Optimal uterine anatomy and physiology necessary for normal implantation and placentation

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The authors review aberrations of uterine anatomy and physiology affecting pregnancy outcomes with IVF. In the case of endometriosis and hydrosalpinx, pathologies outside of the uterus alter the uterine endometrium. In the case of endometriosis, Dominique de Ziegler outlines the numerous changes in gene expression and the central role of inflammation in causing progesterone resistance. With endometriosis, the absence of ovarian function inherent in deferred transfer, with or without a more lengthy suppression of ovarian function, appears to be sufficient to restore normal function of eutopic endometrium. Because laparoscopy is no longer routine in the evaluation of infertility, unrecognized endometriosis then becomes irrelevant in the context of assisted reproductive technology. With hydrosalpinx and submucus myomas, the implantation factor HOXA-10 is suppressed in the endometrium and, with myomas, even in areas of the uterus not directly affected. Daniela Galliano reviews various uterine pathologies, the most enigmatic being adenomyosis, where the endometrium also manifests many of the changes seen in endometriosis and deferred transfer with extended suppression appears to provide the best outcomes. Ettore Cicinelli's group has extensively studied the diagnosis and treatment of endometritis, and although more definitive diagnosis and care of this covert disorder may await techniques such as sequencing of the endometrial microbiome, it undoubtedly is an important factor in implantation failure, deserving our attention and treatment. (Fertil Steril® 2016;105:844–54. ©2016 by American Society for Reproductive Medicine.)

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IMPAIRED IMPLANTATION DUE TO ENDOMETRIOSIS IS AN INFLAMMATORY PROCESS AND ASSOCIATED WITH NUMEROUS CHANGES IN GENE EXPRESSION

Endometrial Alterations in Endometriosis

In assisted reproductive technology (ART), endometriosis impedes success primarily by affecting the endometrium itself, the eutopic endometrium (1, 2). Experimental endometriosis in baboons altered eight endometrial microRNAs (miRs), including miR-451 (3). In an endometriosis mouse model, Lee et al. reported modified endometrial gene expression (4). Alterations of the eutopic endometrium also affect endometrial cells shed via retrograde bleeding, making them more prone to attach and implant in the peritoneal cavity (5). Angiogenesis is stimulated, with expression of vascular endothelial growth factor (VEGF) A and its receptors being increased (6), likely as an effect of inflammation. Yet while angiogenesis is generally increased, prokineticin-1 is decreased locally at the implantation site (7), which may impair endometrial receptivity.

A thinner endometrium has been reported in the proliferative phase of the menstrual cycle (8), and there is a heterogeneous response to progesterone (P) in the luteal phase (9). Nerve fibers have been reported in the endometrium of women suffering from severe endometriosis (10), a phenomenon possibly linked to pelvic pain. However, its value for diagnosing endometriosis has been questioned (11).

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The endometrial response to circulating sex steroids leading to receptivity to embryo implantation is orchestrated by HOXA-10 activation, which regulates a series of downstream target genes (12). In response to HOXA-10 activation, insulin-like growth factor–binding protein 1 are up-regulated, whereas EMX2 is down-regulated (12, 13).

Up-regulation of HOXA-10 induced by E_2, and P is suppressed in endometriosis (14), thus dysregulating matrix remodeling during the implantation window. Artificial induction of endometriosis in baboons lowered HOXA-10 protein levels in both epithelial and stromal cells of the endometrium and as a result reduced β3-integrin expression (12).

Endometriosis, Inflammation, and Progesterone Resistance

Endometrial receptivity and pregnancy rates (PRs) are not reduced in oocyte donation recipients affected by endometriosis (15). Outside of donor-egg ART, however, a host of P-dependent genes are underexpressed in the endometrium, causing P resistance (16). The expression of more than 200 genes is modified in endometrium obtained in the midluteal phase (17, 18), and stromal cell prolactin production is impeded (19).

DNA methylation is dynamically altered during the menstrual cycle (20). Expression of matrix metalloprotease 26, an enzyme involved in implantation, requires exposure to both E_2 and P. Demethylation—possibly induced by inflammation and consequent failure to metabolize E_2 (21)—is associated with changes in the expression of this gene.

Normalizing the Eutopic Endometrium

Ovarian suppression with GnRH agonist (GnRHa) causes a reduction in angiogenesis (22), inhibits cell proliferation, induces apoptosis, and decreases VEGF secretion (23) in the eutopic endometrium. Oral contraceptive (OC) reduces the density of nerve endings (24) and expression of nerve growth factor and its receptor (25). Moreover, OC decreases endometrial aromatase expression, which is elevated in endometriosis (26).

Although GnRHa has been thought to benefit endometriosis by suppressing E_2 (27), add-back therapy with sex steroids for reducing side effects of GnRHa do not impair treatment efficacy (28, 29). Also, OC pills are as effective as GnRHa for treating pelvic pain due to endometriosis (30) and preventing recurrence after surgery (31). Efficacy of medical treatment of endometriosis therefore depends on blocking ovarian function—with the use of GnRHa or OC—possibly by reducing the very high pelvic levels of E_2 accompanying ovulation.

Endometriosis and Clinical Outcome

Optimizing ART outcome in endometriosis. Endometriosis affects fertility by effects on the pelvic cavity, ovaries, or uterus itself (32). In ART, peritoneal factors are bypassed. Ovarian factors affect the response to controlled ovarian stimulation (COS), but not oocyte quality (32). Therefore, in ART the primary concern is to neutralize the endometrial effects of endometriosis.

In a randomized trial, a 3-month ovarian suppression with the use of GnRHa before ART significantly improved outcome (33). Because ovarian suppression with the use of OC appears to be equally effective as GnRHa, we tested the effects of pre-ART treatment with the use of OC. OC for 6–9 weeks before ART normalized implantation rates (IRs) in severe endometriosis compared with control subjects of the same age, whereas IRs were lower in nonsuppressed women (34). Not all studies report reduced IRs in endometriosis. In a recent meta-analysis, Harb et al. found that IRs are diminished in case of severe (stage III–IV) endometriosis (35), whereas others report that ART outcome is not affected in case of endometriomas (36).

Today, embryo vitrification offers new and more practical approaches for ART for women with endometriosis. Antagonist-based COS, GnRHa triggering of ovulation, and deferred embryo transfer (ET) limit side effects and pain and hasten recovery after the oocyte retrieval. With deferred ET, implantation occurs when the ovaries are suppressed, a condition mimicking those prevailing in donor egg recipients whose results are not affected by endometriosis (15). Future experience will tell whether it might be beneficial to extend the duration of ovarian suppression by timely use of GnRHa or OC—i.e., by 2–3 weeks—before proceeding to ET in an E_2 and P replacement cycle.

Obstetrical Outcome

Increased obstetrical complications have been reported in women suffering from endometriosis (37). A Swedish study indicated that ART women with endometriosis had higher risks of preterm birth (38), antepartum bleeding, and preeclampsia. Juang et al. reported that endometriosis and adenomyosis were associated with increased risks of preterm delivery and premature rupture of fetal membranes (39). Brosens et al. contend that preterm birth and other obstetrical complications seen in endometriosis are linked to early pregnancy events and, in particular, the quality of placentation (40). The increased junctional zone as well as inflammation found in endometriosis and adenomyosis (41) alter the implantation process and placentation. However, reporting on 78 ART women with endometriomas, Benaglia et al. found no increase in preterm birth compared with a population of 156 disease-free control subjects (42), possibly owing to low statistical power.

UTERINE STRUCTURAL ABNORMALITIES THAT IMPAIR INITIAL AND ONGOING PLACENTATION

Anomalies in Size and Shape of the Uterus

In women with a septate uterus, a retrospective matched-control study in in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) patients showed significantly increased miscarriage rates in nonoperated patients (77.1% vs. 16.7%), which were reduced to similar levels after surgery (29.2% vs. 18.4%). Likewise, PRs and live birth rates before hysteroscopy