

# Bölüm 4

## İMLANTASYON BAŞARISIZLIĞININ ENDOMETRİAL MOLEKÜLER VE GENETİK MEKANİZMALARI

Uzm. Dr. Emrullah TANRIKUT  
Uzm. Dr. Pınar KIRICI  
Uzm. Dr. Engin YILDIRIM

Endometriozis, hidrosalpinks, leiomyoma, polikistik over sendromu ve endometrial polip gibi çeşitli benign jinekolojik hastalıklar fekundabilitede azalma ve bozulmuş uterin reseptivite ile ilişkili bulunmuşlardır. Bu hastalıkların bazıları endometriuma bası yaparak ya alanı daraltarak ya da genişleterek mekanik etkiyle implantasyon üzerine olumsuz etkide bulunur. Bazıları ise reseptivite ile ilgili genlerin ekspresyonlarını değiştirerek ya da fizyolojik inflamasyonu bozarak olumsuz etkide bulunurlar. İmplantasyon için belli bir miktar inflamasyon gerekli ve zaruri iken artmış veya azalmış inflamasyon reseptivitenin yetersiz olmasına yol açar. Hidrosalpinkte artmış endometrial inflamasyon implantasyonu engellerken salpenjektomi sonrası gebelik oranlarının %50 oranında artması inflamasyon ve reseptivite arasındaki ilişkiyi net olarak gösterir. Benzer şekilde RIA kullanımına bağlı artmış yabancı cisim inflamasyonu ve düşük redoks potansiyelleri gebelik oluşumunu engeller. Endometriomali hastaların ötopik endometriomalarında artmış inflamasyonun endometriomaların cerrahi olarak çıkartılmasından sonra azalması da indirekt inflamasyonun en güzel örneğidir. Endometrioma kistektomi sonrası endometrial NF-kB düzeylerinin azalması ve implantasyonun artması da endometriozis yönetiminde cerrahi yaklaşımlarımızı etkileyecek yeni bilimsel veriler sunması açısından önem arz eder. **Editorial**

### Giriş

Eşişiz bir biyolojik fenomen olan ‘embrio implantasyonu’ üreme sürecinin en kritik adımlarından birini temsil eder. Başarılı bir implantasyon için reseptif bir endometrium, blastokist aşamasında fonksiyonel bir embrio ve anne ile embrionik doku arasında senkronize bir diyalog gerekmektedir (1). Endometrium ovulasyondan yaklaşık 6 gün sonra reseptivite özelliğini kazanır ve bunu 4 gün boyunca (siklusun 20-24. günleri) devam ettirir (2). Eğer bu 4 günlük süre içerisinde implantasyon gerçekleşmez ise, tam olarak gelişmiş olan bu endometriumun dökülmesi ile menstrüasyon oluşur. Ancak, eğer implantasyon gerçekleşirse endometrium gelişimine devam eder ve embrionun gelişimi için önemli destek sağlayan bazı morfolojik ve moleküler değişimler geçirir (3). Endometriozis, hidrosalpinks, leiomyom ve polikistik over sendromu (PKOS) gibi çeşitli benign jinekolojik hastalıklar fekundabilitede azalma ve bozulmuş uterin reseptivite ile ilişkili bulunmuşlardır (4). Günümüzde Yardımlı Üreme Teknikleri (YÜT) araçları yüksek kalitede embrioların seçimini olanak sağlamakta ve daha yüksek gebelik oranlarını elde etmeyi amaçlayan YÜT protokolleri geliştirilmeye devam etmektedir. Ancak implantasyon oranları hala rölatif olarak düşüktür (5). Uterin reseptivite sağlıklı gebeliklerin oluşmasında anahtar bir rol oynar. Uterin reseptivitede bozulma YÜT başarısını sınır-

## Kaynaklar

- Simon C, Martin JC, Pellicer A. Paracrine regulators of implantation. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000;14:815–826.
- Bergh PA, Navot D. The impact of embryonic development and endometrial maturity on the timing of implantation. *Fertil Steril* 1992;58:537–542.
- Strowitzki T, Germeyer A, Popovici R, von Wolff M. The human endometrium as a fertility-determining factor. *Hum Reprod Update* 2006;12:617–630.
- Donaghay M, Lessey BA. Uterine receptivity: alterations associated with benign gynecological disease. *Semin Reprod Med* 2007;25:461–475.
- Andersen AN, Gianaroli L, Felberbaum R, de Mouzon J, Nygren KG. Assisted reproductive technology in Europe, 2001. Results generated from European registers by ESHRE. *Hum Reprod* 2005;20:1158–1176.
- Houston DE. Evidence for the risk of pelvic endometriosis by age, race and socioeconomic status. *Epidemiol Rev* 1984;6:167–191.
- Tummon IS, Maclin VM, Radwanska E, Binor Z, Dmowski WP. Occult ovulatory dysfunction in women with minimal endometriosis or unexplained infertility. *Fertil Steril* 1988;50:716–720.
- Simon C, Gutierrez A, Vidal A, de los Santos MJ, Tarin JJ, Remohi J, Pellicer A. Outcome of patients with endometriosis in assisted reproduction: results from in vitro fertilization and oocyte donation. *Hum Reprod* 1994;9:725–729.
- Ulukus M, Cakmak H, Arici A. The role of endometrium in endometriosis. *J Soc Gynecol Investig* 2006;13:467–476.
- Inoue M, Kobayashi Y, Honda I, Awaji H, Fujii A. The impact of endometriosis on the reproductive outcome of infertile patients. *Am J Obstet Gynecol* 1992; 167:278–282.
- Dmowski WP, Rana N, Michalowska J, Friberg J, Papierniak C, el-Roeiy A. The effect of endometriosis, its stage and activity, and of autoantibodies on in vitro fertilization and embryo transfer success rates. *Fertil Steril* 1995;63:555–562.
- Bukulmez O, Yerali H, Gurgan T. The presence and extent of endometriosis do not effect clinical pregnancy and implantation rates in patients undergoing intracytoplasmic sperm injection. *Eur J Obstet Gynecol Reprod Biol* 2001; 96:102–107.
- Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002;77:1148–1155.
- Diaz I, Navarro J, Blasco L, Simon C, Pellicer A, Remohi J. Impact of stage III-IV endometriosis on recipients of sibling oocytes: matched case-control study. *Fertil Steril* 2000;74:31–34.
- Cakmak H, Taylor HS. Implantation failure: molecular mechanisms and clinical treatment. *Hum Reprod Update*. 2011 Mar-Apr;17(2):242-53. Epub 2010 Aug 21. Review.
- Lessey BA, Castelbaum AJ, Sawin SW, Buck CA, Schinnar R, Bilker W, Strom BL. Aberrant integrin expression in the endometrium of women with endometriosis. *J Clin Endocrinol Metab* 1994;79:643–649.
- Lessey BA, Young SL. Integrins and other cell adhesion molecules in endometrium and endometriosis. *Semin Reprod Endocrinol* 1997;15:291–299.
- Dimitriadis E, Stoikos C, Stafford-Bell M, Clark I, Pava P, Kovacs G, Salamonsen LA. Interleukin-11, IL-11 receptoralpha and leukemia inhibitory factor are dysregulated in endometrium of infertile women with endometriosis during the implantation window. *J Reprod Immunol* 2006;69:53–64.
- Metzger DA, Olive DL, Haney AF. Limited hormonal responsiveness of ectopic endometrium: histologic correlation with intrauterine endometrium. *Hum Pathol* 1988;19:1417–1424.
- Burney RO, Talbi S, Hamilton AE, Vo KC, Nyegaard M, Nezhat CR, Lessey BA, Giudice LC. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology* 2007;148:3814–3826.
- Lee B, Du H, Taylor HS. Experimental murine endometriosis induces DNA methylation and altered gene expression in eutopic endometrium. *Biol Reprod* 2009;80:79–85.
- Fazleabas AT, Brudney A, Chai D, Langoi D, Bulun SE. Steroid receptor and aromatase expression in baboon endometriotic lesions. *Fertil Steril* 2003; 80(Suppl. 2):820–827.
- Kao LC, Germeyer A, Tulac S, Lobo S, Yang JP, Taylor RN, Osteen K, Lessey BA, Giudice LC. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. *Endocrinology* 2003;144:2870–2881.
- Kamat AA, Younes PS, Sayeeduddin M, Wheeler TM, Simpson JL, Agoulnik AI. Protein expression profiling of endometriosis: validation of 2-mm tissue microarrays. *Fertil Steril* 2004;82:1681–1683.
- 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;101:1379–1384.
- Kim JJ, Taylor HS, Lu Z, Ladhani O, Hastings JM, Jackson KS, Wu Y, Guo SW, Fazleabas AT. Altered expression of HOXA10 in endometriosis: potential role in decidualization. *Mol Hum Reprod* 2007;13:323–332.
- Troy PJ, Daftary GS, Bagot CN, Taylor HS. Transcriptional repression of peri-implantation EMX2 expression in mammalian reproduction by HOXA10. *Mol Cell Biol* 2003;23:1–13.
- Daftary GS, Taylor HS. EMX2 gene expression in the female reproductive tract and aberrant expression in the endometrium of patients with endometriosis. *J Clin Endocrinol Metab* 2004;89:2390–2396.
- Taylor HS, Fei X. Emx2 regulates mammalian reproduction by altering endometrial cell proliferation. *Mol Endocrinol* 2005;19:2839–2846.
- 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;193:371–380.
31. Wu Y, Strawn E, Basir Z, Halverson G, Guo SW. Aberrant expression of deoxyribonucleic acid methyltransferases DNMT1, DNMT3A, and DNMT3B in women with endometriosis. *Fertil Steril* 2007;87:24–32.
  32. Zeyneloglu HB, Arici A, Olive DL. Adverse effects of hydrosalpinx on pregnancy rates after in vitro fertilization-embryo transfer. *Fertil Steril* 1998; 70:492–499.
  33. Camus E, Poncelet C, Goffinet F, Wainer B, Merlet F, Nisand I, Philippe HJ. Pregnancy rates after in-vitro fertilization in cases of tubal infertility with and without hydrosalpinx: a meta-analysis of published comparative studies. *Hum Reprod* 1999;14:1243–1249.
  34. Strandell A, Lindhard A, Waldenstrom U, Thorburn J. Hydrosalpinx and IVF outcome: cumulative results after salpingectomy in a randomized controlled trial. *Hum Reprod* 2001;16:2403–2410.
  35. Johnson NP, Mak W, Sowter MC. Laparoscopic salpingectomy for women with hydrosalpinges enhances the success of IVF: a Cochrane review. *Hum Reprod* 2002;17:543–548.
  36. Kodaman PH, Arici A, Seli E. Evidence-based diagnosis and management of tubal factor infertility. *Curr Opin Obstet Gynecol* 2004;16:221–229.
  37. Mansour RT, Aboulghar MA, Serour GI, Riad R. Fluid accumulation of the uterine cavity before embryo transfer: a possible hindrance for implantation. *J In Vitro Fert Embryo Transf* 1991;8:157–159.
  38. Meyer WR, Castelbaum AJ, Somkuti S, Sagoskin AW, Doyle M, Harris JE, Lessey BA. Hydrosalpinges adversely affect markers of endometrial receptivity. *Hum Reprod* 1997;12:1393–1398.
  39. Bildirici I, Bukulmez O, Ensari A, Yarali H, Gurgan T. A prospective evaluation of the effect of salpingectomy on endometrial receptivity in cases of women with communicating hydrosalpinges. *Hum Reprod* 2001;16:2422–2426.
  40. Savaris RF, Pedrini JL, Flores R, Fabris G, Zettler CG. Expression of alpha 1 and beta 3 integrins subunits in the endometrium of patients with tubal phimosi or hydrosalpinx. *Fertil Steril* 2006;85:188–192.
  41. Seli E, Kayisli UA, Cakmak H, Bukulmez O, Bildirici I, Guzeloglu-Kayisli O, Arici A. Removal of hydrosalpinges increases endometrial leukaemia inhibitory factor (LIF) expression at the time of the implantation window. *Hum Reprod* 2005; 20:3012–3017.
  42. Daftary GS, Kayisli U, Seli E, Bukulmez O, Arici A, Taylor HS. Salpingectomy increases peri-implantation endometrial HOXA10 expression in women with hydrosalpinx. *Fertil Steril* 2007;87:367–372.
  43. Day Baird D, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol* 2003;188:100–107.
  44. Donnez J, Jadoul P. What are the implications of myomas on fertility? A need for a debate? *Hum Reprod* 2002;17:1424–1430.
  45. Pritts EA. Fibroids and infertility: a systematic review of the evidence. *Obstet Gynecol Surv* 2001;56:483–491.
  46. Campo S, Campo V, Gambadauro P. Reproductive outcome before and after laparoscopic or abdominal myomectomy for subserous or intramural myomas. *Eur J Obstet Gynecol Reprod Biol* 2003;110:215–219.
  47. Matsuzaki S, Canis M, Darcha C, Pouly JL, Mage G. HOXA-10 expression in the mid-secretory endometrium of infertile patients with either endometriosis, uterine fibromas or unexplained infertility. *Hum Reprod* 2009;24:3180–3187.
  48. Rackow BW, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. *Fertil Steril* 2010; 93:2027–2034.
  49. Ben-Nagi J, Miell J, Yazbek J, Holland T, Jurkovic D. The effect of hysteroscopic polypectomy on the concentrations of endometrial implantation factors in uterine flushings. *Reprod Biomed Online* 2009;19:737–744.
  50. Peng X, Li T, Xia E, Xia C, Liu Y, Yu D. A comparison of oestrogen receptor and progesterone receptor expression in endometrial polyps and endometrium of premenopausal women. *J Obstet Gynaecol* 2009;29:340–346.
  51. Kim MR, Kim YA, Jo MY, Hwang KJ, Ryu HS. High frequency of endometrial polyps in endometriosis. *J Am Assoc Gynecol Laparosc* 2003;10:46–48.
  52. de Sa Rosa e de Silva AC, Rosa e Silva JC, Candido dos Reis FJ, Nogueira AA, Ferriani RA. Routine office hysteroscopy in the investigation of infertile couples before assisted reproduction. *J Reprod Med* 2005;50:501–506.
  53. Perez-Medina T, Bajo-Arenas J, Salazar F, Redondo T, Sanfrutos L, Alvarez P, Engels V. Endometrial polyps and their implication in the pregnancy rates of patients undergoing intrauterine insemination: a prospective, randomized study. *Hum Reprod* 2005;20:1632–1635.
  54. Varasteh NN, Neuwirth RS, Levin B, Keltz MD. Pregnancy rates after hysteroscopic polypectomy and myomectomy in infertile women. *Obstet Gynecol* 1999; 94:168–171.
  55. Spiewankiewicz B, Stelmachow J, Sawicki W, Cendrowski K, Wypych P, Swiderska K. The effectiveness of hysteroscopic polypectomy in cases of female infertility. *Clin Exp Obstet Gynecol* 2003;30:23–25.
  56. Shokeir TA, Shalan HM, El-Shafei MM. Significance of endometrial polyps detected hysteroscopically in eumenorrhic infertile women. *J Obstet Gynaecol Res* 2004; 30:84–89.
  57. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004;89:2745–2749.
  58. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 1997;18:774–800.
  59. Giudice LC. Endometrium in PCOS: Implantation and predisposition to endocrine CA. *Best Pract Res Clin Endocrinol Metab* 2006;20:235–244.
  60. Suikkari AM, Ruutiainen K, Erkkola R, Seppala M. Low levels of low molecular weight insulin-like growth factor-binding protein in patients with polycystic ovarian disease. *Hum Reprod* 1989;4:136–139.
  61. Cermik D, Selam B, Taylor HS. Regulation of HOXA-10 expression by testosterone in vitro and in the endo-

- metrium of patients with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88:238–243.
62. Apparao KB, Lovely LP, Gui Y, Lininger RA, Lessey BA. Elevated endometrial androgen receptor expression in women with polycystic ovarian syndrome. *Biol Reprod* 2002;66:297–304.
  63. Gregory CW, Wilson EM, Apparao KB, Lininger RA, Meyer WR, Kowalik A, Fritz MA, Lessey BA. Steroid receptor coactivator expression throughout the menstrual cycle in normal and abnormal endometrium. *J Clin Endocrinol Metab* 2002;87:2960–2966.
  64. Devi Wold AS, Pham N, Arici A. Anatomic factors in recurrent pregnancy loss. *Semin Reprod Med* 2006;24:25–32.
  65. Romero R, Espinoza J, Mazor M. Can endometrial infection/inflammation explain implantation failure, spontaneous abortion, and preterm birth after in vitro fertilization? *Fertil Steril* 2004;82:799–804.
  66. Feghali J, Bakar J, Mayenga JM, Segard L, Hamou J, Driguez P, Belaisch-Allart J. [Systematic hysteroscopy prior to in vitro fertilization]. *Gynecol Obstet Fertil* 2003;31:127–131.
  67. Varma TR. Genital tuberculosis and subsequent fertility. *Int J Gynaecol Obstet* 1991; 35:1–11.
  68. Sarno JL, Kliman HJ, Taylor HS. HOXA10, Pbx2, and Meis1 protein expression in the human endometrium: formation of multimeric complexes on HOXA10 target genes. *J Clin Endocrinol Metab* 2005;90:522–528.
  69. Taylor HS, Igarashi P, Olive DL, Arici A. Sex steroids mediate HOXA11 expression in the human peri-implantation endometrium. *J Clin Endocrinol Metab* 1999; 84:1129–1135.
  70. Hsieh-Li HM, Witte DP, Weinstein M, Branford W, Li H, Small K, Potter SS. Hoxa 11 structure, extensive antisense transcription, and function in male and female fertility. *Development* 1995;121:1373–1385.
  71. Benson GV, Lim H, Paria BC, Satokata I, Dey SK, Maas RL. Mechanisms of reduced fertility in Hoxa-10 mutant mice: uterine homeosis and loss of maternal Hoxa-10 expression. *Development* 1996;122:2687–2696.
  72. Nikas G, Aghajanova L. Endometrial pinopodes: some more understanding on human implantation? *Reprod Biomed Online* 2002;4(Suppl. 3):18–23.
  73. Bagot CN, Kliman HJ, Taylor HS. Maternal Hoxa10 is required for pinopod formation in the development of mouse uterine receptivity to embryo implantation. *Dev Dyn* 2001;222:538–544.
  74. de Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. *Lancet*. 2010 Aug 28;376(9742):730–8. Review.
  75. Sampson J. Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 1927; 14: 422–69.
  76. Matsuura K, Ohtake H, Katabuchi H, Okamura H. Coelomic metaplasia theory of endometriosis: evidence from in vivo studies and an in vitro experimental model. *Gynecol Obstet Invest* 1999; 47 (suppl 1): 18–22.
  77. Cicinelli E, Einer-Jensen N, Hunter RH, et al. Peritoneal fluid concentrations of progesterone in women are higher close to the corpus luteum compared with elsewhere in the abdominal cavity. *Fertil Steril* 2009; 92: 306–10.
  78. Bulletti C, De Ziegler D, Polli V, Del Ferro E, Palini S, Flamigni C. Characteristics of uterine contractility during menses in women with mild to moderate endometriosis. *Fertil Steril* 2002; 77: 1156–61.
  79. Giudice LC, Kao LC. Endometriosis. *Lancet* 2004; 364: 1789–99.
  80. Dmowski WP, Gebel H, Braun DP. Decreased apoptosis and sensitivity to macrophage mediated cytolysis of endometrial cells in endometriosis. *Hum Reprod Update* 1998; 4: 696–701.
  81. Sharpe-Timms KL, Zimmer RL, Ricke EA, Piva M, Horowitz GM. Endometriotic haptoglobin binds to peritoneal macrophages and alters their function in women with endometriosis. *Fertil Steril* 2002; 78: 810–19.
  82. Rana N, Braun DP, House R, Gebel H, Rotman C, Dmowski WP. Basal and stimulated secretion of cytokines by peritoneal macrophages in women with endometriosis. *Fertil Steril* 1996; 65: 925–30.
  83. Yoshida S, Harada T, Iwabe T, et al. A combination of interleukin-6 and its soluble receptor impairs sperm motility: implications in infertility associated with endometriosis. *Hum Reprod* 2004; 19: 1821–25.
  84. Mansour G, Aziz N, Sharma R, Falcone T, Goldberg J, Agarwal A. The impact of peritoneal fluid from healthy women and from women with endometriosis on sperm DNA and its relationship to the sperm deformity index. *Fertil Steril* 2009; 92: 61–67.
  85. Iborra A, Palacio JR, Martinez P. Oxidative stress and autoimmune response in the infertile woman. *Chem Immunol Allergy* 2005; 88: 150–62.
  86. Kats R, Collette T, Metz CN, Akoum A. Marked elevation of macrophage migration inhibitory factor in the peritoneal fluid of women with endometriosis. *Fertil Steril* 2002; 78: 69–76.
  87. Carli C, Leclerc P, Metz CN, Akoum A. Direct effect of macrophage migration inhibitory factor on sperm function: possible involvement in endometriosis-associated infertility. *Fertil Steril* 2007; 88 (4 suppl): 1240–47.
  88. Taylor RN, Lebovic DI. Endometriosis. In: Strauss JF, Barbieri R, eds. *Yen and Jaffe's reproductive endocrinology: physiology and clinical management* (6th edn). New York: Elsevier, 2009: 577–95.
  89. Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: mechanisms and clinical consequences. *Endocr Rev* 2009; 30: 465–93.
  90. Streuli I, Fraisse T, Chapron C, Bijaoui G, Bischof P, de Ziegler D. Clinical uses of anti-mullerian hormone assays: pitfalls and promises. *Fertil Steril* 2009; 91: 226–30.
  91. Streuli I, Fraisse T, Pillet C, Ibecheole V, Bischof P, de Ziegler D. Serum antimullerian hormone levels remain stable throughout the menstrual cycle and after oral or vaginal administration of synthetic sex steroids. *Fertil Steril* 2008; 90: 395–400.
  92. Shebl O, Ebner T, Sommergruber M, Sir A, Tews G. Anti muellerian hormone serum levels in women with endometriosis: a case-control study. *Gynecol Endocrinol* 2009; 25: 713–16.

93. Matos L, Stevenson D, Gomes F, Silva-Carvalho JL, Almeida H. Superoxide dismutase expression in human cumulus oophorus cells. *Mol Hum Reprod* 2009; 15: 411–19.
94. de Ziegler D, Romoscanu I, Ventura P, Ibecheole V, Fondop JJ, de Candolle G. The uterus and in vitro fertilization. *Clin Obstet Gynecol* 2006; 49: 93–116.
95. Velarde MC, Aghajanova L, Nezhat CR, Giudice LC. Increased mitogen-activated protein 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.
96. Minici F, Tiberi F, Tropea A, et al. Endometriosis and human infertility: a new investigation into the role of eutopic endometrium. *Hum Reprod* 2008; 23: 530–37.
97. Berbic M, Schulke L, Markham R, Tokushige N, Russell P, Fraser IS. Macrophage expression in endometrium of women with and without endometriosis. *Hum Reprod* 2009; 24: 325–32.
98. Noel J-C, Borghese B, Vaiman D, Fayt I, Anaf V, Chapron C. Steroidogenic factor-1 expression in ovarian endometriosis. *Appl Immunohistochem Mol Morphol* 2010; 18: 258–61.
99. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. *Arch Gynecol Obstet* 2009; 280: 529–38.
100. Burney RO, Talbi S, Hamilton AE, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology* 2007; 148: 3814–26.
101. Xue Q, Lin Z, Yin P, et al. Transcriptional activation of steroidogenic factor-1 by hypomethylation of the 5' CpG island in endometriosis. *J Clin Endocrinol Metab* 2007; 92: 3261–67.
102. Tokushige N, Markham R, Russell P, Fraser IS. Different types of small nerve fibers in eutopic endometrium and myometrium in women with endometriosis. *Fertil Steril* 2007; 88: 795–803.
103. Schulke L, Berbic M, Manconi F, Tokushige N, Markham R, Fraser IS. Dendritic cell populations in the eutopic and ectopic endometrium of women with endometriosis. *Hum Reprod* 2009; 24: 1695–703.
104. Tokushige N, Markham R, Russell P, Fraser IS. Nerve fibers in peritoneal endometriosis. *Hum Reprod* 2006; 21: 3001–07.
105. Wang G, Tokushige N, Markham R, Fraser IS. Rich innervation of deep infiltrating endometriosis. *Hum Reprod* 2009; 24: 827–34.
106. 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; 1: CD004635.
107. Bulletti C, De Ziegler D, Setti PL, Cicinelli E, Polli V, Flamigni C. The patterns of uterine contractility in normal menstruating women: from physiology to pathology. *Ann N Y Acad Sci* 2004; 1034: 64–83.
108. Chapron C, Bourret A, Chopin N, et al. Surgery for bladder endometriosis: long term results and concomitant management of associated posterior deep lesions. *Hum Reprod* 2010; 25: 884–89.
109. Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Crosignani PG. Surgery for endometriosis-associated infertility: a pragmatic approach. *Hum Reprod* 2009; 24: 254–69.
110. Kennedy S, Bergqvist A, Chapron C, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005; 20: 2698–704.
111. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility. *Fertil Steril* 2006; 86 (5 suppl 1): S156–60.
112. Vercellini P, Somigliana E, Vigano P, Abbiati A, Barbara G, Crosignani PG. Endometriosis: current therapies and new pharmacological developments. *Drugs* 2009; 69: 649–75.
113. D'Hooghe TM, Debrock S, Hill JA, Meuleman C. Endometriosis and subfertility: is the relationship resolved? *Semin Reprod Med* 2003; 21: 243–54.
114. Tokushige N, Markham R, Russell P, Fraser IS. Effect of progestogens and combined oral contraceptives on nerve fibers in peritoneal endometriosis. *Fertil Steril* 2009; 92: 1234–39.
115. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005; 20: 2698–2704.
116. Liu Y, Luo L, Zhao H. Immunohistochemical study of HLA-DR antigen in endometrial tissue of patients with endometriosis. *J Huazhong Univ Sci Technol Med Sci* 2002; 22: 60–61.
117. Kreiner D, Fromowitz FB, Richardson DA, Kenigsberg D. Endometrial immunofluorescence associated with endometriosis and pelvic inflammatory disease. *Fertil Steril* 1986; 46: 243–246.
118. Klentzeris LD, Bulmer JN, Liu DT, Morrison L. Endometrial leukocyte subpopulations in women with endometriosis. *Eur J Obstet Gynecol Reprod Biol* 1995; 63: 41–47.
119. Nomiyama M, Hachisuga T, Sou H, Nakamura K, Matsumoto Y, Iwasaka T, Sugimori H. Local immune response in infertile patients with minimal endometriosis. *Gynecol Obstet Invest* 1997; 44: 32–37.
120. Mettler L, Volkov NI, Kulakov VI, Jurgensen A, Parwaresch MR. Lymphocyte subsets in the endometrium of patients with endometriosis throughout the menstrual cycle. *Am J Reprod Immunol* 1996; 36: 342–348.
121. Gagne D, Rivard M, Page M, Lepine M, Platon C, Shazand K, Hugo P, Gosselin D. Development of a nonsurgical diagnostic tool for endometriosis based on the detection of endometrial leukocyte subsets and serum CA-125 levels. *Fertil Steril* 2003; 80: 876–885.
122. Berbic M, Hey-Cunningham AJ, Ng C, Tokushige N, Ganewatta S, Markham R, Russell P, Fraser IS. The role of Foxp3+ regulatory T-cells in endometriosis: a potential controlling mechanism for a complex, chronic immunological condition. *Hum Reprod* 2010; 25: 900–907.
123. May KE, Villar J, Kirtley S, Kennedy SH, Becker CM. Endometrial alterations in endometriosis: a systematic

- review of putative biomarkers. *Hum Reprod Update*. 2011 Sep-Oct;17(5):637-53. Review.
124. Noble LS, Simpson ER, Johns A, Bulun SE. Aromatase expression in endometriosis. *J Clin Endocrinol Metab* 1996;81:174-179.
  125. Bukulmez O, Hardy DB, Carr BR, Word RA, Mendelson CR. Inflammatory status influences aromatase and steroid receptor expression in endometriosis. *Endocrinology* 2008;149:1190-1204.
  126. Hatok J, Zubor P, Galo S, Kirschnerova R, Dobrota D, Danko J, Racay P. Endometrial aromatase mRNA as a possible screening tool for advanced endometriosis and adenomyosis. *Gynecol Endocrinol* 2011;27:331-336.
  127. Delvoux B, Groothuis P, D'Hooghe T, Kyama C, Dunselman G, Romano A. Increased production of 17beta-estradiol in endometriosis lesions is the result of impaired metabolism. *J Clin Endocrinol Metab* 2009;94:876-883.
  128. Morsch DM, Carneiro MM, Lecke SB, Araujo FC, Camargos AF, Reis FM, Spritzer PM. c-fos gene and protein expression in pelvic endometriosis: a local marker of estrogen action. *J Mol Histol* 2009;40:53-58.
  129. Carneiro MM, Morsch DM, Camargos AF, Spritzer PM, Reis FM. Expression of 17beta-hydroxysteroid dehydrogenase type 2 in pelvic endometriosis. *Gynecol Endocrinol* 2007;23:188-192.
  130. Rey JM, Pujol P, Dechaud H, Edouard E, Hedon B, Maudelonde T. Expression of oestrogen receptor-alpha splicing variants and oestrogen receptor-beta in endometrium of infertile patients. *Mol Hum Reprod* 1998;4:641-647.
  131. Hudelist G, Keckstein J, Czerwenka K, Lass H, Walter I, Auer M, Wieser F, Wenzl R, Kubista E, Singer CF. Estrogen receptor beta and matrix metalloproteinase 1 are coexpressed in uterine endometrium and endometriotic lesions of patients with endometriosis. *Fertil Steril* 2005;84(Suppl 2):1249-1256.
  132. Kyama CM, Overbergh L, Debrock S, Valckx D, Vander Perre S, Meuleman C, Mihalyi A, Mwenda JM, Mathieu C, D'Hooghe TM. Increased peritoneal and endometrial gene expression of biologically relevant cytokines and growth factors during the menstrual phase in women with endometriosis. *Fertil Steril* 2006a;85:1667-1675.
  133. Johnson MC, Torres M, Alves A, Bacallao K, Fuentes A, Vega M, Boric MA. Augmented cell survival in eutopic endometrium from women with endometriosis: expression of c-myc, TGF-beta1 and bax genes. *Reprod Biol Endocrinol* 2005;3:45.
  134. Akoum A, Lemay A, Lajeunesse Y, Marois M, Koutsilieris M. Immunohistochemical localization of insulin-like growth factor-binding protein-3 in eutopic and ectopic endometrial tissues. *Fertil Steril* 1999;72:1085-1092.
  135. Li CY, Lang JH, Liu HY, Zhou HM. Expression of Annexin-1 in patients with endometriosis. *Chin Med J (Engl)* 2008;121:927-931.
  136. Lessey BA, Yeh I, Castelbaum AJ, Fritz MA, Ilesanmi AO, Korzeniowski P, Sun J, Chwalisz K. Endometrial progesterone receptors and markers of uterine receptivity in the window of implantation. *Fertil Steril* 1996;65:477-483.
  137. Kyama CM, Overbergh L, Mihalyi A, Meuleman C, Mwenda JM, Mathieu C, D'Hooghe TM. Endometrial and peritoneal expression of aromatase, cytokines, and adhesion factors in women with endometriosis. *Fertil Steril* 2008;89:301-310.
  138. van der Linden PJ, de Goeij AF, Dunselman GA, van der Linden EP, Ramaekers FC, Evers JL. Expression of integrins and E-cadherin in cells from menstrual effluent, endometrium, peritoneal fluid, peritoneum, and endometriosis. *Fertil Steril* 1994;61:85-90.
  139. Matsuzaki S, Darcha C, Maleysson E, Canis M, Mage G. Impaired down-regulation of E-cadherin and beta-catenin protein expression in endometrial epithelial cells in the mid-secretory endometrium of infertile patients with endometriosis. *J Clin Endocrinol Metab* 2010;95:3437-3445.
  140. Prefumo F, Semino C, Melioli G, Venturini PL. A defective expression of ICAM-1 (CD54) on secretory endometrial cells is associated with endometriosis. *Immunol Lett* 2002;80:49-53.
  141. Stephens AN, Hannan NJ, Rainczuk A, Meehan KL, Chen J, Nicholls PK, Rombauts LJ, Stanton PG, Robertson DM, Salamonsen LA. Post-Translational Modifications and Protein-Specific Isoforms in Endometriosis Revealed by 2D DIGE. *J Proteome Res* 2010;9:2438-2449.
  142. Jabbour HN, Kelly RW, Fraser HM, Critchley HOD. Endocrine Regulation of Menstruation. *Endocr Rev* 2006;27:17-46.
  143. Donnez J, Smoes P, Gillerot S, Casanas-Roux F, Nissolle M. Vascular endothelial growth factor (VEGF) in endometriosis. *Hum Reprod* 1998;13:1686-1690.
  144. Tan XJ, Lang JH, Liu DY, Shen K, Leng JH, Zhu L. Expression of vascular endothelial growth factor and thrombospondin-1 mRNA in patients with endometriosis. *Fertil Steril* 2002;78:148-153.
  145. Di Carlo C, Bonifacio M, Tommaselli GA, Bifulco G, Guerra G, Nappi C. Metalloproteinases, vascular endothelial growth factor, and angiopoietin 1 and 2 in eutopic and ectopic endometrium. *Fertil Steril* 2009;91:2315-2323.
  146. Khan KN, Masuzaki H, Fujishita A, Kitajima M, Sekine I, Ishimaru T. Immunoeexpression of hepatocyte growth factor and c-Met receptor in the eutopic endometrium predicts the activity of ectopic endometrium. *Fertil Steril* 2003;79:173-181.
  147. Takehara M, Ueda M, Yamashita Y, Terai Y, Hung YC, Ueki M. Vascular endothelial growth factor A and C gene expression in endometriosis. *Hum Pathol* 2004;35:1369-1375.
  148. Gilabert-Estelles J, Ramon LA, Espana F, Gilabert J, Vila V, Reganon E, Castello R, Chirivella M, Estelles A. Expression of angiogenic factors in endometriosis: relationship to fibrinolytic and metalloproteinase systems. *Hum Reprod* 2007;22:2120-2127.
  149. Cosin R, Gilabert-Estelles J, Ramon LA, Espana F, Gilabert J, Romeu A, Estelles A. Vascular endothelial growth factor polymorphisms (-460C/T, +405G/C, and

- 936C/T) and endometriosis: their influence on vascular endothelial growth factor expression. *Fertil Steril* 2009;92:1214–1220.
150. Thomas M, Augustin H. The role of the angiopoietins in vascular morphogenesis. *Angiogenesis* 2009;12:125–137.
  151. Hur SE, Lee JY, Moon HS, Chung HW. Angiopoietin-1, angiopoietin-2 and Tie-2 expression in eutopic endometrium in advanced endometriosis. *Mol Hum Reprod* 2006;12:421–426.
  152. Liu Y, Lu L, Zhu G. Anginogenesis of eutopic and ectopic endometria in endometriosis. *J Huazhong Univ Sci Technolog Med Sci* 2003;23:190–191.
  153. Burlev VA, Il'yasova NA, Dubinskaya ED. Proliferative activity of microvessels and angiogenesis in eutopic endometrium in patients with peritoneal endometriosis. *Bull Exp Biol Med* 2005;139:727–731.
  154. Bourlev V, Volkov N, Pavlovitch S, Lets N, Larsson A, Olovsson M. The relationship between microvessel density, proliferative activity and expression of vascular endothelial growth factor-A and its receptors in eutopic endometrium and endometriotic lesions. *Reproduction* 2006;132:501–509.
  155. Kim SH, Choi YM, Chae HD, Kim KR, Kim CH, Kang BM. Increased expression of endoglin in the eutopic endometrium of women with endometriosis. *Fertil Steril* 2001;76:918–922.
  156. Lee SR, Kim SH, Lee YJ, Hong SH, Chae HD, Kim CH, Kang BM, Choi YM. Expression of epidermal growth factor, fibroblast growth factor-2, and platelet-derived growth factor-A in the eutopic endometrium of women with endometriosis. *J Obstet Gynaecol Res* 2007;33:242–247.
  157. Tiberi F, Tropea A, Apa R, Romani F, Lanzone A, Marana R. Prokineticin 1 mRNA expression in the endometrium of healthy women and in the eutopic endometrium of women with endometriosis. *Fertil Steril* 2010;96:2145–2149.
  158. Lee KF, Lee YL, Chan RW, Cheong AW, Ng EH, Ho PC, Yeung WS. Up-regulation of endocrine gland-derived vascular endothelial growth factor but not vascular endothelial growth factor in human ectopic endometriotic tissue. *Fertil Steril* 2010;93:1052–1060.
  159. Gebel HM, Braun DP, Tambur A, Frame D, Rana N, Dmowski WP. Spontaneous apoptosis of endometrial tissue is impaired in women with endometriosis. *Fertil Steril* 1998;69:1042–1047.
  160. Braun DP, Ding J, Shen J, Rana N, Fernandez BB, Dmowski WP. Relationship between apoptosis and the number of macrophages in eutopic endometrium from women with and without endometriosis. *Fertil Steril* 2002; 78:830–835.
  161. Meresman GF, Auge L, Baranao RI, Lombardi E, Tesone M, Sueldo C. Oral contraceptives suppress cell proliferation and enhance apoptosis of eutopic endometrial tissue from patients with endometriosis. *Fertil Steril* 2002;77:1141–1147.
  162. Hassa H, Tanir HM, Tekin B, Artan S, Dundar E, Kirilmaz SD, Sahin Mutlu F. Apoptosis patterns in eutopic and ectopic endometrium, adhesions and normal-looking peritoneum from women with or without endometriosis. *Arch Gynecol Obstet* 2009;280:195–199.
  163. Burlev VA, Pavlovich SV, Il'yasova NA. Apoptosis and proliferative activity in endometrium during peritoneal endometriosis. *Bull Exp Biol Med* 2006; 141:204–207.
  164. Park JS, Lee JH, Kim M, Chang HJ, Hwang KJ, Chang KH. Endometrium from women with endometriosis shows increased proliferation activity. *Fertil Steril* 2009; 92:1246–1249.
  166. Penna I, Du H, Ferriani R, Taylor HS. Calpain5 expression is decreased in endometriosis and regulated by HOXA10 in human endometrial cells. *Mol Hum Reprod* 2008;14:613–618.
  167. Braun DP, Ding J, Shaheen F, Willey JC, Rana N, Dmowski WP. Quantitative expression of apoptosis-regulating genes in endometrium from women with and without endometriosis. *Fertil Steril* 2007;87:263–268.
  168. Hapangama DK, Turner MA, Drury JA, Quenby S, Hart A, Maddick M, Martin-Ruiz C, von ZT. Sustained replication in endometrium of women with endometriosis occurs without evoking a DNA damage response. *Hum Reprod* 2009;24:687–696.
  169. Wingfield M, Macpherson A, Healy DL, Rogers PA. Cell proliferation is increased in the endometrium of women with endometriosis. *Fertil Steril* 1995; 64:340–346.
  170. Ota H, Igarashi S, Tanaka T. Xanthine oxidase in eutopic and ectopic endometrium in endometriosis and adenomyosis. *Fertil Steril* 2001;75:785–790.
  171. Khorram O, Lessey BA. Alterations in expression of endometrial endothelial nitric oxide synthase and alpha(v)beta(3) integrin in women with endometriosis. *Fertil Steril* 2002;78:860–864.
  172. Matsuzaki S, Canis M, Vaur-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):1180–1190.
  173. Matsuzaki S, Canis M, Pouly JL, Dechelotte PJ, Mage G. Analysis of aromatase and 17 beta-hydroxysteroid dehydrogenase type 2 messenger ribonucleic acid expression in deep endometriosis and eutopic endometrium using laser capture microdissection. *Fertil Steril* 2006;85:308–313.
  174. Kyama CM, T'Jampens D, Mihalyi A, Simsa P, Debrock S, Waelkens E, Landuyt B, Meuleman C, Fulop V, Mwenda JM et al. ProteinChip technology is a useful method in the pathogenesis and diagnosis of endometriosis: a preliminary study. *Fertil Steril* 2006b;86:203–209.
  175. Zhang H, Niu Y, Feng J, Guo H, Ye X, Cui H. Use of proteomic analysis of endometriosis to identify different protein expression in patients with endometriosis versus normal controls. *Fertil Steril* 2006;86:274–282.
  176. Wang G, Tokushige N, Russell P, Dubinovsky S, Markham R, Fraser IS. Neuroendocrine cells in eutopic endometrium of women with endometriosis. *Hum Reprod* 2010;25:387–391.

177. Chenna-Patel N, Sachdeva G, Gajbhiye R, Warty N, Khole V. 'Spot'-ting differences between the ectopic and eutopic endometrium of endometriosis patients. *Fertil Steril* 2010;94:1964–1971.
178. Fedele L, Marchini M, Bianchi S, Dorta M, Arcaini L, Fontana PE. Structural and ultrastructural defects in preovulatory endometrium of normo-ovulating infertile women with minimal or mild endometriosis. *Fertil Steril* 1990;53:989–993.
179. Cunha-Filho JS, Gross JL, Lemos NA, Brandelli A, Castillos M, Passos EP. Hyperprolactinemia and luteal insufficiency in infertile patients with mild and minimal endometriosis. *Horm Metab Res* 2001;33:216–220.
180. Moeloek FA, Moegny E. Endometriosis and luteal phase defect. *Asia Oceania J Obstet Gynaecol* 1993;19:171–176.
181. Ordi J, Creus M, Casamitjana R, Cardesa A, Vanrell JA, Balasch J. Endometrial pinopode and alphav-beta3 integrin expression is not impaired in infertile patients with endometriosis. *J Assist Reprod Gene* 2003;20:465–473.
182. Al-Jefout M, Andreadis N, Tokushige N, Markham R, Fraser I. A pilot study to evaluate the relative efficacy of endometrial biopsy and full curettage in making a diagnosis of endometriosis by the detection of endometrial nerve fibers. *Am J Obstet Gynecol* 2007;197:578.e1–578.e4.
183. Al-Jefout M, Dezarnaulds G, Cooper M, Tokushige N, Luscombe GM, Markham R, Fraser IS. Diagnosis of endometriosis by detection of nerve fibres in an endometrial biopsy: a double blind study. *Hum Reprod* 2009;24:3019–3024.
184. Bokor A, Kyama CM, Vercruyse L, Fassbender A, Gevaert O, Vodolazkaia A, De MB, Fulop V, D'Hooghe T. Density of small diameter sensory nerve fibres in endometrium: a semi-invasive diagnostic test for minimal to mild endometriosis. *Hum Reprod* 2009;24:3025–3032.
185. Zhang X, Lu B, Huang X, Xu H, Zhou C, Lin J. Endometrial nerve fibers in women with endometriosis, adenomyosis, and uterine fibroids. *Fertil Steril* 2009b;92:1799–1801.

**Not:** Bu bölüm temel olarak “K.E. May et al, Endometrial alterations in endometriosis: a systematic review of putative biomarkers, *Human Reproduction Update*, Vol.17, No.5 pp. 637–653, 2011”, “Hakan Cakmak and Hugh S. Taylor Implantation failure: molecular mechanisms and clinical treatment *Human Reproduction Update*, Vol.17, No.2 pp. 242–253, 2011”, “de Ziegler D et al. Endometriosis and infertility: pathophysiology and management. *Lancet*. 2010 28;376:730-8. Review” isimli üç ana yazıyı özetleyen bir derlemedir. Ayrıntılı bilgi için bu kaynaklara bakınız.