectopic and eutopic endometrium from women with endometriosis, adjusted for menstrual phase and location of lesions. Regulators of the MAPK signaling pathway, including DUSP5, AKT1, HSPB2, PDGFB, PDGFRA, PLA2G5, MAPK6, MAPK7, RAC1, RAF1, RPS6KA3, TGFB3, and MKNK1, were altered. Global analysis of genes performed by Burney et al. (105) of eutopic endometrium from women with endometriosis identified genes associated with inactivation of MAPK signaling cascades, such as ERBB receptor feedback inhibitor 1, and regulators of G-protein–signaling 1, which is an activator of GTPases that rapidly turn off G-protein–coupled receptor signaling pathways to be decreased in endometriosis. Velarde et al. (130) showed that increased ERK1/2 activity in eutopic endometrial stromal cells from women with endometriosis inhibited cAMP-mediated down-regulation of cyclin D1. FOXO1, an important mediator of decidualization of endometrial stromal cells, can be phosphorylated and its function modified by ERK and p38 (135) as well as other kinases, such as DYRK1a (136), CK1 (137), and SGK (138).

SUMMARY: CLINICAL CORRELATES

Although clinical studies support the concept of endometrial receptivity defects in endometriosis, these observations need to be based on a physiologic mechanism. With this review, we hope that the reader can better understand how those changes noted in the eutopic endometrium of women with infertility and endometriosis biologically affect endometrial receptivity. IVF is taking on a larger role for the treatment of infertile couples and is a platform on which endometrial receptivity defects are increasingly being tested (139). Many of the defective pathways described here contribute to infertility and have therapeutic and diagnostic implications. Increasingly, it appears that endometriosis has a negative effect on IVF outcomes, and treatment strategies are evolving to address such defects. Endometrial receptivity defects should remain a relevant and vital part of the workup of couples with infertility.

CONCLUSION

Strong evidence supports the concept that endometrial defects exist in women with endometriosis. The inflammatory nature of this disease, accompanied by excess estrogen action, leads to a constellation of changes in the eutopic endometrium that interferes with normal embryo implantation. Signaling pathways associated with proliferation and cell survival are activated in endometriosis, and antiproliferative progesterone pathways are turned off. Progesterone resistance results in inadequate antagonism of estrogen action, increased inflammation, inadequate differentiation of the stroma, and remodeling of the endometrium, all of which can lead to a nonreceptive endometrium for embryo implantation. Inflammation appears to be central to these defects. For these reasons, it seems clear that the eutopic endometrium is a primary barrier to implantation in women with active endometriosis.

REFERENCES

1. Carson DD, Bagchi I, Dey SK, Enders AC, Fazleabas AT, Lessey BA, et al. Embryo implantation. Dev Biol 2000;223:217–37.
2. Evans J, Salamonsen LA. Inflammation, leukocytes and menstruation. Rev Endocr Metab Disord 2012;13:277–88.
3. Critchley HO, Jones RL, Lea RG, Drudy TA, Kelly RW, Williams AR, et al. Role of inflammatory mediators in human endometrium during progesterone withdrawal and early pregnancy. J Clin Endocrinol Metab 1999;84:240.
4. Lessey BA, Young SL. Homeostasis imbalance in the endometrium of women with implantation defects: the role of estrogen and progesterone. Semin Reprod Med 2014;32:365–75.
5. Lessey BA, Lebovic DI, Taylor RN. Eutopic endometrium in women with endometriosis: ground zero for the study of implantation defects. Semin Reprod Med 2013;31:109–24.
6. Vercellini P, Vigano P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 2014;10:261–75.
7. Pfeifer S, Fritz MA, Goldberg J, McClure R, Lobo R, Thomas M, et al. Endometriosis and infertility: a committee opinion. Fertil Steril 2012;98:591–8.
8. Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod 2016;31:1475–82.
9. Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in endometriosis-associated infertility. Fertil Steril 1993;59:963.
10. Daya S. Endometriosis and spontaneous abortion. In: Infertility and Reproductive Medicine Clinics of North America. Vol. 7. Philadelphia: W. B. Saunders; 1996:759–73.
11. Vercammen EE, d'Hooghe TM. Endometriosis and recurrent pregnancy loss. Semin Reprod Med 2000;18:363–8.
12. Fox C, Morin S, Jeong JW, Scott RT Jr, Lessey BA. Local and systemic factors and implantation: what is the evidence? Fertil Steril 2016;105:873–84.
13. Kim BG, Yoo JY, Kim TH, Shin JH, Langenheim JF, Ferguson SD, et al. Aberrant activation of signal transducer and activator of transcription-3 (STAT3) signaling in endometriosis. Hum Reprod 2015;30:1069–78.
14. Vannuccini S, Clifton VL, Fraser IS, Taylor HS, Critchley H, Giudice LC, et al. Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome. Hum Reprod Update 2016;22:104–15.
15. Strathy JH, Molgaard CA, Coulam CB, Melton LJ. Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women. Fertil Steril 1982;38:667–72.
16. Verkauf BS. Incidence, symptoms, and signs of endometriosis in fertile and infertile women. J Fla Med Assoc 1987;74:671–5.
17. Hammond MG, Jordan S, Sloan CS. Factors affecting pregnancy rates in a donor insemination program using frozen semen. Am J Obstet Gynecol 1986;155:480.
18. Omland AK, Tanbo T, Dale PO, Abyholm T. Artificial insemination by husband in unexplained infertility compared with infertility associated with peritoneal endometriosis. Hum Reprod 1998;13:2602.
19. Jansen RP. Minimal endometriosis and reduced fecundability: prospective evidence from an artificial insemination by donor program. Fertil Steril 1986;46:141–3.
20. Hughes EG. The effectiveness of ovulation induction and intrauterine insemination in the treatment of persistent infertility: a meta-analysis. Hum Reprod 1997;12:1865–72.

21. Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, d'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril 2009;92:68–74.
22. Marcoux S, Maheux R, Bérubé S, Canadian Collaborative Group on Endometriosis. Laparoscopic surgery in infertile, women with minimal or mild endometriosis. N Engl J Med 1997;337:217–22.
23. Jacobson TZ, Barlow DH, Koninckx PR, Olive D, Farquhar C. Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database Syst Rev 2002:CD001398.
24. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. Fertil Steril 2002;77:1148–55.
25. Hamdan M, Omar SZ, Dunselman G, Cheong Y. Influence of endometriosis on assisted reproductive technology outcomes: a systematic review and meta-analysis. Obstet Gynecol 2015;125:79–88.
26. Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. Cochrane Database Syst Rev 2006:CD004635.
27. Littman E, Giudice L, Lathi R, Berker B, Milki A, Nezhat C. Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. Fertil Steril 2005;84:1574–8.
28. Miller PB, Parnell BA, Bushnell G, Tallman N, Forstein DA, Higdon HL 3rd, et al. Endometrial receptivity defects during IVF cycles with and without letrozole. Hum Reprod 2012;27:881–8.
29. Simón C, Gutiérrez A, Vidal A, de los Santos MJ, Tarín JJ, Remohí J, et al. Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. Hum Reprod 1994;9:725–9.
30. Prapas Y, Goudakou M, Matalliotakis I, Kalogeraki A, Matalliotaki C, Panagiotidis Y, et al. History of endometriosis may adversely affect the outcome in menopausal recipients of sibling oocytes. Reprod Biomed Online 2012;25:543–8.
31. Schenken RS, Asch RH. Surgically induction of endometriosis in the rabbit: effects on fertility and concentration of peritoneal fluid prostaglandins. Fertil Steril 1980;34:581–7.
32. d'Hooghe TM, Bambra CS, Raeymaekers BM, Riday AM, Suleman MA, Koninckx PR. The cycle pregnancy rate is normal in baboons with stage I endometriosis but decreased in primates with stage II and stage III–IV disease. Fertil Steril 1996;66:809–13.
33. Vernon MW. Experimental endometriosis in laboratory animals as a research model. Prog Clin Biol Res 1990;323:49.
34. Fazleabas AT. Progesterone resistance in a baboon model of endometriosis. Semin Reprod Med 2010;28:75–80.
35. Hahn DW, Carraher RP, Foldesy RG, McGuire JL. Experimental evidence for failure to implant as a mechanism of infertility associated with endometriosis. Am J Obstet Gynecol 1986;155:1109–13.
36. Illera MJ, Juan L, Stewart CL, Cullinan E, Ruman J, Lessey BA. Effect of peritoneal fluid from women with endometriosis on implantation in the mouse model. Fertil Steril 2000;74:41–8.
37. Braundmeier A, Jackson K, Hastings J, Koehler J, Nowak R, Fazleabas A. Induction of endometriosis alters the peripheral and endometrial regulatory T cell population in the nonhuman primate. Hum Reprod 2012;27:1712–22.
38. May KE, Villar J, Kirtley S, Kennedy SH, Becker CM. Endometrial alterations in endometriosis: a systematic review of putative biomarkers. Hum Reprod Update 2011;17:637–53.
39. Aghajanova L, Velarde MC, Giudice LC. Altered gene expression profiling in endometrium: evidence for progesterone resistance. Semin Reprod Med 2010;28:51–8.
40. Lessey BA. Implantation defects in infertile women with endometriosis. Ann N Y Acad Sci 2002;955:265–80, discussion 293–5, 396–406.
41. Lessey BA, Damjanovich L, Coutifaris C, Castelbaum A, Albelda SM, Buck CA. Integrin adhesion molecules in the human endometrium. Correlation with the normal and abnormal menstrual cycle. J Clin Invest 1992;90:188–95.
42. Tabibzadeh S. Pattern of expression of integrin molecules in human endometrium throughout the menstrual cycle. Hum Reprod 1992;7:876–82.
43. Lessey BA, Castelbaum AJ, Buck CA, Lei Y, Yowell CW, Sun J. Further characterization of endometrial integrins during the menstrual cycle and in pregnancy. Fertil Steril 1994;62:497–506.
44. Tabibzadeh S. Patterns of expression of integrin molecules in human endometrium throughout the menstrual cycle. Hum Reprod 1992;7:876–82.
45. Lessey BA, Castelbaum AJ, Sawin SW, Buck CA, Schinnar R, Bilker W, et al. Aberrant integrin expression in the endometrium of women with endometriosis. J Clin Endocrinol Metab 1994;79:643–9.
46. Lessey BA, Castelbaum AJ, Sawin SW, Sun J. Integrins as markers of uterine receptivity in women with primary unexplained infertility. Fertil Steril 1995;63:535–42.
47. Kao LC, Germeyer A, Tulac S, Lobo S, Yang JP, Taylor RN, et al. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. Endocrinology 2003;144:2870–81.
48. Margarit L, Gonzalez D, Lewis PD, Hopkins L, Davies C, Conlan RS, et al. L-Selectin ligands in human endometrium: comparison of fertile and infertile subjects. Hum Reprod 2009;24:2767–77.
49. Foulk RA, Zdravkovic T, Genbacev O, Prakobphol A. Expression of L-selectin ligand MECA-79 as a predictive marker of human uterine receptivity. J Assist Reprod Genet 2007;24:316–21.
50. Kitawaki J, Kado N, Ishihara H, Koshiba H, Kitaoka Y, Honjo H. Endometriosis: the pathophysiology as an estrogen-dependent disease. J Steroid Biochem Mol Biol 2002;83:149–55.
51. Yoo JY, Shin H, Kim TH, Choi WS, Ferguson SD, Fazleabas AT, et al. CRISPLD2 is a target of progesterone receptor and its expression is decreased in women with endometriosis. PLoS One 2014;9:e100481.
52. Young SL, Lessey BA. Progesterone function in human endometrium: clinical perspectives. Semin Reprod Med 2010;28:5–16.
53. Igarashi TM, Bruner-Tran KL, Yeaman GR, Lessey BA, Edwards DP, Eisenberg E, et al. Reduced expression of progesterone receptor-B in the endometrium of women with endometriosis and in cocultures of endometrial cells exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Fertil Steril 2005;84:67–74.
54. Park JS, Lee JH, Kim M, Chang HJ, Hwang KJ, Chang KH. Endometrium from women with endometriosis shows increased proliferation activity. Fertil Steril 2009;92:1246–9.
55. Lessey BA, Palomino WA, Apparao KB, Young SL, Lininger RA. Estrogen receptor-alpha (ER-alpha) and defects in uterine receptivity in women. Reprod Biol Endocrinol 2006;1(4 Suppl):S9.
56. Large MJ, Demayo FJ. The regulation of embryo implantation and endometrial decidualization by progesterone receptor signaling. Mol Cell Endocrinol 2012;358:155–65.
57. Weiss G, Goldsmith LT, Taylor RN, Bellet D, Taylor HS. Inflammation in reproductive disorders. Reprod Sci 2009;16:216–29.
58. Agic A, Xu H, Finas D, Banz C, Diedrich K, Hornung D. Is endometriosis associated with systemic subclinical inflammation? Gynecol Obstet Invest 2006;62:139–47.
59. Ahn SH, Khalaj KL, Young SL, Lessey BA, Koti M, Tayade C. Nanostring gene profiling reveals unique immune-inflammation signatures in endometriosis patients. Fertil Steril 2016;106:1420–31.
60. Ahn SH, Khalaj K, Young SL, Lessey BA, Koti M, Tayade C. Immune-inflammation gene signatures in endometriosis patients. Fertil Steril 2016;106:1420–31.
61. Ahn SH, Edwards AK, Singh SS, Young SL, Lessey BA, Tayade C. IL-17A contributes to the pathogenesis of endometriosis by triggering proinflammatory cytokines and angiogenic growth factors. J Immunol 2015;195:2591–600.
62. Khoufache K, Michaud N, Harir N, Kibangou Bondza P, Akoum A. Anomalies in the inflammatory response in endometriosis and possible consequences: a review. Minerva Endocrinol 2012;37:75–92.
63. Monsanto SP, Edwards AK, Zhou J, Nagarkatti P, Nagarkatti M, Young SL, et al. Surgical removal of endometriotic lesions alters local and systemic proinflammatory cytokines in endometriosis patients. Fertil Steril 2016;105:968–77.e5.

64. Attar E, Bulun SE. Aromatase inhibitors: the next generation of therapeutics for endometriosis? Fertil Steril 2006;85:1307–18.
65. Kitawaki J, Noguchi T, Amatsu T, Maeda K, Tsukamoto K, Yamamoto T, et al. Expression or aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. Biol Reprod 1997;57:514–9.
66. Simpson ER, Mahendroo MS, Means GD, Kilgore MW, Hinshelwood MM, Graham-Lorence S, et al. Aromatase cytochrome P450, the enzyme responsible for estrogen biosynthesis. Endocr Rev 1994;15:342–55.
67. Bulun SE, Yang S, Fang Z, Gurates B, Tamura M, Zhou J, et al. Role of aromatase in endometrial disease. J Steroid Biochem Mol Biol 2001;79:19–25.
68. Bukulmez O, Hardy DB, Carr BR, Word RA, Mendelson CR. Inflammatory status influences aromatase and steroid receptor expression in endometriosis. Endocrinology 2008;149:1190–204.
69. Brosens J, Verhoeven H, Campo R, Gianaroli L, Gordts S, Hazekamp J, et al. High endometrial aromatase P450 mRNA expression is associated with poor IVF outcome. Hum Reprod 2004;19:352–6.
70. Somkuti SG, Yuan L, Fritz MA, Lessey BA. Epidermal growth factor and sex steroids dynamically regulate a marker of endometrial receptivity in Ishikawa cells. J Clin Endocrinol Metab 1997;82:2192–7.
71. Stewart CL, Kaspar P, Brunet LJ, Bhatt H, Gadi I, Kontgen F, et al. Blastocyst implantation depends on maternal expression of leukaemia inhibitory factor. Nature 1992;359:76–9.
72. Cullinan EB, Abbondanzo SJ, Anderson PS, Pollard JW, Lessey BA, Stewart CL. Leukemia inhibitory factor (LIF) and LIF receptor expression in human endometrium suggests a potential autocrine/paracrine function in regulating embryo implantation. Proc Natl Acad Sci U S A 1996;93:3115–20.
73. Franasiak JM, Holoch KJ, Yuan L, Schammel DP, Young SL, Lessey BA. Prospective assessment of midsecretory endometrial leukemia inhibitor factor expression versus $\alpha v\beta 3$ testing in women with unexplained infertility. Fertil Steril 2014;101:1724–31.
74. Du H, Taylor HS. The role of Hox genes in female reproductive tract development, adult function, and fertility. Cold Spring Harb Perspect Med 2015;6:a023002.
75. Celik O, Unlu C, Otlu B, Celik N, Caliskan E. Laparoscopic endometrioma resection increases peri-implantation endometrial HOXA-10 and HOXA-11 mRNA expression. Fertil Steril 2015;104:356–65.
76. Wu Y, Halverson G, Basir Z, Strawn E, Yan P, Guo SW. Aberrant methylation at HOXA10 may be responsible for its aberrant expression in the endometrium of patients with endometriosis. Am J Obstet Gynecol 2005;193:371–80.
77. Evans J, Salamonsen LA. Decidualized human endometrial stromal cells are sensors of hormone withdrawal in the menstrual inflammatory cascade. Biol Reprod 2014;90:14.
78. Osteen KG, Bruner-Tran KL, Keller NR, Eisenberg E. Progesterone-mediated endometrial maturation limits matrix metalloproteinase (MMP) expression in an inflammatory-like environment: a regulatory system altered in endometriosis. Ann N Y Acad Sci 2002;955:37–47, discussion 86–8, 396–406.
79. Li X, Large MJ, Creighton CJ, Lanz RB, Jeong JW, Young SL, et al. COUP-TFII regulates human endometrial stromal genes involved in inflammation. Mol Endocrinol 2013;27:2041–54.
80. Kalkhoven E, Wissink S, van der Saag PT, van der Burg B. Negative interaction between the RelA(p65) subunit of NF-kappaB and the progesterone receptor. J Biol Chem 1996;271:6217–24.
81. Chandler RL, Damrauer JS, Raab JR, Schisler JC, Wilkerson MD, Didion JP, et al. Coexistent ARID1A-PIK3CA mutations promote ovarian clear-cell tumorigenesis through pro-tumorigenic inflammatory cytokine signalling. Nat Commun 2015;6:6118.
82. Kim M, Lu F, Zhang Y. Loss of HDAC-mediated repression and gain of NF-κB activation underlie cytokine induction in ARID1A- and PIK3CA-mutation-driven ovarian cancer. Cell Rep 2016;17:275–88.
83. Kim TH, Yoo JY, Wang Z, Lydon JP, Khatri S, Hawkins SM, et al. ARID1A is essential for endometrial function during early pregnancy. PLoS Genet 2015;11:e1005537.
84. Yoo JY, Jeong JW, Fazleabas AT, Tayade C, Young SL, Lessey BA. Protein inhibitor of activated STAT3 (PIAS3) is down-regulated in eutopic endometrium of women with endometriosis. Biol Reprod 2016;95:11.
85. Dechaud H, Maudelonde T, Daures JP, Rossi JF, Hedon B. Evaluation of endometrial inflammation by quantification of macrophages, T lymphocytes, and interleukin-1 and -6 in human endometrium. J Assist Reprod Genet 1998;15:612–8.
86. Othman Eel D, Hornung D, Salem HT, Khalifa EA, El-Metwally TH, Al-Hendy A. Serum cytokines as biomarkers for nonsurgical prediction of endometriosis. Eur J Obstet Gynecol Reprod Biol 2008;137:240–6.
87. Kalu E, Sumar N, Giannopoulos T, Patel P, Croucher C, Sherriff E, et al. Cytokine profiles in serum and peritoneal fluid from infertile women with and without endometriosis. J Obstet Gynaecol Res 2007;33:490–5.
88. Ulukus EC, Ulukus M, Seval Y, Zheng W, Arici A. Expression of interleukin-8 and monocyte chemotactic protein-1 in adenomyosis. Hum Reprod 2005;20:2958–63.
89. Akoum A, Kong J, Metz C, Beaumont MC. Spontaneous and stimulated secretion of monocyte chemotactic protein-1 and macrophage migration inhibitory factor by peritoneal macrophages in women with and without endometriosis. Fertil Steril 2002;77:989–94.
90. Garcia-Velasco JA, Seli E, Arici A. Regulation of monocyte chemotactic protein-1 expression in human endometrial stromal cells by integrin-dependent cell adhesion. Biol Reprod 1999;61:548–52.
91. Miller JE, Ahn SH, Monsanto SP, Khalaj K, Koti M, Tayade C. Implications of immune dysfunction on endometriosis associated infertility. Oncotarget 2017;8:7138–47.
92. Hirata T, Osuga Y, Takamura M, Saito A, Hasegawa A, Koga K, et al. Interleukin-17F increases the secretion of interleukin-8 and the expression of cyclooxygenase 2 in endometriosis. Fertil Steril 2011;96:113–7.
93. Ota H, Igarashi S, Sasaki M, Tanaka T. Distribution of cyclooxygenase-2 in eutopic and ectopic endometrium in endometriosis and adenomyosis. Hum Reprod 2001;16:561–6.
94. Wu MH, Lu CW, Chuang PC, Tsai SJ. Prostaglandin E2: the master of endometriosis? Exp Biol Med (maywood) 2010;235:668–77.
95. Wu MH, Shoji Y, Chuang PC, Tsai SJ. Endometriosis: disease pathophysiology and the role of prostaglandins. Expert Rev Mol Med 2007;9:1–20.
96. Li MQ, Luo XZ, Meng YH, Mei J, Zhu XY, Jin LP, et al. CXCL8 enhances proliferation and growth and reduces apoptosis in endometrial stromal cells in an autocrine manner via a CXCR1-triggered PTEN/AKT signal pathway. Hum Reprod 2012;27:2107–16.
97. Ponce C, Torres M, Galleguillos C, Sovino H, Boric MA, Fuentes A, et al. Nuclear factor kappaB pathway and interleukin-6 are affected in eutopic endometrium of women with endometriosis. Reproduction 2009;137:727–37.
98. Boutten A, Dehoux M, Edelman P, Seta N, Menard A, Madelenat P, et al. IL6 and acute phase plasma proteins in peritoneal fluid of women with endometriosis. Clin Chim Acta 1992;210:187.
99. Evans-Hoeker E, Lessey BA, Jeong JW, Savaris RF, Palomino WA, Yuan L, et al. Endometrial BCL6 overexpression in eutopic endometrium of women with endometriosis. Reprod Sci 2016;23:1234–41.
100. Bruner-Tran KL, Herington JL, Duleba AJ, Taylor HS, Osteen KG. Medical management of endometriosis: emerging evidence linking inflammation to disease pathophysiology. Minerva Ginecol 2013;65:199–213.
101. Bulun SE, Cheng YH, Yin P, Imir G, Utsunomiya H, Attar E, et al. Progesterone resistance in endometriosis: link to failure to metabolize estradiol. Mol Cell Endocrinol 2006;248:94–103.
102. Yin P, Lin Z, Cheng YH, Marsh EE, Utsunomiya H, Ishikawa H, et al. Progesterone receptor regulates Bcl-2 gene expression through direct binding to its promoter region in uterine leiomyoma cells. J Clin Endocrinol Metab 2007;92:4459–66.
103. Yin X, Pavone ME, Lu Z, Wei J, Kim JJ. Increased activation of the PI3K/AKT pathway compromises decidualization of stromal cells from endometriosis. J Clin Endocrinol Metab 2012;97:E35–43.
104. Attia GR, Zeitoun K, Edwards D, Johns A, Carr BR, Bulun SE. Progesterone receptor isoform A but not B is expressed in endometriosis. J Clin Endocrinol Metab 2000;85:2897–902.

105. Burney RO, Talbi S, Hamilton AE, Vo KC, Nyegaard M, Nezhat CR, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. Endocrinology 2007;148:3814–26.
106. Osteen KG, Bruner-Tran KL, Eisenberg E. Reduced progesterone action during endometrial maturation: a potential risk factor for the development of endometriosis. Fertil Steril 2005;83:529–37.
107. Patel BG, Rudnicki M, Yu J, Shu Y, Taylor RN. Progesterone resistance in endometriosis: origins, consequences and interventions. Acta Obstet Gynecol Scand 2017;96:623–32.
108. Patel B, Elguero S, Thakore S, Dahoud W, Bedaiwy M, Mesiano S. Role of nuclear progesterone receptor isoforms in uterine pathophysiology. Hum Reprod Update 2015;21:155–73.
109. Klemmt PA, Carver JG, Kennedy SH, Koninckx PR, Mardon HJ. Stromal cells from endometriotic lesions and endometrium from women with endometriosis have reduced decidualization capacity. Fertil Steril 2006;85:564–72.
110. Kim JJ, Taylor HS, Lu Z, Ladhani O, Hastings JM, Jackson KS, et al. Altered expression of HOXA10 in endometriosis: potential role in decidualization. Mol Hum Reprod 2007;13:323–32.
111. Minici F, Tiberi F, Tropea A, Orlando M, Gangale MF, Romani F, et al. Endometriosis and human infertility: a new investigation into the role of eutopic endometrium. Hum Reprod 2008;23:530–7.
112. Lee CH, Kim TH, Lee JH, Oh SJ, Yoo JY, Kwon HS, et al. Extracellular signal-regulated kinase 1/2 signaling pathway is required for endometrial decidualization in mice and human. PLoS One 2013;8:e75282.
113. Ahn JI, Yoo JY, Kim TH, Kim YI, Ferguson SD, Fazleabas AT, et al. cAMP-response element–binding 3–like protein 1 (CREB3L1) is required for decidualization and its expression is decreased in women with endometriosis. Curr Mol Med 2016;16:276–87.
114. Brar AK, Frank GR, Kessler CA, Cedars MI, Handwerger S. Progesterone-dependent decidualization of the human endometrium is mediated by cAMP. Endocrine 1997;6:301–7.
115. Brosens JJ, Hayashi N, White JO. Progesterone receptor regulates decidual prolactin expression in differentiating human endometrial stromal cells. Endocrinology 1999;140:4809–20.
116. Telgmann R, Maronde E, Tasken K, Gellersen B. Activated protein kinase A is required for differentiation-dependent transcription of the decidual prolactin gene in human endometrial stromal cells. Endocrinology 1997;138:929–37.
117. Tierney EP, Tulac S, Huang ST, Giudice LC. Activation of the protein kinase A pathway in human endometrial stromal cells reveals sequential categorical gene regulation. Physiol Genomics 2003;16:47–66.
118. Takano M, Lu Z, Goto T, Fusi L, Higham J, Francis J, et al. Transcriptional cross talk between the forkhead transcription factor forkhead box O1A and the progesterone receptor coordinates cell cycle regulation and differentiation in human endometrial stromal cells. Mol Endocrinol 2007;21:2334–49.
119. Aghajanova L, Hamilton A, Kwintkiewicz J, Vo KC, Giudice LC. Steroidogenic enzyme and key decidualization marker dysregulation in endometrial stromal cells from women with versus without endometriosis. Biol Reprod 2008;80:105–14.
120. Yoshino O, Osuga Y, Hirota Y, Koga K, Yano T, Tsutsumi O, et al. Akt as a possible intracellular mediator for decidualization in human endometrial stromal cells. Mol Hum Reprod 2003;9:265–9.
121. Kim JJ, Buzzio OL, Li S, Lu Z. Role of FOXO1A in the regulation of insulin-like growth factor–binding protein-1 in human endometrial cells: interaction with progesterone receptor. Biol Reprod 2005;73:833–9.
122. Campbell RA, Bhat-Nakshatri P, Patel NM, Constantinidou D, Ali S, Nakshatri H. Phosphatidylinositol 3-kinase/AKT–mediated activation of estrogen receptor alpha: a new model for antiestrogen resistance. J Biol Chem 2001;276:9817–24.
123. Sanchez M, Sauve K, Picard N, Tremblay A. The hormonal response of estrogen receptor beta is decreased by the phosphatidylinositol 3-kinase/Akt pathway via a phosphorylation-dependent release of CREB-binding protein. J Biol Chem 2007;282:4830–40.
124. Cui X, Zhang P, Deng W, Oesterreich S, Lu Y, Mills GB, et al. Insulin-like growth factor-I inhibits progesterone receptor expression in breast cancer cells via the phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway: progesterone receptor as a potential indicator of growth factor activity in breast cancer. Mol Endocrinol 2003;17:575–88.
125. Pant A, Lee II, Lu Z, Rueda BR, Schink J, Kim JJ. Inhibition of AKT with the orally active allosteric AKT inhibitor, MK-2206, sensitizes endometrial cancer cells to progestin. PLoS One 2012;7:e41593.
126. Eaton JL, Unno K, Caraveo M, Lu Z, Kim JJ. Increased AKT or MEK1/2 activity influences progesterone receptor levels and localization in endometriosis. J Clin Endocrinol Metab 2013;98:E1871–9.
127. Lee II, Maniar K, Lydon JP, Kim JJ. Akt regulates progesterone receptor B–dependent transcription and angiogenesis in endometrial cancer cells. Oncogene 2016;35:5191–201.
128. Su RW, Strug MR, Joshi NR, Jeong JW, Miele L, Lessey BA, et al. Decreased Notch pathway signaling in the endometrium of women with endometriosis impairs decidualization. J Clin Endocrinol Metab 2015;100:E433–42.
129. Marcel N, Perumalsamy LR, Shukla SK, Sarin A. The lysine deacetylase Sirtuin 1 modulates the localization and function of the Notch1 receptor in regulatory T cells. Sci Signal 2017;10.
130. Velarde MC, Aghajanova L, Nezhat CR, Giudice LC. Increased mitogen-activated protein kinase kinase/extracellularly regulated kinase activity in human endometrial stromal fibroblasts of women with endometriosis reduces 3′,5′-cyclic adenosine 5′-monophosphate inhibition of cyclin D1. Endocrinology 2009;150:4701–12.
131. Matsuzaki S, Canis M, Vaurs-Barriere C, Boespflug-Tanguy O, Dastugue B, Mage G. DNA microarray analysis of gene expression in eutopic endometrium from patients with deep endometriosis using laser capture microdissection. Fertil Steril 2005;84(Suppl 2):1180–90.
132. Matsuzaki S, Canis M, Pouly JL, Botchorishvili R, Dechelotte PJ, Mage G. Differential expression of genes in eutopic and ectopic endometrium from patients with ovarian endometriosis. Fertil Steril 2006;86:548–53.
133. Uimari O, Rahmioglu N, Nyholt DR, Vincent K, Missmer SA, Becker C, et al. Genome-wide genetic analyses highlight mitogen-activated protein kinase (MAPK) signaling in the pathogenesis of endometriosis. Hum Reprod 2017;32:1–14.
134. Wu Y, Kajdacsy-Balla A, Strawn E, Basir Z, Halverson G, Jailwala P, et al. Transcriptional characterizations of differences between eutopic and ectopic endometrium. Endocrinology 2006;147:232–46.
135. Asada S, Daitoku H, Matsuzaki H, Saito T, Sudo T, Mukai H, et al. Mitogen-activated protein kinases, Erk and p38, phosphorylate and regulate Foxo1. Cell Signal 2007;19:519–27.
136. Woods YL, Rena G, Morrice N, Barthel A, Becker W, Guo S, et al. The kinase DYRK1A phosphorylates the transcription factor FKHR at Ser329 in vitro, a novel in vivo phosphorylation site. Biochem J 2001;355:597–607.
137. Rena G, Bain J, Elliott M, Cohen P. D4476, a cell-permeant inhibitor of CK1, suppresses the site-specific phosphorylation and nuclear exclusion of FOXO1a. EMBO Rep 2004;5:60–5.
138. Brunet A, Park J, Tran H, Hu LS, Hemmings BA, Greenberg ME. Protein kinase SGK mediates survival signals by phosphorylating the forkhead transcription factor FKHRL1 (FOXO3a). Mol Cell Biol 2001;21:952–65.
139. Opoien HK, Fedorcsak P, Omland AK, Abyholm T, Bjercke S, Ertzeid G, et al. In vitro fertilization is a successful treatment in endometriosis-associated infertility. Fertil Steril 2012;97:912–8.
140. Nakagawa K, Ohgi S, Horikawa T, Kojima R, Ito M, Saito H. Laparoscopy should be strongly considered for women with unexplained infertility. J Obstet Gynaecol Res 2007;33:665–70.
141. Tsuji I, Ami K, Miyazaki A, Hujinami N, Hoshiai H. Benefit of diagnostic laparoscopy for patients with unexplained infertility and normal hysterosalpingography findings. Tohoku J Exp Med 2009;219:39–42.
142. Sampson JA. Benign and malignant endometrial implants in the peritoneal cavity and their relation to certain ovarian tumors. Surg Gynecol Obstet 1924;38:287–311.
143. Jones GS. Some newer aspects of management of infertility. JAMA 1949;141:1123–9.
144. Noyes RW, Hertig AI, Rock J. Dating the endometrial biopsy. Fertil Steril 1950;1:3–25.

145. Psychoyos A, Mandon P. Étude de la surface de l'épithélium utérin au microscope électronique à balayage. C R Acad Sci Hebd Seances Acad Sci D 1971;272:2723–5.
146. Rutanen EM, Koistinen R, Seppala M, Julkunen M, Suikkari AM, Huhtala ML. Progesterone-associated proteins PP12 and PP14 in the human endometrium. J Steroid Biochem 1987;27:25.
147. Lessey BA, Killam AP, Metzger DA, Haney AF, Greene GL, McCarty KS Jr. Immunohistochemical analysis of human uterine estrogen and progesterone receptors throughout the menstrual cycle. J Clin Endocrinol Metab 1988;67:334–40.
148. Bhatt H, Brunet LJ, Stewart CL. Uterine expression of leukemia inhibitory factor coincides with the onset of blastocyst implantation. Proc Natl Acad Sci U S A 1991;88:11408–12.
149. Surveyor GA, Gendler SJ, Pemberton L, Spicer AP, Carson DD. Differential expression of Muc-1 at the apical cell surface of mouse uterine epithelial cells. FASEB J 1993;7:1151a.
150. Apparao KB, Murray MJ, Fritz MA, Meyer WR, Chambers AF, Truong PR, et al. Osteopontin and its receptor alphavbeta(3) integrin are coexpressed in the human endometrium during the menstrual cycle but regulated differentially. J Clin Endocrinol Metab 2001;86:4991–5000.
151. Simon C, Piquette GN, Frances A, Polan ML. Localization of interleukin-1 type I receptor and interleukin-1 beta in human endometrium throughout the menstrual cycle. J Clin Endocrinol Metab 1993;77:549–55.
152. Simon C, Piquette GN, Frances A, El-Danasouri I, Irwin JC, Polan ML. The effect of interleukin-1β (IL-1β) on the regulation of IL-1 receptor type I messenger ribonucleic acid and protein levels in cultured human endometrial stromal and glandular cells. J Clin Endocrinol Metab 1994;78:760–70.
153. Kliman HJ, Feinberg RF, Schwartz LB, Feinman MA, Lavi E, Meaddough EL. A mucin-like glycoprotein identified by MAG (mouse ascites Golgi) antibodies: menstrual cycle–dependent localization in human endometrium. Am J Pathol 1995;146:166–81.
154. Yoo HJ, Barlow DH, Mardon HJ. Temporal and spatial regulation of expression of heparin-binding epidermal growth factor–like growth factor in the human endometrium: a possible role in blastocyst implantation. Dev Genet 1997;21:102–8.
155. Taylor HS, Arici A, Olive D, Igarashi P. HOXA10 is expressed in response to sex steroids at the time of implantation in the human endometrium. J Clin Invest 1998;101:1379–84.
156. Carson DD. Changes in gene expression during the early to mid-luteal (receptive phase) transition in human endometrium detected by high-density microarray screening. Mol Hum Reprod 2002;8:871–9.
157. Dominguez F, Remohí J, Pellicer A, Simón C. Human endometrial receptivity: a genomic approach. Reprod Biomed Online 2003;6:332–8.
158. Kao LC, Yang J, Lessey BA, Giudice LC. Microarray expression profiling reveals candidate genes for human uterine receptivity. Fertil Steril 2001;76:S59.
159. Genbacev OD, Prakobphol A, Foulk RA, Krtolica AR, Ilic D, Singer MS, et al. Trophoblast L-selectin–mediated adhesion at the maternal-fetal interface. Science 2003;299:405–8.
160. Fassbender A, Vodolazkaia A, Saunders P, Lebovic D, Waelkens E, de Moor B, et al. Biomarkers of endometriosis. Fertil Steril 2013;99:1135–45.
161. Scotchie JG, Fritz MA, Mocanu M, Lessey BA, Young SL. Proteomic analysis of the luteal endometrial secretome. Reprod Sci 2009;16:883–93.
162. Diaz-Gimeno P, Ruiz-Alonso M, Blesa D, Bosch N, Martinez-Conejero JA, Alama P, et al. The accuracy and reproducibility of the endometrial receptivity array is superior to histology as a diagnostic method for endometrial receptivity. Fertil Steril 2013;99:508–17.
163. Ohlsson Teague EM, van der Hoek KH, van der Hoek MB, Perry N, Wagaarachchi P, Robertson SA, et al. MicroRNA-regulated pathways associated with endometriosis. Mol Endocrinol 2009;23:265–75.