

# Bölüm 20

## ENDOMETRİOZİS VE ÇEVRESEL FAKTÖRLER

Prof. Dr. Yakup KUMTEPE

ÜNİTE 2

Klinisyenler tarafından ayrıntılı bilgi sahibi olunmayan bu bölüm okuyucuya, hastalarına güncel yaşamdan öneriler sunmak açısından değerli bilgiler içermektedir. Diyetinde omega-3 yağ asidi tüketimi daha fazla olan kadınlarda endometriozis riski azalırken, trans-doymamış yağ tüketimi yüksek seviyedeki kadınlarda endometriozis görülme riskinin anlamlı derecede arttığı rapor edilmiştir. A vitamininin prekürsörü olan ve havuç, kayısı, biber gibi bitkilerde bol miktarda bulunan beta-karotenin ektojik endometrial dokunun büyümesi için gerekli olan anjiogenezi inhibe ettiği gösterilmiştir. Endometriozisli kadın fenotipinde kütanöz nevüslerin anlamlı şekilde daha sık görüldüğünü gösteren ve endometriozis ve cilt tümörleri ile ilişkili genlerin ortaklığına dair ipuçları sunan çalışmalar mevcuttur. Öte yandan aşırı alkol tüketiminin endometriozis semptomlarını alevlendirdiği ve hastalığın ilerlemesine katkıda bulunduğu öne sürülmüştür. Bölüm yeni bilimsel çalışmalara ışık tutacak bilgiler içermesi nedeniyle önem arz etmektedir. **Editorial**

### Giriş

Postmenopozal kadınlarda da nadiren görülmesine rağmen endometriozis bir üreme dönemi hastalığıdır. Üreme dönemindeki kadınların %10 unda endometriozis olduğunu varsayarsak tahmini bir ifade ile ülkemizde iki milyona yakın endometriozisli kadın olduğunu söyleyebiliriz. Endomet-

riozisli hastaların önemli bir kısmı asemptomatik olmasına rağmen hastalar hekime infertilite ve ağrı gibi iki önemli şikayetle başvururlar. Endometriozis oluşumunda 1921'deki Sampsonun retrograd menstrüasyon teorisinden sonra çöломik metaplazi teorisi gibi farklı teoriler ortaya atıldı. 1992'de Koninckx (1) endometriozisi peritoneal, ovarian ve rektovaginal septum endometriozis olarak 3 farklı kategoride topladı ve günümüzde özellikle klinisyenler arasında büyük kabul gördü. Son yıllarda endometriozis patogenezinde çalışmalar immunolojik faktörler üzerine yoğunlaştı (2,3). Retrograd menstrüasyonla pelvik kaviteye ulaşan endometrial hücreler bir şekilde immün disfonksiyon olan bazı hastalarda temizlenemiyor ve abdominal kaviteye implante oluyor böylece hastalık gelişiyor (4). Oysa normal süreçte pelvik kaviteye dökülen endometrial hücreler bir antijen olarak kabul edilir ve lokal immün cevap oluşur. Makrofaj gibi bazı hücreler bu antijen olarak kabul edilen endometrial hücreleri T hücrelerine sunarlar. Bunun sonucunda ya sitotoksik T hücreler bir takım lethal substanslar salarak hedef hücreleri öldürür veya T helper hücreler sitokinler salgılayarak hücre ölümüne sebep olur.

İnsanlar günlük yaşamda, fizyolojik süreçler üzerinde istenmeyen etkiler yaparak hastalık oluşturma potansiyeline sahip pek çok doğal ve sentetik kimyasal maddeye maruz kalarak hastalıklara yakalanabilirler. Bu çevresel faktörler endometriozis oluşum mekanizmalarından birini etkileyerek

## Kaynaklar

- Koninckx PR, Martin MD. Deep endometriosis: a consequence of infiltration or retraction or possibly adenomyosis externa? 1992. *Fertil Steril* 58(5):924-8.
- Podgaec S, Abrao MS, Dias JA Jr, Rizzo LV, de Oliveira RM, Baracat EC. Endometriosis: an inflammatory disease with a Th2 immune response component. *Hum Reprod*. 2007; 22(5):1373-9.
- Fairbanks F, Abrao MS, Podgaec S, Dias JA Jr, de Oliveira RM, Rizzo LV. Interleukin-12 but not interleukin-18 is associated with severe endometriosis. *Fertil Steril*. 2009;91(2):320-4.
- Harada T, Iwaba T, Terakawa N. Role of cytokines in endometriosis. *Fertil Steril* 2001; 76(1):1-10.
- Carpenter DO. Polychlorinated biphenyls (PCBs): routes of exposure and effects of human health. *Rev Environ Health* 2006; 21(1):1-23.
- Safe S. Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), dibenzofurans (PCDFs), and related compounds: environmental and mechanistic considerations which support the development of toxic equivalency factors (TEFs). *Crit. Rev. Toxicol*. 21:51-58
- Devito MJ, Birnbaum LS, Farland WH, Gazievichz TA. Comparisons of estimated human body burdens of dioxinlike chemicals and TCDD body burdens in experimentally exposed animals. *Environ. Health Perspect*. 1995 .103(9):820-31.
- Clark G, Tritscher A, Bell D, Lucier G. Integrated approach for evaluating species and interindividual differences in responsiveness to dioxins and structural analogs. *Environ Health Perspect*. 1992 ;98:125-32.
- Environmental Working Group. 2005. Body burden—the pollution in newborns: a benchmark investigation of industrial chemicals, pollutants and pesticides in umbilical cord blood. Adres: <http://www.ewg.org/reports/bodyburden2/execsumm.php>.
- Anway MD, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors. *Endocrinology*. 2006 ;147(6 Suppl):43-9.
- Anway MD, Skinner MK. Epigenetic programming of the germ line: effects of endocrine disruptors on the development of transgenerational disease. *Reprod Biomed Online*. 2008 ;16(1):23-5. Review.
- Jacobson-Dickman E, Lee MM. The influence of endocrine disruptors on pubertal timing. *Curr Opin Endocrinol Diabetes Obes*. 2009;16(1):25-30. Review.
- Bulun SE. Endometriosis. *N Engl J Med*. 2009 15;360(3):268-79. Review.
- 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 Oct;78(4):830-5.
- Gregoraszczyk EL, Zabiely E, Ochwat D. Aryl hydrocarbon receptor (AhR)-linked inhibition of luteal cell progesterone secretion in 2,3,7,8-tetrachlorodibenzo-p-dioxin treated cells. *J Physiol Pharmacol*. 2001;52(2):303-11.
- Bruner-Tran KL, Ding T, Osteen KG. Dioxin and endometrial progesterone resistance. *Semin Reprod Med*. 2010;28(1):59-68. Review.
- Ovekamp-Swan T, Davis BJ. Mechanisms of phthalate ester toxicity in the female reproductive system. *Environ Health Perspect* 2003;111:139–45.
- Foster PM, Thomas LV, Cook MW, Gangolli SD. Study of the testicular effects and changes in zinc excretion produced by some n-alkyl phthalates in the rat. *Toxicol Appl Pharmacol*. 1980;54:392–8.
- Itoh H, Iwasaki M, Hanaoka T, Sasaki H, Tanaka T, Tsugane S. Urinary phthalate monoesters and endometriosis in infertile Japanese women. *Sci Total Environ* 2009;408:37–42.
- Weuve J, Hauser R, Calafat AM, Missmer SA, Wise LA. Association of exposure to phthalates with endometriosis and uterine leiomyomata: findings from NHANES, 1999–2004. *Environ Health Perspect* 2010;118:825–32.
- Cobellis L, Latini G, De Felice C, Razzi S, Paris I, Ruggieri F, et al. High plasma concentrations of di-(2-ethylhexyl) phthalate in women with endometriosis. *Hum Reprod* 2003;18:1512–5.
- Reddy BS, Rozati R, Reddy BV, Raman NV. Association of phthalate esters with endometriosis in Indian women. *Br J Obstet Gynaecol* 2006;113: 515–20.
- Kim SH, Chun S, Jang JY, Chae HD, Kim CH, Kang BM. Increased plasma levels of phthalate esters in women with advanced-stage endometriosis: a prospective case-control study. *Fertil Steril*. 2011; 95(1):357-9.
- Birnbaum LS. The mechanism of dioxin toxicity: relationship to risk assessment. *Environ Health Perspect*. 1994;102 Suppl 9:157-67.
- Michalek JE, Tripathi RC, Kulkarni PM, Pirkle JL. The reliability of the serum dioxin measurement in veterans of Operation Ranch Hand. *J Expo Anal Environ Epidemiol*. 1996;6(3):327-38.
- Pocar P, Fischer B, Klönisch T, Hombach-Klönisch S. Molecular interactions of the aryl hydrocarbon receptor and its biological and toxicological relevance for reproduction. *Reproduction*. 2005;129(4):379-89. Review.
- Gerhard I, Runnebaum B. [The limits of hormone substitution in pollutant exposure and fertility dis-

- orders]. *Zentralbl Gynakol.* 1992;114(12):593-602. Review.
28. Koninckx PR, Braet P, Kennedy SH, Barlow DH. Dioxin pollution and endometriosis in Belgium. *Hum Reprod.* 1994;9(6):1001-2.
29. World Health Organization, 1989. Levels of PCBs, PCDDs and PCDFs in breast milk: Result of WHO Coordinated Interlaboratory Quality Control Studies and Analytical Field Studies. Environmental Series. World Health Organization, Geneva.
30. Rier SE, Martin DC, Bowman RE, Dmowski WP, Becker JL. Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fundam Appl Toxicol.* 1993 ;21(4):433-41.
31. Rier SE, Turner WE, Martin DC, Morris R, Lucier GW, Clark GC. Serum levels of TCDD and dioxin-like chemicals in Rhesus monkeys chronically exposed to dioxin: correlation of increased serum PCB levels with endometriosis. *Toxicol Sci.* 2001;59(1):147-59.
32. Martin MB, Reiter R, Pham T, Avellanet YR, Camara J, Lahm M, Pentecost E, Pratap K, Gilmore BA, Divekar S et al. Estrogen-like activity of metals in MCF-7 breast cancer cells. *Endocrinology* 2003;144:2425–2436.
33. Stoica A, Katzenellenbogen BS, Martin MB. Activation of estrogen receptor-alpha by the heavy metal cadmium. *Mol Endocrinol* 2000;14:545–553.
34. Brama M, Gnessi L, Basciani S, Cerulli N, Politi L, Spera G, Mariani S, Cherubini S, d'Abusco AS, Scandurra R et al. Cadmium induces mitogenic signaling in breast cancer cell by an ERalpha-dependent mechanism. *Mol Cell Endocrinol* 2007;264:102–108
35. Martin MB, Reiter R, Pham T, Avellanet YR, Camara J, Lahm M, Pentecost E, Pratap K, Gilmore BA, Divekar S et al. Estrogen-like activity of metals in MCF-7 breast cancer cells. *Endocrinology* 2003;144:2425–2436.
36. Young PC, Cleary RE, Ragan WD. Effect of metal ions on the binding of 17beta-estradiol to human endometrial cytosol. *Fertil Steril* 1977;28:459–463.
37. Heilier JF, Donnez J, Verougstraete V, Donnez O, Grandjean F, Haufroid V, Nackers F, Lison D. Cadmium lead and endometriosis. *Int Arch Occup Environ Health.* 2006 ;80(2):149-53.
38. Jackson LW, Zullo MD, Goldberg JM. The association between heavy metals, endometriosis and uterine myomas among premenopausal women: National Health and Nutrition Examination Survey 1999–2002. *Hum Reprod* 2008. 23.(3) 679–687.
39. Silva N, Peiris-John R, Wickremasinghe R, Senanayake H, Sathikumar N. Cadmium a metalloestrogen: are we convinced? *J Appl Toxicol.* 2012. 32(5):318-32.
40. Parazzini F, Chiaffarino F, Surace M, Chatenoud L, Cipriani S, Chiantera V, Benzi G, Fedele L. Selected food intake and risk of endometriosis. *Hum Reprod.* 2004 ;19(8):1755-9.
41. Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, Barbieri RL, Willett WC, Hankinson SE. A prospective study of dietary fat consumption and endometriosis risk. *Hum Reprod.* 2010;25(6):1528-35.
42. Smith MF. Recent advances in corpus luteum physiology. *J Dairy Sci.* 1986; 69:911-926.
43. Gorbach SL, Goldin BR. Diet and the excretion and enterohepatic cycling of estrogens. *Prev Med.* 1987; 16:525-531.
44. Bosetti C, Altieri A, La Vecchia C. Diet and environmental carcinogenesis in breast/gynaecological cancers. *Curr Opin Obstet Gynecol.* 2002; 14:13-18.
45. Alsharif NZ, Hassoun EA. Protective effects of vitamin A and vitamin E succinate against 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)-induced body wasting, hepatomegaly, thymic atrophy, production of reactive oxygen species and DNA damage in C57BL/6J mice. *Basic Clin Pharmacol Toxicol.* 2004;95(3):131-8.
46. Jackson LW, Schisterman EF, Dey-Rao R, Browne R, Armstrong D. Oxidative stress and endometriosis. *Hum Reprod.* 2005;20(7):2014-20.
47. Tee MK, Vigne JL, Taylor RN. All-trans retinoic acid inhibits vascular endothelial growth factor expression in a cell model of neutrophil activation. *Endocrinology.* 2006;147(3):1264-70.
48. Pasquali R, Vicennati V, Bertazzo D, Casimirri F, Pascal G, Tortelli O, Labate AM. Determinants of sex hormone-binding globulin blood concentrations in premenopausal and postmenopausal women with different estrogen status. Virgilio-Menopause-Health Group. *Metabolism.* 1997;46(1):5-9.
49. Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? *Cancer Causes Control.* 1996;7(6):605-25.
50. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest.* 2006;116(7):1784-92. Review.
51. Takemura Y, Osuga Y, Harada M, Hirata T, Koga K, Morimoto C, Hirota Y, Yoshino O, Yano T, Taketani Y. Serum adiponectin concentrations are decreased in women with endometriosis. *Hum Reprod.* 2005; 20(12):3510-3.
52. Uno S, Zembutsu H, Hirasawa A, Takahashi A, Kubo M, Akahane T, Aoki D, Kamatani N, Hirata K, Nakamura Y. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. *Nat Genet* 2010;42:707-710.

53. Vigano P, Somigliana E, Panina P, Rabellotti E, Vercellini P, Candiani M. Principles of phenomics in endometriosis. *Hum Reprod Update*. 2012;18(3): 248-59.
54. Hornstein MD, Thomas PP, Sober AJ, Wyshak G, Albright NL, Frisch RE. Association between endometriosis, dysplastic naevi and history of melanoma in women of reproductive age. *Hum Reprod* 1997;12:143-145.
55. Uno S, Zembutsu H, Hirasawa A, Takahashi A, Kubo M, Akahane T, Aoki D, Kamatani N, Hirata K, Nakamura Y. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. *Nat Genet* 2010;42:707-710.
56. Perper MM, Breitkopf LJ, Breitstein R, Cody RP, Manowitz P. MAST scores, alcohol consumption, and gynecological symptoms in endometriosis patients. *Alcohol Clin Exp Res*. 1993 Apr;17(2):272-8.
57. Mendelson JH, Lukas SE, Mello NK, Amass L, Elingboe J, Skupny A. Acute alcohol effects on plasma estradiol levels in women. *Psychopharmacology*. 1988; 94(4): 464-7.
58. Dorgan JF, Reichman ME, Judd JT, Brown C, Longcope C, Schatzkin A, Campbell WS, Franz C, Kahle L, Taylor PR. The relation of reported alcohol ingestion to plasma levels of estrogens and androgens in premenopausal women (Maryland, United States). *Cancer Causes Control*. 1994;5(1):53-60.
59. Ginsburg ES, Walsh BW, Shea BF, Gao X, Gleason RE, Barbieri RL. The effects of ethanol on the clearance of estradiol in postmenopausal women. *Fertil Steril*. 1995;63(6):1227-30.
60. Bounds W, Betzing KW, Stewart RM, Holcombe RF. Social drinking and the immune response: impairment of lymphokine-activated killer activity. *Am J Med Sci*. 1994;307(6):391-5.
61. Michnovicz JJ, Hershcopf RJ, Naganuma H, Bradlow HL, Fishman J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. *N Engl J Med*. 1986;315(21):1305-9.
62. Matorras R, Rodríguez F, Pijoan JI, Ramón O, Gutierrez de Terán G, Rodríguez-Escudero F. Epidemiology of endometriosis in infertile women. *Fertil Steril*. 1995;63(1):34-8.
63. Muto H, Takizawa Y. Potential health risk via inhalation/ingestion exposure to polychlorinated dibenzop-dioxins and dibenzofurans. *Bull Environ Contam Toxicol*. 1992;49(5):701-7.
64. Reed GA, Peterson KS, Smith HJ, Gray JC, Sullivan DK, Mayo MS, Crowell JA, Hurwitz A. A phase I study of indole-3-carbinol in women: tolerability and effects. *Cancer Epidemiol Biomarkers Prev*. 2005;14(8):1953-60.
65. Verma SP, et al. 1997. Curcumin and genistein, plant natural products, show synergistic inhibitory effects on the growth of human breast cancer MCF-7 cells induced by estrogenic pesticides. *Biochem Biophys Res Comm* 233:692-96.
66. Verma SP, et al. 1998. The inhibition of the estrogenic effects of pesticides and environmental chemicals by curcumin and isoflavonoids. *Environ Health Perspect* 106:807-12.
67. Ma L, Lin S, Chen R, Zhang Y, Chen F, Wang X. Evaluating therapeutic effect in symptoms of moderate-to-severe premenstrual syndrome with *Vitex agnus castus* (BNO 1095) in Chinese women. *Aust N Z J Obstet Gynaecol*. 2010;50(2):189-93.
68. Ylikorkala O, Mäkilä UM. Prostacyclin and thromboxane in gynecology and obstetrics. *Am J Obstet Gynecol*. 1985;152(3):318-29. Review.
69. An P, Rice T, Gagnon J, et al. A genetic study of sex hormone--binding globulin measured before and after a 20-week endurance exercise training program: the HERITAGE Family Study. *Metabolism*. 2000;49:1014-20.)
70. Stoll BA. Adiposity as a risk determinant for postmenopausal breast cancer. *Int J Obes Relat Metab Disord*. 2000;24:527-33. Kaaks R. Nutrition, hormones, and breast cancer: Is insulin the missing link? *Cancer Causes Control*. 1996;7:605-625.
71. Cramer DW, Wilson E, Stillman RJ, et al. The relation of endometriosis to menstrual characteristics, smoking, and exercise. *Jama*. 1986;255:1904-8.
72. Signorello LB, Harlow BL, Cramer DW, Spiegelman D, Hill JA. Epidemiologic determinants of endometriosis: a hospital-based case-control study. *Ann Epidemiol*. 1997;7:267-741.
73. Dhillon PK, Holt VL. Recreational physical activity and endometrioma risk. *Am J Epidemiol*. 2003;158:156-64.
74. Heilier JF, Donnez J, Nackers F, et al. Environmental and host-associated risk factors in endometriosis and deep endometriotic nodules: a matched case-control study. *Environ Res*. 2007;103:121-9.
75. Vitton AF, Hankinson SE, Hornstein MD, Missmer SA. Adult physical activity and endometriosis risk. *Epidemiology*. 2010 ;21(1):16-23.