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Invited Review / *Davetli Derleme*

Endometriosis and Implantation

Endometriosis ve implantasyon

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Implantation is a complex process by which the embryo attaches to the endometrium. The human endometrium becomes receptive to the embryo during the luteal phase of the menstrual cycle under the influence of steroid hormones and paracrine factors originating from endometrial cells and the embryo. Several paracrine factors influencing the implantation include leukemia inhibitory factor (LIF) and interleukin (IL)-11. Moreover, timely development of pinopodes, and expression of integrins and Hox genes in endometrium, and oocyte quality also determines the implantation outcome. Endometriosis is a common gynecologic disorder and estimated that 25 to 50% of infertile women have endometriosis. Although the mechanisms contributing to infertility are poorly understood, accumulating evidence suggests that altered folliculogenesis, sperm dysfunction, impaired fertilization, toxicity against early embryonic development, defective implantation, and poor oocyte quality with decreased ability to implant may be the contributing factors in some endometriosis patients.

Key Words: Implantation; endometriosis; infertility, oocyte quality.

İmplantasyon, embriyonun endometriuma yerleşmesinin gerçekleştiği kompleks bir işlemdir. İnsan endometriumu; endometrial hücreler ve embriyodan kaynaklanan steroid hormonlar ve parakrin faktörlerin etkisi altında, luteal faz süresince embriyoyu kabul etmeye hazır hale gelir. Lösemi inhibitor faktör (LİF) ve interlökin (İL)-11'de dahil olmak üzere, pek çok parakrin faktör implantasyonu etkiler. Bunun yanısıra endometriyumda gelişen pinopodlar, integrinler, HOX genleri ve aynı zamanda oosit kalitesi de implantasyon sonucunu belirler. Endometriosis; yaygın bir jinekolojik hastalıktır ve infertil kadınların yaklaşık %25-50'si endometriosislidir. İnfertiliteye sebep olan mekanizmalar tam olarak anlaşılamamış olmasına rağmen, bu konu hakkındaki genel kanı; normal olmayan folikülogenez, sperm disfonksiyonu, implantasyon başarısızlığı, erken dönem embriyo gelişimine karşı oluşan toksisite, implante olma yeteneği azalmış düşük oosit kalitesinin bazı endometriosisli hastalarda infertiliteye neden olan etkili faktörler olabileceği yönündedir.

Anahtar Sözcükler: İmplantasyon; endometriosis; infertilite; oosit kalitesi.

Endometriosis is a common gynecologic disorder characterized by the presence of endometrial tissue outside the uterine cavity. Nearly more than a century has passed since the first description of endometriosis by Von Rokitansky in 1860 but our current understanding of the pathogenesis of the disease still remains unclear.[1]

Endometriosis is one of the leading causes of disability among reproductive age women and represents a major personal and public health

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concern.[2] It affects 10 to 15% of women of reproductive age. It is estimated that 25 to 50% of infertile women have endometriosis, and among women with endometriosis 30 to 50% are infertile.[3,4] Although the mechanisms contributing to infertility are poorly understood, accumulating evidence suggests that altered folliculogenesis,[5] ovulatory dysfunction,[6] sperm dysfunction,[7] impaired fertilization,[8,9] toxicity against early embryonic development,[10,11] defective implantation[12] and poor oocyte quality with decreased ability to implant[13] may be the contributing factors in some endometriosis patients.

ENDOMETRIOSIS IS AN INFLAMMATORY DISEASE

The peritoneal environment of women with endometriosis is pro-inflammatory and may play a prominent role in the establishment and progression of endometriosis.[14] The peritoneal fluid of women with endometriosis contains increased numbers of immune cells, and macrophages are known to be the immune cell type found in the greatest quantity in the peritoneal fluid.[15] Macrophages that would be expected to clear endometrial cells from the peritoneal cavity seem to allow endometriosis implants to persist and progress by secreting growth factors and cytokines. In women with endometriosis, the peritoneal fluid has high concentrations of pro-inflammatory cytokines, growth factors including interleukin (IL)-1,[16-18] IL-8,[18-20] monocyte chemotactic protein-1 (MCP-1),[21,22] regulated upon activation, normal T cell expressed and secreted (RANTES),[23] tumor necrosis factor-α (TNF-α)[24] and vascular endothelial growth factor (VEGF).[24] Pelvic inflammation in endometriosis may lead to adhesion formation and scarring, disruption of fallopian tube patency, and anatomical distortion of the reproductive tract, which may affect the fertility. However, infertility is also associated with minimal or mild endometriosis and therefore, ıt requires the identification of other pathophysiological mechanisms.

EFFECTS OF ENDOMETRIOSIS ON OOCYTE QUALITY

Embryo competence is determined, at least in part, by the quality of the original gametes. The impaired quality of the embryos in endometriosis points to the follicular microenvironment and the quality of the oocyte that might be compromised. This suggests that infertility may be related to alterations within the follicle, which results in embryos of lower quality and capacity to implant.[25] Multivariate analysis also shows a decrease in fertilization and implantation rates and a significant decrease in the number of oocytes retrieved for endometriosis patients. Stage of disease is also influential, because women with severe endometriosis displays significantly lower rates than women with mild disease.[25]

Autocrine and paracrine factors are able to modulate ovarian function apart from gonadotropins and ovarian steroids. These factors can be secreted by granulosa cells and ovarian leukocytes. In the follicular fluid of women with endometriosis, the level of VEGF is decreased, and the levels of IL-1, IL-6, IL-8, TNF-α, MCP-1, growth regulated-α (Gro-α) and endothelin-1 are elevated.[26-29] Increased follicular fluid TNF-α level corresponds with poor-quality oocytes.[30] Moreover, decreased follicular fluid VEGF levels have been correlated with unhealthy follicular vascular network.[31] Elevated IL-1 and TNF-α may also inhibit gonadotropin-induced progesterone production by granulosa cells as well as androgen production by theca cells.[32,33] On the other hand, granulosa cell apoptosis, which may affect oocyte quality, has been shown to be increased in women with endometriosis.[34,35] Patients with more advanced stages of endometriosis presents a higher apoptotic incidence in their granulosa cells, and significant differences are found in the number of oocytes and the fertilization rate.[36] Furthermore, patients with endometriomas have even a higher incidence of apoptosis than women with endometriosis but without endometriomas.[37]

EFFECT OF ENDOMETRIOSIS ON EARLY EMBRYONIC DEVELOPMENT

A hostile peritoneal environment to the embryo has been postulated as a cause for the decreased

fertility in endometriosis. Several studies reveal that peritoneal fluid from women with endometriosis impairs early embryo development.[38-40] The peritoneal fluid from infertile women with endometriosis is embryotoxic to two-cell mouse embryos. However, this embryotoxicity is not prominent when peritoneal fluid is taken from fertile women with endometriosis.[41] Moreover, increased aberrant nuclear and cytoplasmic events in embryos, decreased embryo cleavage rates, increased percentage of arrested development, and a significant decrease in the number of blastomeres has been demonstrated in women with endometriosis.[42-44]

EFFECTS OF ENDOMETRIOSIS IN IMPLANTATION

Implantation is a complex process by which the embryo attaches to the endometrium, first penetrating the endometrial epithelium and then invading the maternal circulatory system to form the placenta.[45] Timely modifications in the endometrium to become receptive to the developing embryo are crucial for successful implantation.[46] The human endometrium becomes receptive to the embryo only for a limited period during the luteal phase of the menstrual cycle, under the influence of steroid hormones and paracrine factors originating from endometrial cells and the embryo.[47] The period during which endometrium is receptive to implantation, termed the implantation window, begins approximately six days after ovulation and is believed to encompass cycle days 20-24.[48]

Impaired endometrial receptivity is considered to be a major limiting factor for the establishment of pregnancy.[49] In an attempt to develop a clinically relevant and reproducible evaluation of endometrial function, a number of molecular and morphological markers specific to the implantation window have been identified. These include pinopodes, integrins, leukemia inhibitory factor (LIF), the IL-1 system, glycodelin, colony stimulating factor-1 (CSF-1), heparin-binding epidermal growth factor (HB-EGF) and the Hox genes.[45,47,50,51] Although these markers have been shown to be essential for implantation in animal models, further studies are needed to reveal their roles in human implantation.[47,48]

Pinopodes are cytoplasmic protrusions on the apical surface of the luminal epithelium. They can be visualized by scanning electron microscopy and the surfaces pinopodes may have some receptors for adhesion molecules, which are essential of embryo implantation.[52] Human blastocysts are reported to attach preferentially to cultured endometrial epithelial cells expressing pinopodes rather than to areas of microvilli. Pinopodes are progesterone dependent structures whose appearance coincides with the onset of the receptive phase.[53] They may therefore provide a measure of adequate endometrial maturation in response to progesterone. However, to date, there are no convincing data to show that pinopode expression in women correlates with implantation success. Nor is it clear whether pinopodes participate directly in the attachment of the embryo to the endometrium. In a prospective study evaluating pinopode formation in women with and without endometriosis, who undergo oocyte donation, demonstrates no difference between the two groups.[54]

Hox genes are transcriptional regulators that play an essential role in determining tissue identity during embryonic development.[55] They are involved in the development of the Mullerian duct system and then continue to be expressed in the adult uterus.[50] Hox genes are likely key regulators of human implantation.[55] Hoxa-10 and Hoxa-11 genes are essential for implantation in the mouse and appear to play a similar role in human endometrium.[55] However, eutopic endometrium of women with endometriosis fails to show the expected mid-luteal rise in Hox 10 and Hoxa-11 gene expression as demonstrated in the controls.[56] Aberrant Hox gene expression suggests that altered development of the endometrium at the molecular level may contribute to the etiology of infertility in women with endometriosis.

Empty spiracles homolog 2 (EMX2) is also a transcriptional factor necessary for reproductive tract development and Hoxa-10, which is regulat-

ed by sex steroids, negatively regulates EMX2 expression.[57] Menstrual cycle dependent expression of EMX2 is demonstrated in eutopic endometrium of women with and without endometriosis. In women without endometriosis, EMX2 mRNA levels decline by 50% in peri-implantation endometrium compared with levels in the proliferative phase. However, in the eutopic endometrium of women with endometriosis, such decline is not observed in the peri-implantation period.[57] These findings suggest that EMX2 expression is also aberrant in eutopic endometrium of women with endometriosis and is mediated by altered Hoxa-10 expressions.

Integrins are a family of cell adhesion molecules that function in both cell-cell and cell-substratum adhesion. They promote cell attachment to proteins within the extracellular matrix and potentiate cell migration and invasion. Many members of the integrin family are expressed by the endometrium throughout the menstrual cycle. Among these, the expression of $\alpha_v\beta_3$ integrin by endometrial epithelium is critical since its expression is coincident with the period of uterine receptivity.[58] The apical surface of the luminal epithelium expresses the $\alpha_v\beta_3$ integrin and localizes to the pinopodes.[59] This localization to the apical pole of the luminal epithelium suggests a role for this integrin in the initial embryo-endometrial interaction.[60] The expression of integrin subunit β_3 seems to be significantly reduced in endometrium from women with unexplained infertility, endometriosis, hydrosalpinges, and luteal phase defect. In a prospective and double blind study, eighty-nine endometrial biopsies were taken before a diagnostic laparoscopy and the majority of women with reduced $\alpha_v\beta_3$ integrin expression during the time of implantation were shown to have stage I or II endometriosis. Based on these results, reduced $\alpha_v\beta_3$ integrin expression in endometriosis may be associated with decreased cycle fecundity due to defects in uterine receptivity.[61] Interestingly, improvement of fertility and return of normal $\alpha_v\beta_3$ levels are observed after treating women with endometriosis with GnRH analogs and laser ablation of implants.[62]

Leukemia inhibitory factor and IL-11 belong to the IL-6-type cytokine family, which frequently exhibit pleiotropy and often have overlapping functions.[63,64] Both IL-11 and LIF signal via a heterodimeric receptor complex comprising either the specific IL-11 receptor (R) α-chain or the low affinity receptor LIF-R, associated with the common signaling component gp130 and signal transduction is through the JAK/STAT pathway.[63,64] Studies in mice have identified IL-11 and LIF to be obligatory for the earliest stages of implantation. Female mice with a null mutation of the IL- 11Rα gene are infertile due to a defective decidualization response to the implanting blastocyst and female mice with no functional LIF gene are infertile due to an inability of normal embryos to implant.[65-67] In mid-secretory phase human endometrium, IL-11, LIF, and LIF-R are both expressed predominantly in glandular and luminal epithelium and are also thought to be important in decidualization and implantation in human.[68-70] It is demonstrated that IL-11 and IL-11Rα are not expressed in endometrium of infertile women with endometriosis.[71] Moreover, LIF expression in eutopic glandular epithelium is significantly lower in infertile women with endometriosis compared to fertile controls.[71] These results suggest that reduced endometrial IL-11 and LIF expression may contribute to infertility in some women with endometriosis.

The development of assisted reproductive techniques provides a tool to study the components involved in implantation separately. Most data from *in-vitro* fertilization (IVF) cycles fail to show any difference between implantation rates in women with and without endometriosis.[72-76] Only a few studies show statistically significant lower implantation and pregnancy rates with IVF in women with early as well as late stages of the disease.[12,13,77] Oocyte donation programs allow us to better understand whether the endometrium or the oocyte or both are affected in endometriosis. In women with endometriosis, donor oocytes obtained from women without the disease implant as efficiently as in other recipients. Furthermore, reduced pregnancy and implantation rates are observed when

oocytes come from donors with endometriosis.[13] In another study, oocytes from healthy donors are split in the same cycle and "sibling" oocytes are given to different recipients with or without endometriosis. Recipients in that study have stage III-IV endometriosis, and they have the same implantation rates as controls.[78] These data are confirmed by another study in which women received fresh donor oocytes because of a low response in their previous IVF cycles. In the donor oocyte cycle, women with endometriosis have a similar pregnancy rate as other women without endometriosis but with premature ovarian failure or menopause.[79] These data suggest that endometriosis may affect the oocyte/embryo and not the endometrium, because the implantation rates are similar to those of women without endometriosis when oocytes are donated by healthy women. Although it may not be appropriate to compare natural cycles with IVF cycles, where hormone levels are elevated, we would speculate that subtle impairments in the endometrial receptivity that may be relevant in natural cycles may be overcome by supraphysiologic hormone levels.

CONCLUSION

Endometriosis is associated with a decrease in cycle fecundity, and the prevalence of endometriosis is increased in infertile women. The study of endometrium in women with endometriosis continues to yield interesting differences when compared to women without this disease. The greatest obstacle to understanding how endometriosis alters fertility is the heterogeneity of this disorder. In addition, in lieu of biomarkers that predict the presence of endometriosis in the general population, our control groups may also contain confounding and occult disease that limits our ability to study this disorder. Biomarkers of uterine receptivity may provide a key to both of these questions. If we can develop markers that predict all endometriosis, we will be able to ascertain the true prevalence of this disease. If we find endometrial biomarkers that predict potential for pregnancy, then studies to examine the effect of endometriosis on fertility will likely have greater concordance. We also predict that studies to examine the effect of medical treatment will demonstrate efficacy in select populations of women. Further research into the use of such biomarkers holds the key to our future successes in these areas.

Clinical studies suggest decreased oocyte and embryo quality with lower capacity to implant in women with endometriosis. This can be explained by altered intrafollicular milieu influencing oocyte growth and development, and embryotoxicity of intraperitoneal environment.

In summary, women with endometriosis display lower implantation capacity and diminished pregnancy rates. However, the pathophysiology by which endometriosis affects implantation is an unresolved medical question.

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