

Bölüm 5

ÇEVRESEL VE BESİN MADDELERİ KAYNAKLI KİMYASAL MARUZİYETİN İNFERTİLİTE ÜZERİNE ETKİSİ

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GİRİŞ

İnfertilite yani halk arasında yaygın ismi ile kısırlık, genellikle 12 ay düzenli, korunmasız cinsel ilişkiden sonra hamileliğin sağlanamaması olarak tanımlanır. İnfertilite, batı ülkelerindeki çiftlerin %15-25'ini etkilemektedir (1). İnfertilite yaşamı tehdit eden bir sağlık problemi olarak tanımlanmamasına rağmen; sağlık, ekonomi ve sosyal hayat üzerinde olumsuz etkileri her geçen gün artmaktadır. Son yıllarda üreme sağlık sorunu olarak infertiliteye olan ilgi artmıştır. Dünya Sağlık Örgütü (DSÖ) verilerine göre nüfus artışına bağlı olarak, kısırlıktan etkilenen mutlak çift sayısı 1990'da 42,0 milyon iken 2010'da 48,5 milyona yükselmiştir (2). Dünyada 60-80 milyon infertil çift olduğu tahmin edilmektedir (3). Bu artış nedeniyle infertilitenin anlaşılması önem arz etmekle birlikte elimizdeki tanımlayıcı ve epidemiyolojisi hakkındaki bilgiler sınırlıdır.

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fertilitesini etkilemektedir (98). Yetişkinlerde TCDD maruziyeti doğurganlığı azaltabilir. TCDD maruziyetinin gebelik ve infertiliteye daha uzun bir süre ile ilişkili olduğu bulunmuştur (99). Ek olarak, İtalya'da TCDD'ye maruz kaldıktan sonraki ilk 8 yıl içinde, anne serum TCDD düzeylerinin daha düşük doğum ağırlığı ve daha küçük gebelik yaşı ile ilişkili olduğunu gösterilmiştir (100). Hayvan çalışmalarında TCDD, memeli türlerinde östrojen siklusu, hamileliğe kadar geçen süre, gebeliğin sürdürülmesi, fetal gelişim ve doğum sonuçları dahil olmak üzere doğurganlık parametrelerine müdahale etmiştir (37). Son zamanlarda yapılan bazı çalışmalar, insanların ve hayvanların hâlâ çeşitli yollarla dioksine maruz kaldıklarını göstermektedir (101).

SONUÇ

Canlı doğasının temelini oluşturan üreme psikolojik, biyolojik ve toplumsal bir ihtiyaçtır. İnfertilite oranlarının hızla artmasında büyük rol oynayan, çevresel ve besin maddeleri ile maruz kalınan endokrin bozucu ve diğer kimyasal maddeler hakkında daha fazla çalışmaya ihtiyaç vardır. Bu maddelerin güvenli kabul edilen maruziyet miktarları belirlenmeli ve yasal düzenlemelerle denetim altında tutulmalıdır. Aksi takdirde doğada ve canlı organizmasında biriken koruyucu ve/veya kirletici maddeler insan sağlığını ve üreme sistemi için ciddi risk taşımaktadır. Oluşan sağlık problemlerinin tedavi maliyeti, riskleri ortadan kaldırmak için yapılan girişimlerin tutarında çok daha fazla olmakla beraber bu makas gelecekte daha fazla açılacaktır.

Anahtar Kelimeler: İnfertilite, Endokrin Bozucular, Gıda Katkı Maddeleri, Gıda Kirleticileri

KAYNAKLAR

1. Thoma ME, McLain AC, Louis JF, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. *Fertil Steril.* 2013;99:1324–31. e1.

2. Mascarenhas MN, Flaxman SR. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS medicine*, 2012, 9(12).
3. Calverton, Maryland. "USA: ORC Macro and the WoGreenwald D, Ohlander S. Environmental toxins Health Organization; 2004." World Health Organization. Infecundity, Infertility, and Childlessness in Developing Countries. DHS Comparative Reports 9.
4. Careghini A, Mastorgio AF, Saponaro S, et al. Bisphenol A, nonylphenols, benzophenones, and benzotriazoles in soils, groundwater, surface water, sediments, and food: a review. *Environ Sci Pollut Res Int*. 2015;22:5711–5741.
5. Jenardhanan P, Panneerselvam M, Mathur PP. Effect of environmental contaminants on spermatogenesis. *Semin Cell Dev Biol*. 2016;59:126–40.
6. Kavlock RJ, Daston GP, DeRosa C, et al. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: a report of the U.S. EPA-sponsored workshop. *Environ Health Perspect*. 1996;104(Suppl 4):715–40.
7. Kabir ER, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. *Environ Toxicol Pharmacol*. 2015;40(1):241–58.
8. Krieg SA, Shahine LK, Lathi RB. Environmental exposure to endocrine-disrupting chemicals and miscarriage. *Fertil Steril*. 2016;106(4):941–7.
9. Mima M, Greenwald D, Ohlander S. Environmental toxins and male fertility. *Current Urology Reports* 2018, 19(7): 50.
10. Hauser R, Skakkebaek NE, Hass U, et al. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*. 2015;100(4):1267–77.
11. Dohle GR, Weidner W, Jungwirth A, et al. Guidelines on male infertility. European Association of Urology; 2015.
12. Nuti F, Krausz C. Gene polymorphisms/mutations relevant to abnormal spermatogenesis. *Reproductive Biomedicine Online*. 2008;16(4):504–513.
13. Madaan EP, Williams DE. Environmental PAH exposure and male idiopathic infertility: a review on early life exposures and adult diagnosis. *Reviews on Environmental Health*, 2017, 32(1-2) 73-81.
14. Mengeot MA, Vogel L. Üretmek ve Üretmek (2008) .
15. Joffe M. Infertility and environmental pollutants. *British Medical Bulletin*, 2003, 68(1), 47-70.
16. Beck AB. Clover disease of sheep in Western Australia. *Journal of the Department of Agriculture, Western Australia*, 1965, Series 4, 6(7), 388-400.
17. Committee on Toxicity of Chemicals in Food, Consumer Products and the

- Environment. Phytoestrogens and Health. London: Food Standards Agency, 2003.
18. Dieckmann WJ , Davis ME, Rynkiewicz LM. et al. Does the administration of diethylstilbestrol during pregnancy have therapeutic value? 1953, Am J Obstet Gynecol; 66;5;1062-1081.
 19. Goldberg JM , Falcone TF. Effect of diethylstilbestrol on reproductive function. Fertil Steril 1999; 72: 1-7.
 20. Pavlovich CP, King P, Goldstein M, et al. Evidence of a treatable endocrinopathy in infertile men. J Urol. 2001;165:837-41.
 21. Luboshitzky R, Kaplan-Zverling M, Shen-Orr Z, et al. Seminal plasma androgen/oestrogen balance in infertile men. Int J Androl. 2002;25:345-51.
 22. Zhang Q, Bai Q, Yuan Y, et al. Assessment of seminal estradiol and testosterone levels as predictors of human spermatogenesis. J Androl. 2010;31:215-20.
 23. Sharpe RM. The 'oestrogen hypothesis'-where do we stand now? Int J Androl 2003; 26: 2-15.
 24. Hannon PR, Flaw JA. The effects of phthalates on the ovary. Frontiers in Endocrinology. 2015 6, 8.
 25. Meeker JD, Ferguson KK. Relationship between urinary phthalate and bisphenol A concentrations and serum thyroid measures in U.S. adults and adolescents from the National Health and Nutrition Examination Survey (NHANES)2007-2008. Environ Health Perspect. 2011 Oct;119(10):1396-402.
 26. Wang C, Yang L, Wang S, et al. The classic EDCs, phthalate esters and organochlorines, in relation to abnormal sperm quality: a systematic review with meta-analysis. Sci Rep. 2016 Jan 25; (6):19982.
 27. Mariana M, Feiteiro J, Verde I, et al. The effects of phthalates in the cardiovascular and reproductive systems: A review. Environ Int. 2016 Sep; (94):758-776.
 28. Hauser R, Gaskins AJ, Souter I, et al. Urinary Phthalate Metabolite Concentrations and Reproductive Outcomes among Women Undergoing in Vitro Fertilization: Results from the EARTH Study. Environ Health Perspect. 2016 Jun; 124(6):831-9.
 29. Menzie CA, Potocki BB, Santodonato J. Exposure to Carcinogenic PAHs in the Environment. Environmental Science & Technology. 1992;26(7).
 30. Zhang YY, Dong S, Wang H, et al. Biological impact of environmental polycyclic aromatic hydrocarbons (ePAHs) as endocrine disruptors. Environmental Pollution. 2016;213:809-824.
 31. Peterson BS, Rauh VA, Bansal R, et al. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. Jama Psychiatry.

2015;72(6):531–540.

32. Dennis MJ, Massey RC, Cripps G, et al. Factors Affecting the Polycyclic Aromatic Hydrocarbon Content of Cereals, Fats and Other Food-Products. *Food Additives and Contaminants*. 1991;8(4).
33. Archibong AE, Ramesh A, Niaz MS, et al. Effects of benzo(a)pyrene on intra-testicular function in F-344 rats. *Int J Environ Res Public Health*. 2008 Mar; 5(1):32-40.
34. Jeng HA, Pan CH, Chao MR et al. Sperm DNA oxidative damage and DNA adducts. *Mutation Research-Genetic Toxicology and Environmental Mutagenesis*. 2015;794:75–82.
35. Gaspari L, Chang, SS, Santella RM, et al. Polycyclic aromatic hydrocarbon-DNA adducts in human sperm as a marker of DNA damage and infertility. *Mutation Research-Genetic Toxicology and Environmental Mutagenesis*. 535(2), 155-160.
36. Anderson L, Dere E, Hall S, et al. Sperm MRNAs are molecular markers of minimal testicular injury in rats. *Andrology*. 2013;1:85–85.
37. Rattan S, Zhou C, Chiang C, et al. Exposure to endocrine disruptors during adulthood: consequences for female fertility. *Journal of Endocrinology*,2017, 233(3), R109-R129.
38. Toft G, Thulstrup AM, Jonsson BA, Fetal loss and maternal serum levels of hexachlorobiphenyl (CB-153) and 1,1-dichloro-2,2-bis(p-chlorophenyl) ethylene (p,p'-DDE) exposure: a cohort study in Greenland and two European populations. *Environ Health*. 2010;9:22.
39. Chevrier C, Warembourg C, Gaudreau E, et al. Organochlorine pesticides, polychlorinated biphenyls, seafood consumption, and time-to-pregnancy. *Epidemiology*. 2013;24:251–260.
40. Mahalingaiah S, Missmer SA, Maity A, et Association of hexachlorobenzene (HCB), dichlorodiphenyltrichloroethane (DDT), and dichlorodiphenyldichloroethylene (DDE) with in vitro fertilization (IVF) outcomes. *Environ Health Perspect*. 2012 Feb; 120(2):316-20.
41. Naidoo S, London L, Burdorf A, et al. Spontaneous miscarriages and infant deaths among female farmers in rural South Africa. *Scand J Work Environ Health*. 2011 May; 37(3):227-36.
42. Bastos AM, Souza Mdo C, Almeida Filho GL, et al. Organochlorine compound levels in fertile and infertile women from Rio de Janeiro, Brazil. *Arq Bras Endocrinol Metabol*. 2013 Jul; 57(5):346-53.
43. Rahman SN, Fatima P, Chowdhury AQ, et al. Blood level of lead in women with unexplained infertility. *Mymensingh Med J*. 2013;22:508–512.
44. Colquitt PJ. The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. *Occupational and Environmental Medicine*. 1995;52:214.

45. Cole DC, Wainman B, Sanin LH, Weber JP, Muggah H, Ibrahim S. Environmental contaminant levels and fecundability among non-smoking couples. *Reproductive Toxicology*. 2006;22:13–19.
46. Sukhn C, Awwad J, Ghantous A, et al. Associations of semen quality with non-essential heavy metals in blood and seminal fluid: data from the EMI study in Lebanon. *Journal of Assisted Reproduction and Genetics*. 2018, 35(9), 1691-1701.
47. Nsonwu-Anyanwu AC, Ekong ER, Offor SJ, et al. Heavy metals, biomarkers of oxidative stress and changes in sperm function: A case-control study. *International Journal of Reproductive Bio Medicine*,2019, 17(3).
48. Bernard L, Decaudin B, Lecoeur M, et al. Analytical methods for the determination of DEHP plasticizer alternatives present in medical devices: a review. *Talanta*. 2014;129:39–54.
49. Peretz J, Vrooman L, Ricke WA, et al. Bisphenol a and reproductive health: update of experimental and human evidence, 2007–2013. *Environ Health Perspect*. 2014;122:775–786.
50. Usman A, Ahmad M. From BPA to its analogues: Is it a safe journey? *Chemosphere*. 2016;158:131–142.
51. Liao C, Kannan K. A survey of bisphenol A and other bisphenol analogues in foodstuffs from nine cities in China. *Food Additives & Contaminants: Part A*. 2014;31:319–329.
52. Fujimoto VY, Kim D, Vom Saal FS et al. Serum unconjugated bisphenol A concentrations in women may adversely influence oocyte quality during in vivo fertilization. *Fertil Steril*. 2011;95:1816–1819.
53. Mok-Lin E, Ehrlich S, Williams PL, et al. Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. *Int J Androl*. 2010;33:385–393.
54. Ehrlich S, Williams PL, Missmer SA, et al. Urinary bisphenol A concentrations and implantation failure among women undergoing in vitro fertilization. *Environ Health Perspect*. 2012 a Jul; 120(7):978-83.
55. Li DK, Zhou Z, Miao M, et al. Urine bisphenol-A (BPA) level in relation to semen quality. *Fertil Steril*. 2011;95:625–630.
56. Meeker JD, Calafat AM, Hauser R. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. *Environ Sci Technol*. 2010a ;44:1458–1463.
57. Mendiola J, Jørgensen N, Andersson AM, et al. Are environmental levels of bisphenol a associated with reproductive function in fertile men? *Environ Health Perspect*. 2010 Sep; 118(9):1286-91.
58. Ying G, Williams B, Kookana R et al. Environmental fate of alkylphenols and alkylphenol ethoxylates: a review. *Environment international*, 2002, 28.3: 215-226.

59. Chang CH, Chen ML, Liao KW, et al. The association between maternal nonylphenol exposure and parity on neonatal birth weight: a cohort study in Taiwan. *Chemosphere*. 2013 Oct; 93(6):1145-52.
60. Tsai MS, Chang CH, Tsai YA, et al. Neonatal outcomes of intrauterine nonylphenol exposure--a longitudinal cohort study in Taiwan. *Sci Total Environ*. 2013 Aug 1; 458-460:367-73.
61. Tang R, Chen MJ, Ding GD, et al. Associations of prenatal exposure to phenols with birth outcomes. *Environ Pollut*. 2013 Jul; 178:115-20.
62. Laws SC, Carey SA, Ferrell JM, et al. Estrogenic activity of octylphenol, nonylphenol, bisphenol A and methoxychlor in rats. *Toxicol Sci*. 2000 Mar; 54(1):154-67.
63. Noorimotlagh Z, Haghighi NJ, Ahmadimoghadam M, et al. An updated systematic review on the possible effect of nonylphenol on male fertility. *Environmental Science and Pollution Research*, 2017, 24(4), 3298-3314.
64. Kyselova V, Peknicova J, Buckiova D, et al. Effects of p-nonylphenol and resveratrol on body and organ weight and in vivo fertility of outbred CD-1 mice. *Reprod Biol Endocrinol*, 2003, 1:30.
65. Qiu Y, Wu D, Zeng X, et al. Adverse effects of nonylphenol on the reproductive development of F1 male SD rats in sexual maturation period. *Sichuan da xue xue bao. Yi xue ban= Journal of Sichuan University. Medical science edition*, 2005, 36.3: 382-385.
66. Rochester JR, Bolden AL, Pelch KE, et al. Potential Developmental and Reproductive Impacts of Triclocarban: A Scoping Review. *J Toxicol*. 2017; 2017:9679738.
67. Ye X, Zhou X, Furr J, et al. Biomarkers of exposure to triclocarban in urine and serum. *Toxicology*. 2011 Aug 15; 286(1-3):69-74.
68. US Food and Drug Administration Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Re-opening of Administrative Record, 2013.
69. Stoker TE, Gibson EK, Zorrilla LM et al. Triclosan exposure modulates estrogen-dependent responses in the female wistar rat. *Toxicol Sci*. 2010 Sep; 117(1):45-53.
70. Hua R, Zhou Y, Wu B, et al. Urinary triclosan concentrations and early outcomes of in vitro fertilization-embryo transfer. *Reproduction*. 2017 Mar; 153(3):319-325.
71. Gee RH, Charles A, Taylor N, et al. Oestrogenic and androgenic activity of triclosan in breast cancer cells. *J Appl Toxicol*. 2008 Jan; 28(1):78-91.
72. Erkmen O. Gıda kaynaklı tehlikeler ve güvenli gıda üretimi. *Çocuk Sağlığı ve Hastalıkları Dergisi*, 2010, 53(3), 220-235.
73. Ham J, Lim W, Park S, et al. Synthetic phenolic antioxidant propyl galla-

- te induces male infertility through disruption of calcium homeostasis and mitochondrial function. *Environmental Pollution*.2019, 248, 845-856.
74. Ham J, Lim W, You S. Butylated hydroxyanisole induces testicular dysfunction in mouse testis cells by dysregulating calcium homeostasis and stimulating endoplasmic reticulum stress. *Science of The Total Environment*, 2020, 702, 134775.
 75. Diniz YS, Faine LA, Galhardi CM, et al. Monosodium glutamate in standard and high fiber diets: metabolic syndrome and oxidative stress in rats. *Nutrition*. 2005;21:749–755.
 76. Mallick HN. Understanding safety of glutamate in food and brain. *Ind J Physiol Pharmacol*. 2007;51:216–234.
 77. Eweka AO, Eweka A, Om’Iniabohs, FA. Histological studies of the effects of monosodium glutamate on the ovaries of adult Wistar rats. *Ann Med Health Sci Res*. 2011;1(1):37–44.
 78. Abdel-Aziem SH, El-Kader HAA, Evaluation of the alleviative role of *Chlorella vulgaris* and *Spirulina platensis* extract against ovarian dysfunctions induced by monosodium glutamate in mice. *Journal of Genetic Engineering and Biotechnology*, 16(2), 653-660. 2018.
 79. Kayode OT, Rotimi DE, Kayode AA. Monosodium Glutamate (MSG)-Induced Male Reproductive Dysfunction: A Mini Review. *Toxics*,2020, 8(1), 7.
 80. Onakewhor JUE, Oforofuo IAO, Singh SP. Chronic administration of Monosodium glutamate Induces Oligozoospermia and glycogen accumulation in Wister rat testes. *Africa J Reprod Health*. 1998;2(2):190–197.
 81. Oforofuo IAO, Onakewhor JUE, Idaewor PE. The effect of chronic admin of MSG on the histology of the Adult Wister rat testes. *Biosc Resch Comms*. 1997;9(2):6–15.
 82. Calafat AM, Ye X, Wong LY et al. Urinary concentrations of four parabens in the U.S. population: NHANES 2005-2006. *Environ Health Perspect*. 2010 May; 118(5):679-85.
 83. Barr L, Metaxas G, Harbach CA, et al. Measurement of paraben concentrations in human breast tissue at serial locations across the breast from axilla to sternum. *J Appl Toxicol*.2012 Mar; 32(3):219-32.
 84. Vo TT, Yoo YM, Choi KC, et al. Potential estrogenic effect(s) of parabens at the prepubertal stage of a postnatal female rat model. *Reprod Toxicol*. 2010 Jun; 29(3):306-16.
 85. Tavares RS, Martins FC, Oliveira PJ et al. Parabens in male infertility-is there a mitochondrial connection? *Reprod Toxicol*.2009 Jan; 27(1):1-7.
 86. Jurewicz J, Radwan M, Wielgomas B, et al. Human semen quality, sperm DNA damage, and the level of reproductive hormones in relation to urinary concentrations of parabens. *Journal of Occupational and Environ-*

- mental Medicine.2017, 59(11), 1034-1040.
87. Aydin Y, Erkan M. The toxic effects of polychlorinated biphenyl (Aroclor 1242) on Tm3 Leydig cells. *Toxicology and Industrial Health*, 2017, 33(8), 636-645.
 88. Mendola P, Buck GM, Sever LE et al. Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. *Am J Epidemiol* 1997 Dec 1; 146(11):955-60.
 89. Kezios KL,Liu X,Cirill PM et al.Prenatal polychlorinated biphenyl exposure is associated with decreased gestational length but not birth weight: archived samples from the Child Health and Development Studies pregnancy cohort. *EnvironHealth*.2012, Jul20;11:49.
 90. Louis GMB. Persistent environmental pollutants and couple fecundity: an overview. *Reproduction*. 2014; 147(4):R97-R104.
 91. Gallo MV, Ravenscroft J, Carpenter DO, et al. Endocrine disrupting chemicals and ovulation: Is there a relationship? *Environ Res*. 2016 Nov; 151:410-418.
 92. AL-Hussaini TK, Abdelaleem AA, Elnashar I, et al. The effect of follicular fluid pesticides and polychlorinated biphenyls concentrations on intracytoplasmic sperm injection (ICSI) embryological and clinical outcome. *European Journal of Obstetrics & Gynecology and Reproductive Biology*,2018, 220, 39-43.
 93. Aydin Y, Erkan M. The toxic effects of polychlorinated biphenyl (Aroclor 1242) on Tm3 Leydig cells. *Toxicology and Industrial Health*, 2017, 33(8), 636-645.
 94. Jiang LG, Cheng LY, Kong SH et al. Toxic effects of polychlorinated biphenyls (Aroclor 1254) on human sperm motility. *Asian Journal of Andrology*, 2017, 19(5), 561.
 95. Salahov M, Ayvaz Z. Dioksin problemi. *Çevre Dergisi* 1993; 7: 34-35.
 96. Young RA. Dioxins. In: Wexler P (ed). *Encyclopedia of Toxicology* (4th ed) Vol. 1. New York: Elsevier Inc., 2005: 70-72.
 97. Galimova EF, Amirova ZK, Galimov SN. Dioxins in the semen of men with infertility. *Environmental Science and Pollution Research*,2015, 22(19), 14566-14569.
 98. Jin M, Lou J, Yu H, et al. Exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin promotes inflammation in mouse testes: The critical role of Klotho in Sertoli cells. *Toxicology Letters*, 2018, 295, 134-143.
 99. Eskenazi B, Warner M, Marks AR, et al. Serum dioxin concentrations and time to pregnancy. *Epidemiology*. 2010 Mar; 21(2):224-31.
 100. Eskenazi B, Mocarelli P, Warner M et al. Maternal serum dioxin levels and birth outcomes in women of Seveso, Italy. *Environ Health Perspect*. 2003 Jun; 111(7):947-53.

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101. Tavakoly SSB, Hashim R, Salleh A et al. Dioxin risk assessment: mechanisms of action and possible toxicity in human health. *Environ Sci Pollut Res Int.* 2015;22:19434–19450.