

Bölüm 16

ENDOMETRİOTİK İMLANTLARIN ADEZYON İNVAZYON VE BÜYÜME MEKANİZMALARI

Prof. Dr. İ. İpek MÜDERRİS
Uzm. Dr. Gökhan AÇMAZ

Endometriozisin RGM'ye sekonder olarak gelişğini kabul edersek, periton'a dökülen endometrial dokunun viabilitiesi, HLA-G içeriği, peritoneal tutunma ve invazyon aşamalarını geçtikten sonra yeni habitatında yerleşmesi ve büyümeye için birçok moleküler ve genetik olayın koordineli bir şekilde gerçekleşmesi gerekmektedir. Her RGM endometriozisle sonuçlanmadığına göre periton ve endometrial hücreleri bu hastalığı geliştirmek için klonal bir şekilde programlanmış kişiler klinik olarak hasta hale geleceklerdir. Bu bölüm periton ve endometrial doku ilişkilerini detaylarıyla kaleme alan eski ve yeni teorileri karşılaştırma fırsatı sağlayan birçok güncel bilgiyi bünyesinde barındırmaktadır. **Editorial**

Giriş

Endometriozis ilk kez 1860'lı yıllarda tanımlanmış olup, oldukça agresif ve ilerleyici bir hastaluktur. Bugüne kadar patofizyolojisi ile ilgili konular açıklığa kavuşmamıştır. Bu yıllarda Sampson'un (1) yaptığı çalışmalarla ilk kez peritoneal endometriozisin menstrual reflü sonucunda oluştuğu teorisini ortaya atılmıştır. Günümüzde hiçbir teori tek başına endometriozis etyolojisini açıklamak için yeterli olmadığından bu konuya ilişkin pek çok görüş ileri sürülmüştür. Bunlar arasında başlıca; retrograd menstruasyon, endometriozisin metaplazi ve lenfovasküler yayılımla oluştuğuna dair hipotezler bulunmaktadır (2). Bu konuda ilk olarak ileri sü-

rulen teori Sampson'un (1) viable endometrial hücrelerin menstruasyon sırasında fallop tüpleri yolu ile batına geçtiği retrograd menstruasyon (RGM) teorisidir ilerleyen yıllarda bu yaklaşımı destekleyen pek çok çalışma yapılmıştır. Bu konuya ilişkin olarak

1. Menstrasyon sırasında kadınlarından alınan periton sıvısında viable endometrial hücrelerin bulunduğu saptanmıştır (3).
2. Deneyel olarak endometrial hücreler periton'a implante edilebilmekte daha sonra bu odaklardan endometriozis gelişebilmektedir (4).
3. Kadınların pek çokunda retrograd menstruasyon olduğu saptanmıştır (5).
4. Menstruel akım engellendiğinde endometriozis geliştiği deneyel olarak gösterilmiştir (6).

Transtubal yayılının bahsi geçen nedenlerden dolayı en sık saptanan mekanizma olduğu düşünülse de metaplazi ve lenfovasküler yayılım, retrograd menstruasyonun açıklayamadığı endometriozisi açıklaması açısından önemli görülmektedir. RGM'de endometriozis gelişimi ile ilgili olarak önemli noktalardan biriside menstrual debinin içeriğidir. Bu konu periton sıvısından alınan örneklerin incelenmesi ile ortaya konulmaya çalışılmıştır. Kırmızı lekeli periton sıvısı menstruasyon sırasında kuldosentez ile % 50 laparoskopı sırasında % 70-90 oranında saptanmaktadır (5,7). Ancak periton sıvısında kırmızı lekelerin saptanması, viable

Kaynaklar

1. Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. American Journal of Obstetrics and Gynecology 1927; 14: 422–469.
2. Stanley J Robboy, Sarah M Bean Pathogenesis of endometriosis Reproductive BioMedicine Online. 2010; 21, 4-5
3. Keettel WC & Stein RJ. The viability of the cast-off menstrual endometrium. American Journal of Obstetrics and Gynecology 1951; 61: 440–442.
4. Ridley JH & Edwards IK. Experimental endometriosis in the human. American Journal of Obstetrics and Gynecology 1958; 76: 783–790.
5. Halme J, Hammond MG, Hulka JF et al. Retrograde menstruation in healthy women and in patients with endometriosis. Obstetrics and Gynecology 1984; 64: 151–154.
6. D'Hooghe, T.M, Kyama CM, Chai D, et al. Non-human primate models for translational research in endometriosis. Reprod. Sci. 2009;16:152-161
7. Polishuk WZ, Sharf M: Culdoscopic findings in primary dysmenorrhea. *Obstet Gynecol* 1965, 26(5):746-748.
8. Bartosik D, Jacobs SL, Kelly LJ: Endometrial tissue in peritoneal fluid. *Fertil Steril* 1986, 46:796-800.
9. Gomez-Fernandez CR, Ganjei-Azar P, Behshid K, et al. Normal endometrial cells in Papanicolaou smears: prevalence in women with and without endometrial disease. *Obstet Gynecol* 2000, 96(6):874-878.
10. Kruitwagen RFPM, Poels LG, Willemsen WNP et al. Endometrial epithelial cells in peritoneal fluid during the early follicular phase. *Fertil Steril* 1991, 55:297-303.
11. Linden PJ van der, Dunselman GA, de Goeij AF, et al. Epithelial cells in peritoneal fluid-of endometrial origin? *Am J Obstet Gynecol* 1995, 173(2):566-570.
12. Saad Amer Endometriosis Obstetrics, Gynecology and Reproductive Medicine 2008;18:5
13. Van Langendonck A, Casanas-Roux F, Dolmans MM, et al. Potential involvement of hemoglobin and heme in the pathogenesis of peritoneal endometriosis. *Fertil Steril* 2002, 77(3):561-570.
14. Wagener FADTG, Feldman E, De Witte T, et al. Heme induces the expression of adhesion molecule ICAM-1, VCAM-1 and E selectin in vascular endothelial cells. *Proc Soc Exp Biol Med* 1997, 216:456-463.
15. Defrère S, Lousse JC, González-Ramos R, et al. Potential involvement of iron in the pathogenesis of peritoneal endometriosis. *Mol Hum Reprod* 2008, 14(7):377-385.
16. Balla J, Nath KA, Balla G, et al. Endothelial cell heme oxygenase and ferritin induction in rat lung by hemoglobin in vivo. *Am J Physiol* 1995, 268:321-327.
17. Khan KN, Masuzaki H, Fujishita A, et al. Regulation of hepatocyte growth factor by basal and stimulated macrophages in women with endometriosis. *Hum Reprod* 2005, 20(1):49-60.
18. D'Hooghe TM, Hill JA: Endometriosis. In *Novak's Gynecology Volume Chapter 29*. 14th edition. Edited by: Williams, Wilkins, Berek JS. Philadelphia, USA; 2006:1137-1184.
19. Hill JA: Immunology and endometriosis. *Fertil Steril* 1992, 58:262-264.
20. Bokor A, Debrock S, Drijkoningen M et al. Quantity and quality of retrograde menstruation: a case control Study Reprod Biol Endocrinol 2009;30;7:123
21. D'Hooghe TM, Hill JA, Oosterlynck DJ, et al. Effect of endometriosis on white blood cell subpopulations in peripheral blood and peritoneal fluid of baboons. *Hum Reprod* 1996, 11(8):1736-1740.
22. D'Hooghe TM, Scheerlinck JP, Koninckx PR, et al. Anti-endometrial lymphocytotoxicity and natural killer cell activity in baboons (Papio anubis and Papio cynocephalus) with endometriosis. *Hum Reprod* 1995, 10 (3):558-562.
23. Oral E & Arici A. Pathogenesis of endometriosis. *Obstetrics and Gynecology Clinics of North America* 1997;24: 219–233.
24. Lebovic DI, Mueller MD & Taylor RN. Immunobiology of endometriosis. *Fertility and Sterility* 2001; 75:1–10.
25. Simpson JL, Farideh ZB, Kamat A et al. Genetics of endometriosis. *Obstetrics and Gynecology Clinics of North America* 2003; 30: 21–40.
26. Bischoff FZ & Simpson JL. Heritability and molecular genetic studies of endometriosis. *Human Reproduction Update* 2000; 6: 37–44.
27. Luisi S, Galleri L, Marini F, et al. Estrogen receptor gene polymorphisms are associated with recurrence of endometriosis. *Fertil Steril* 2006;85:764–6.
28. Renner SP, Strick R, Oppelt P, et al. Evaluation of clinical parameters and estrogen receptor alpha gene polymorphisms morphisms for patients with endometriosis. *Reproduction* 2006;131:153–61.
29. Jingyan Xie, Shukui Wang, Bangshun He, et al. Association of estrogen receptor alpha and interleukin-10 gene polymorphisms with endometriosis in a Chinese population *Fertility and Sterility*. 2009 Vol. 92, No. 1,
30. Dmowski WP, Ding J, Shen J et al. Apoptosis in endometrial glandular and stromal cells in women with and without endometriosis. *Human Reproduction* 2001; 16: 1802–1808.
31. Gebel HM, Braun DP, Tambur A et al. Spontaneous apoptosis of endometrial tissue is impaired in women with endometriosis. *Fertility and Sterility* 1998; 69: 1042–1047.
32. Krzysztof Szymanowski Apoptosis pattern in human endometrium in women with pelvic endometriosis European Journal of Obstetrics & Gynecology and Reproductive Biology (2007) ;132: 107–110.
33. Donald P. Braun, Jianchi Ding, Fehr Shaheen, et al. Quantitative expression of apoptosis-regulating genes

- in endometrium from women with and without endometriosis. *Fertility and Sterility* Vol. 87, No. 2, February 2007.
34. Meresman GF, Vighi S, Buquet RA et al. Apoptosis and expression of Bcl-2 and Bax in eutopic endometrium from women with endometriosis. *Fertility and Sterility* 2000; 74: 760–766.
 35. Goumenou A, Panayiotides I, Matalliotakis I et al. Bcl-2 and Bax expression in human endometriotic and adenomyotic tissues. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 2001; 99: 256–260.
 36. Watanabe H, Kanzaki H, Narakuwa S et al. Bcl-2 and Fas expression in eutopic and ectopic human endometrium during the menstrual cycle in relation to endometrial cell apoptosis. *American Journal of Obstetrics and Gynecology* 1997; 176: 360–368.
 37. Jones RK, Searle RF & Bulmer JN. Apoptosis and bcl-2 expression in normal human endometrium, endometriosis and adenomyosis. *Human Reproduction* 1998; 13: 3496–3502.
 38. Ho HN, Wu MY & Yang YS. Peritoneal cellular immunity and endometriosis. *American Journal of Reproductive Immunology* 1997; 38: 400–412.
 39. D'Hooghe TM, Bambra CS, Raeymaekers BM et al. The effects of immunosuppression on development and progression of endometriosis in baboons (*Papio anubis*). *Fertility and Sterility* 1995; 64: 172–178.
 40. Braun DP & Dmowski WP. Endometriosis: abnormal endometrium and dysfunctional immune response. *Current Opinion in Obstetrics and Gynecology* 1998; 10: 365–369.
 41. Semino C, Barrocci S, Semino A et al. Role of major histocompatibility complex class I expression and natural killer-like T cells in the genetic control of endometriosis. *Fertility and Sterility* 1995; 64: 909–916.
 42. Somigliana E, Vigano P, Gaffuri B et al. Human endometrial stromal cells as a source of soluble intercellular adhesion molecule (ICAM)-1 molecules. *Human Reproduction* 1996; 11: 1190–1194. 196
 43. De Placido G, Alaviggi C, Di Palma G et al. Serum concentrations of soluble human leukocyte class I antigens and of the soluble intercellular adhesion molecule-1 in endometriosis: relationship with stage and non-pigmented peritoneal lesions. *Human Reproduction* 1998; 13: 3206–3210.
 44. Hirata J, Kikuchi Y, Imaizumi E et al. Endometriotic tissues produce immunosuppressive factors. *Gynecologic and Obstetric Investigation* 1994; 37: 43–47.
 45. Somigliana E, Vigano P & Vignali M. Endometriosis and unexplained recurrent spontaneous abortion: pathological states resulting from aberrant modulation of natural killer cell function? *Human Reproduction Update* 1999; 5: 40–51.
 46. Garcia-Velasco JA, Arici A, Zreik T et al. Macrophage derived growth factors modulate Fas ligand expression in cultured endometrial stromal cells: a role in endometriosis. *Molecular Human Reproduction* 1999; 5: 642–650.
 47. Vigano P, Vercellini P, Di Blasio AM et al. Deficient antiendometrium lymphocyte-mediated cytotoxicity in patients with endometriosis. *Fertility and Sterility* 1991; 56: 894–899.
 48. Oosterlynck DJ, Cornillie FJ, Waer M et al. Women with endometriosis show a defect in natural killer activity resulting in a decreased cytotoxicity to autologous endometrium. *Fertility and Sterility* 1991; 56: 45–51.
 49. Oosterlynck DJ, Meuleman C, Waer M et al. The natural killer activity of peritoneal fluid lymphocytes is decreased in women with endometriosis. *Fertility and Sterility* 1992; 58: 290–295.
 50. Tanaka E, Sendo F, Kawagoe S & Hiroi M. Decreased natural killer cell activity in women with endometriosis. *Gynecologic and Obstetric Investigation* 1992; 34: 27–30.
 51. Garzetti GG, Ciavattini A, Provinciali M et al. Natural killer cell activity in endometriosis: correlation between serum estradiol levels and cytotoxicity. *Obstetrics and Gynecology* 1993; 81: 665–668.
 52. Melioli G, Semino C, Semino A et al. Recombinant interleukin-2 corrects in vitro the immunological defect of endometriosis. *American Journal of Reproductive Immunology* 1993; 30: 218–227.
 53. Iwasaki K, Makino T, Maruyama T et al. Leukocyte subpopulations and natural killer activity in endometriosis. *International Journal of Fertility and Menopausal Studies* 1993; 38: 229–234.
 54. Wilson TJ, Hertzog PJ, Angus D et al. Decreased natural killer cell activity in endometriosis patients: relationship to disease pathogenesis. *Fertility and Sterility* 1994; 62: 1086–1088.
 55. Ho HN, Chao KH, Chen HF et al. Peritoneal natural killer cell cytotoxicity and CD25 § CD3 § lymphocyte subpopulation are decreased in women with stage III–IV endometriosis. *Human Reproduction* 1995; 10: 2671–2675.
 56. Wu MY, Yang JH, Chao KH et al. Increase in the expression of killer cell inhibitory receptors on peritoneal natural killer cells in women with endometriosis. *Fertility and Sterility* 2000; 74: 1187–1191.
 57. Smyth MJ, Godfrey DI & Trapani JA. A fresh look at tumor immunosurveillance and immunotherapy. *Nature Immunology* 2001; 2: 293–299.
 58. Maeda N, Izumiya C, Yamamoto Y et al. Increased killer inhibitory receptor KIR2DL1 expression among natural killer cells in women with pelvic endometriosis. *Fertility and Sterility* 2002; 77: 297–302.
 59. Maeda N, Izumiya C, Oguri H et al. Aberrant expression of intercellular adhesion molecule-1 and killer inhibitory receptors induces immune tolerance in women with pelvic endometriosis. *Fertility and Sterility* 2002; 77: 679–683.
 60. Ewa Barcz, Lukasz Milewski, Piotr Dziunycz, et al. Peritoneal cytokines and adhesion formation in endometriosis: an inverse association with vascular endothelial growth factor concentration. *Fertility and Sterility* Vol. 97, No. 6, June 2012

61. Beliard A, Donne J, Nisolle M & Foidart JM. Localization of laminin, fibronectin, E-cadherin, and integrins in endometrium and endometriosis. *Fertility and Sterility* 1997; 67: 266–272.
62. Darai E, Leblanc M, Walker-Combrouze F et al. Expression of cadherins and CD44 isoforms in ovarian endometrial cysts. *Human Reproduction* 1998; 13: 1346–1352.
63. Starzinski-Powitz A, Handrow-Metzmacher H & Kotzian S. The putative role of cell adhesion molecules in endometriosis: can we learn from tumour metastasis? *Molecular Medicine Today* 1999; 5: 304–309.
64. Ruthy Shaco-Levy, Shalom Sharabi, Daniel Benharoch, et al. Matrix metalloproteinases 2 and 9, E-cadherin, and b-catenin expression in endometriosis, low-grade endometrial carcinoma and non-neoplastic eutopic endometrium. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2008; 139: 226–232.
65. van der Linden PJ, de Goeij AF, Dunselman GA et al. Expression of cadherins and integrins in human endometrium throughout the menstrual cycle. *Fertility and Sterility* 1995; 63: 1210–1216.
66. Brooks PC, Sromblad S, Sanders LC et al. Localization of matrix metalloproteinase MMP-2 to the surface of invasive cells by interaction with integrin alphav beta3. *Cell* 1996; 85: 683–693.
67. Dechaud H, Craig A, Monotoya-Rodriguez IA et al. Mesothelial cell-associated hyaluronic acid promotes adhesion of endometrial cells to mesothelium. *Fertility and Sterility* 2001; 76: 1012–1018.
68. Zeitoun KM & Bulun SE. Aromatase: a key molecule in the pathophysiology of endometriosis and a therapeutic target. *Fertility and Sterility* 1999; 72: 961–969.
69. Gazvani R & Templeton A. Peritoneal environment, cytokines and angiogenesis in the pathophysiology of endometriosis. *Reproduction* 2002; 123: 217–226.
70. Fujimoto J, Hori M, Ichigo S & Tamaya T. Expression of basic fibroblast growth factor and its mRNA in uterine endometrium during the menstrual cycle. *Gynecological Endocrinology* 1996; 10: 193–197.
71. Di Blasio AM, Centinaio G, Carniti C et al. Basic fibroblast growth factor messenger ribonucleic acid levels in eutopic and ectopic human endometrial stromal cells as assessed by competitive polymerase chain reaction amplification. *Molecular and Cellular Endocrinology* 1995; 115: 169–175.
72. Mihalich A, Reina M, Mangioni S et al. Different basic fibroblast growth factor and fibroblast growth factor antisense expression in eutopic endometrial stromal cells derived from women with and without endometriosis. *Journal of Clinical Endocrinology and Metabolism* 2003; 88: 2853–2859.
73. Rusnati M, Casarotti G, Pecorelli S et al. Basic fibroblast growth factor in ovulatory cycle and postmenopausal human endometrium. *Growth Factors* 1990; 3: 299–307.
74. Sangha RK, Li XF, Shams M & Ahmed A. Fibroblast growth factor receptor-1 is a critical component for endometrial remodeling: localization and expression of basic fibroblast growth factor and FGF-R1 in human endometrium during the menstrual cycle and decreased FGF-R1 expression in menorrhagia. *Laboratory Investigation* 1997; 77: 389–402.
75. Attia GR, Zeitoun K, Edwards D et al. Progesterone receptor isoform A but not B is expressed in endometriosis. *Journal of Clinical Endocrinology and Metabolism* 2000; 85: 2897–2902.
76. Kitawaki J, Koshiba H, Ishihara H et al. Progesterone induction of 17beta-hydroxysteroid dehydrogenase type 2 during the secretory phase occurs in the endometrium of estrogen-dependent benign diseases but not in normal endometrium. *Journal of Clinical Endocrinology and Metabolism* 2000; 85: 3292–3296.
77. De La Garza EM, Binkley PA, Ganapathy M, et al. Raf-1, a Potential Therapeutic Target, Mediates Early Steps in Endometriosis Lesion Development by Endometrial Epithelial and Stromal Cells. *Endocrinology*. 2012 May 22.
78. Rodgers WH, Matrisian LM, Giudice LC et al. Patterns of matrix metalloproteinase expression in cycling endometrium imply differential functions and regulation by steroid hormones. *Journal of Clinical Investigation* 1994; 94: 946–953.
79. Salamonsen LA, Butt AR, Hammond FR et al. Production of endometrial matrix metalloproteinases, but not their tissue inhibitors, is modulated by progesterone withdrawal in an in vitro model for menstruation. *Journal of Clinical Endocrinology and Metabolism* 1997; 82: 1409–1415.
80. Bruner KL, Eisenberg E, Gorstein F & Osteen KG. Progesterone and transforming growth factor-beta co-ordinately regulate suppression of endometrial matrix metalloproteinases in a model of experimental endometriosis. *Steroids* 1999; 64: 648–653.
81. Bruner KL, Matrisian LM, Rodgers WH et al. Suppression of matrix metalloproteinases inhibits establishment of ectopic lesions by human endometrium in nude mice. *Journal of Clinical Investigation* 1997; 99: 2851–2857.
82. Chung HW, Lee JY, Moon HS et al. Matrix metalloproteinase-2, membranous type 1 matrix metalloproteinase, and tissue inhibitor of metalloproteinase-2 expression in ectopic and eutopic endometrium. *Fertility and Sterility* 2002; 78: 787–795.
83. Sharpe-Timms KL. Basic research in endometriosis. *Obstetrics and Gynecology Clinics of North America* 1997; 24: 269–290.
84. Sharpe-Timms KL. Endometrial anomalies in women with endometriosis. *Annals of New York Academy of Sciences* 2001; 943: 131–147.
85. Sharpe-Timms KL, Keisler LW, McIntush EW & Keisler DH. Tissue inhibitor of metalloproteinase-1 concentrations are attenuated in peritoneal fluid and sera of women with endometriosis and restored in sera by gonadotropin-releasing hormone agonist therapy. *Fertility and Sterility* 1998; 69: 1128–1134.

86. Martelli M, Campana A & Bischof P. Secretion of matrix metalloproteinases by human endometrial cells in vitro. *Journal of Reproduction and Fertility* 1993; 98: 67–76.
87. Rawdanowicz TJ, Hampton AL, Nagase H et al. Matrix metalloproteinase production by cultured human endometrial stromal cells: identification of interstitial collagenase, gelatinase-A, gelatinase-B, and stromelysin-1 and their differential regulation by interleukin-1 alpha and tumor necrosis factor-alpha. *Journal of Clinical Endocrinology and Metabolism* 1994; 79: 530–536.
88. Groothuis PG, Nap AW, Winterhager E, et al. Vascular development in endometriosis. *Angiogenesis* 2005; 8:147-156.
89. Ricci AG, Olivares CN, Bilotas MA, et al. Effect of vascular endothelial growth factor inhibition on endometrial implant development in a murine model of endometriosis. *Reprod Sci*. 2011 Jul;18(7):614-22.
90. McLaren J. Vascular endothelial growth factor and endometriotic angiogenesis. *Human Reproduction Update* 2000; 6: 45–55.
91. Donnez J, Smoes P, Gillerot S et al. Vascular endothelial growth factor (VEGF) in endometriosis. *Human Reproduction* 1998; 13: 1686–1690.
92. Shifren JL, Tseng JF, Zaloudek CJ et al. Ovarian steroid regulation of vascular endothelial growth factor in the human endometrium: implications for angiogenesis during the menstrual cycle and in the of endometriosis. *Journal of Clinical Endocrinology and Metabolism* 1996; 81: 3112–3118.
93. McLaren J, Prentice A, Charnock-Jones DS & Smith SK. Vascular endothelial growth factor (VEGF) concentrations are elevated in peritoneal fluid of women with endometriosis. *Human Reproduction* 1996; 11: 220–223.
94. Tan XJ, Lang JH, Liu DY et al. Expression of vascular endothelial growth factor and thrombospondin-1 mRNA in patients with endometriosis. *Fertility and Sterility* 2002; 78: 148–153.
95. Koch AE, Polverini PJ, Kunkel SL, et al. Interleukin 8 as a macrophage derived mediator of angiogenesis. *Science* 1992; 258: 1798–1801.
96. Arici A, Seli E, Zeyneloglu HB et al. Interleukin 8 induces proliferation of endometrial stromal cells: a potential autocrine growth factor. *Journal of Clinical Endocrinology and Metabolism* 1998; 83: 1201–1205.
97. Rana N, Braun DP, House R et al. Basal and stimulated secretion of cytokines in peritoneal macrophages in women with endometriosis. *Fertility and Sterility* 1996; 65: 925–930.
98. Christodoulakos G, Augoulea A, Lambrinoudaki I, et al. Pathogenesis of endometriosis: the role of defective ‘immunosurveillance’. *Eur J Contracept Reprod Health Care* 2007; 12:194–202.
99. Abrao MS, Podgaec S, Filho BM, et al. The use of biochemical markers in the diagnosis of pelvic endometriosis. *Hum Reprod* 1997; 12:2523–2527.
100. Osuga Y, Koga K, Hirota Y, et al. Lymphocytes in endometriosis. *Am J Reprod Immunol* 2011; 65:1–10.
101. Berbic M, Fraser IS: Regulatory T cells and other leukocytes in the of endometriosis. *J Reprod Immunol* 2011; 88:149–155.
102. Sikora J, Mielczarek-Palacz A, Kondera-Anasz Z: Role of natural killer cell activity in the pathogenesis of endometriosis. *Curr Med Chem* 2011; 18:200–208.
103. Bullimore DW. Endometriosis is sustained by tumor necrosis factor-alfa. *Medical Hypothesis* 2003; 60: 84–88.
104. Mori H, Sawairi M, Nakagawa M et al. Peritoneal fluid interleukin-1 beta and tumor necrosis factor in patients with benign gynecologic disease. *American Journal of Reproductive Immunology* 1991; 26: 62–67.
105. Overton C, Fernandez-Shaw S, Hicks B et al. Peritoneal fluid cytokines and the relationship with endometriosis and pain. *Human Reproduction* 1996; 11: 380–386.
106. Halme J. Release of tumor necrosis factor-alpha by human peritoneal macrophages in vivo and in vitro. *American Journal of Obstetrics and Gynecology* 1989; 161: 1718–1725.
107. Richter O, Mallmann P, van der Ven H & Krebs D. TNF-alpha secretion by peritoneal macrophages in endometriosis. *Zentralblatt fur Gynakologie* 1998; 120: 332–336.
108. Hammond MG, Oh ST, Annas J, Surrey ES & Halme J. The effect of growth factor on the proliferation of human endometrial stromal cells in culture. *American Journal of Obstetrics and Gynecology* 1993; 168: 1131–1136.
109. Witz CA, Montiaga-Rodriguez IA, Doucet RV, et al. Tumor necrosis factor-(alpha) increases endometrial stromal cell adhesion to extracellular matrix proteins. 44th Annual meeting of the Society for Gynecologic Investigation, San Diego, California; 1997.
110. Sillem M, Prifti S, Koch A et al. Regulation of matrix metalloproteinases and their inhibitors in uterine endometrial cells of patients with and without endometriosis. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 2001; 95: 167–174.
111. Iwabe T, Harada T, Tsudo Tet al. Tumor necrosis factor-alpha promotes proliferation of endometriotic stromal cells by inducing interleukin-8 gene and protein expression. *Journal of Clinical Endocrinology and Metabolism* 2000; 85: 824–829.
112. Taketani Y, Kuo TM& Mizuno M. Comparison of cytokine levels and embryo toxicity in peritoneal fluid in infertile women with untreated or treated endometriosis. *American Journal of Obstetrics and Gynecology* 1992; 167: 265–270.
113. Harada T, Yoshioka H, Yoshida S et al. Increased interleukin-6 levels in peritoneal fluid of infertile patients with active endometriosis. *American Journal of Obstetrics and Gynecology* 1997; 176: 593–597.

114. Matts Olovsson Immunological Aspects of Endometriosis: An Update American Journal of Reproductive Immunology 66 (Suppl. 1) (2011) 101–104
115. Stanley J Robboy, Sarah M Bean Pathogenesis of endometriosis Reproductive BioMedicine Online (2010) 21, 4-5
116. Saad Amer Endometriosis Obstetrics, Gynecology and Reproductive Medicine 18:5;2008
117. Stanley J Robboy, Sarah M Bean Pathogenesis of endometriosis Reproductive BioMedicine Online (2010) 21, 4-5
118. Batt, R.E., Smith, R.A., Buck Louis, G.M., et al., 2007. Mullerianosis. *Histol. Histopathol.* 22, 1161–1166.
119. Yap C, Furness S, Farquhar C. Pre and post operative medical therapy for endometriosis surgery. Cochrane Database Syst Rev 2004;3:CD003678.
120. Mousa NA, Bedaiwy MA, Casper RF. Aromatase inhibitors in the treatment of severe endometriosis. *Obstet Gynecol* 2007;109:1421–3.
121. Lyons SD, Chew SS, Thomson AJ, Lenart M, Camarais C, Vanaillie TG, et al. Clinical and quality of life outcomes after fertility-sparing laparoscopic surgery with bowel resection for severe endometriosis. *J Minim Invasive Gynecol* 2006;13:436–41.
122. Ballouk F, Ross JS, Wolf BC. Ovarian endometriotic cysts: an analysis of cytologic atypia and DNA ploidy patterns. *Am J Clin Pathol* 1994;102:415–9.
123. Jimbo H, Hitomi Y, Yoshikawa H, et al. Evidence for monoclonal expansion of epithelial cells in ovarian endometrial cysts. *Am J Pathol* 1997;150:1173–8.
124. Nezhat F, Cohen C, Rahaman J, et al. Comparative immunohistochemical studies of bcl-2 and p53 proteins in benign and malignant ovarian endometriotic cysts. *Cancer* 2002;1:2935–40.
125. Lorente Poyatos R, Palacios Perez A, Bravo Bravo F, et al. Rectosigmoid endometriosis lymph node involvement. *Gastroenterol Hepatol* 2003;26:23–5.
126. Insabato L, Pettinato G. Endometriosis of the bowel with lymph node involvement: a report of three cases and review of the literature. *Pathol Res Pract* 1996;192:957–61.
127. Thomakos N, Rodolakis A, Vlachos G, et al. A rare case of rectovaginal endometriosis with lymph node involvement. *Gynecol Obstet Invest* 2006;62:45–7.
128. Abrao MS, Podgaec S, Dias JA Jr, et al. Deeply infiltrating endometriosis affecting the rectum and lymph nodes. *Fertil Steril* 2006;86:543–7.
129. Noel JC, Chapron C, Fayt I, Anaf V. Lymph node involvement and lymphovascular invasion in deep infiltrating rectosigmoid endometriosis. *Fertil Steril* 2008;89:1069–72.
130. Mechsner S, Weichbrodt M, Riedlinger WF, et al. Immunohistochemical evaluation of endometriotic lesions and disseminated endometriosis-like cells in incidental lymph nodes of patients with endometriosis. *Fertil Steril* 2010;94:457–63.
131. Mechsner S, Weichbrodt M, Riedlinger WF, et al. Estrogen and progestogen receptor positive endometriotic lesions and disseminated cells in pelvic sentinel lymph nodes of patients with deep infiltrating rectovaginal endometriosis: a pilot study. *Hum Reprod* 2008;23:2202–9.
132. Tempfer CB, Wenzl R, Horvat R, Grimm C, Pöltnerauer S, Buerkle B, Reinthaller A, Huber JC. Lymphatic spread of endometriosis to pelvic sentinel lymph nodes: a prospective clinical study. *Fertil Steril*. 2011 Sep;96(3):692-6.
133. Gunes M, Kayikcioglu F, Ozturkoglu E, Haberal A. Incisional endometriosis after cesarean section, episiotomy and other gynecologic procedures. *J Obstet Gynaecol Res*. 2005;31(5):471-5.
134. Picod G, Boulanger L, Bounoua F, Leduc F, Duval G. Endométriose pariétale sur cicatrice de césarienne: à propos de 15 cas [Abdominal wall endometriosis after caesarean section: report of fifteen cases]. *Gynecol Obstet Fertil*. 2006;34(1):8-13.
135. Kocakusak A, Arpinar E, Arikan S, Demirbag N, Tarlaci A, Kabaca C. Abdominal wall endometriosis: a diagnostic dilemma for surgeons. *Med Princ Pract*. 2005;14(6):434-7.
136. Nominato NS, Prates LFVS, Lauar I, Morais J, Maia L, Geber S. Endometriose de cicatriz cirúrgica: estudo retrospectivo de 72 casos [Scar endometriosis: a retrospective study of 72 patients]. *Rev Bras Ginecol Obstet*. 2007;29(8):423-7.
137. Guilherme Karam Corrêa Leite, Luis Fernando Pina de Carvalho, Henri Korkes, Thiago Falbo Guazzelli, Greycy Kenj, Arildo de Toledo Viana Scar endometrioma following obstetric surgical incisions: retrospective study on 33 cases and review of the literature Sao Paulo Med J. 2009; 127(5):270-7
138. Ding DC, Hsu S. Scar endometriosis at the site of cesarean section. *Taiwan J Obstet Gynecol*. 2006;45(3):247-9.
139. Purvis RS, Tyring SK. Cutaneous and subcutaneous endometriosis. Surgical and hormonal therapy. *J Dermatol Surg Oncol*. 1994;20(10):693-5.