

BÖLÜM 21

OBEZİTE VE ÜREME SAĞLIĞI

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Giriş

Obezite, nüfusun üçte birinden fazlasını etkileyen küresel bir sağlık sorunu olarak kabul edilmektedir. Obezite komplikasyonları arasında kar-diyovasküler hastalıklar, tip 2 diabetes mellitus, malignite, nörodejenerasyon ve erken yaşlanma yer alır. Ek olarak, hiperinsülinemi, hiperleptinem, kronik inflamasyon ve oksidatif stres gibi patolojileri nedeniyle obezite hem kadınlarda hem erkeklerde üreme sağlığını bozarak fertilitenin azalmasına ve infertilite riskinin artmasına neden olabilir. Kadın obezitesinin üreme fonksyonları üzerindeki olumsuz etkileri, çeşitli ovaryan ve over dışı faktörlere bağlanmaktadır. Fazla kilolu veya obez kadınların normal kilolu kadınlara kıyasla gebe kalma süresinin daha uzun olduğu ve daha düşük fertilité oranı, daha yüksek gonadotropin gereksinimi ve daha yüksek abortus oranına sahip oldukları bilinmektedir. Bunun nedenleri arasında ovaryan folikül gelişiminin, oosit gelişiminin ve kalitesinin, oositin fertilizasyo-

nunun, embriyo gelişiminin ve implantasyonun bozulması yer alır. Erkek obezitesi ise esas olarak hipotalamo-hipofizier-gonadal aksin bozulması, testiküler ısısının artması, spermin fiziksel ve moleküler yapısının bozulması, sperm kalitesinin azalması ve periferik damar hastalıklarına bağlı erektil disfonksiyon nedeniyle subfertiliteye yol açabilir. Kitabın bu bölümünde, obezitenin kadın ve erkek üreme sistemi ve fertilité üzerindeki potansiyel olumsuz etkileri ve ilişkili mekanizmaları gözden geçirilecektir.

Kadın obezitesi ve üreme

Obezite, kadın fertilitesine oldukça karmaşık ve çok faktörlü mekanizmalar aracılığıyla etki eder⁽¹⁾. Obezite, ovaryan foliküllerin gelişimini, oosit gelişimini ve kalitesini, oositin fertilizasyonunu, embriyo gelişimini ve implantasyonu etkileyerek fertiliteyi bozabilir⁽²⁾. Ayrıca nöroendokrin ve ovaryan fonksyonları etkileyerek, ovulatuvar siklusların ve dolayısıyla fertilité oranlarının

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ile obezitenin üreme sistemi üzerindeki olumsuz etkilerini azaltmak mümkündür.

KAYNAKÇA

- Kasum M, Orešković S, Čehić E, et al. The role of female obesity on in vitro fertilization outcomes. *Gynecological Endocrinology*, 2018; 34(3):184-188. doi:10.1080/09513590.2017.1391209.
- Jungheim ES, Travieso JL, Hopeman MM. Weighing the impact of obesity on female reproductive function and fertility. *Nutrition Reviews*, 2013; 71 Suppl 1(0 1):S3-8. doi:10.1111/nure.12056.
- Pasquali R, Pelusi C, Genghini S, et al. Obesity and reproductive disorders in women. *Human Reproduction Update*, 2003; 9(4):359-372. doi:10.1093/humupd/dmg024.
- Talmor A, Dunphy B. Female obesity and infertility. *Best Practice & Research: Clinical Obstetrics & Gynaecology*, 2015; 29(4):498-506. doi:10.1016/j.bpobgyn.2014.10.014.
- Belan M, Harnois-Leblanc S, Laferrère B, et al. Optimizing reproductive health in women with obesity and infertility. *CMAJ: Canadian Medical Association Journal*, 2018; 190(24):E742-e745. doi:10.1503/cmaj.171233.
- Slopien R, Horst N, Jaremek JD, et al. The impact of surgical treatment of obesity on the female fertility. *Gynecological Endocrinology*, 2019; 35(2):100-102. doi:10.1080/09513590.2018.1500536.
- Gaskins AJ. Recent advances in understanding the relationship between long- and short-term weight change and fertility. *F1000Res*, 2018; 7. doi:10.12688/f1000research.15278.1.
- Broughton DE, Moley KH. Obesity and female infertility: potential mediators of obesity's impact. *Fertility and Sterility*, 2017; 107(4):840-847. doi:10.1016/j.fertnstert.2017.01.017.
- Silvestris E, de Pergola G, Rosania R, et al. Obesity as disruptor of the female fertility. *Reproductive Biology and Endocrinology*, 2018; 16(1):22. doi:10.1186/s12958-018-0336-z.
- Brannian JD, Zhao Y, McElroy M. Leptin inhibits gonadotrophin-stimulated granulosa cell progesterone production by antagonizing insulin action. *Human Reproduction*, 1999; 14(6):1445-1448. doi:10.1093/humrep/14.6.1445.
- Psilopanagioti A, Papadaki H, Kranioti EF, et al. Expression of adiponectin and adiponectin receptors in human pituitary gland and brain. *Neuroendocrinology*, 2009; 89(1):38-47. doi:10.1159/000151396.
- Hug C, Wang J, Ahmad NS, et al. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proceedings of the National Academy of Sciences of the United States of America*, 2004; 101(28):10308-10313. doi:10.1073/pnas.0403382101.
- Kim KH, Lee K, Moon YS, et al. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. *Journal of Biological Chemistry*, 2001; 276(14):11252-11256. doi:10.1074/jbc.C100028200.
- Spicer LJ, Schreiber NB, Lagaly DV, et al. Effect of resistin on granulosa and theca cell function in cattle. *Animal Reproduction Science*, 2011; 124(1-2):19-27. doi:10.1016/j.anireprosci.2011.01.005.
- Fukuhara A, Matsuda M, Nishizawa M, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science*, 2005; 307(5708):426-430. doi:10.1126/science.1097243.
- Tan BK, Chen J, Digby JE, et al. Increased visfatin messenger ribonucleic acid and protein levels in adipose tissue and adipocytes in women with polycystic ovary syndrome: parallel increase in plasma visfatin. *Journal of Clinical Endocrinology and Metabolism*, 2006; 91(12):5022-5028. doi:10.1210/jc.2006-0936.
- Bray GA. Obesity and reproduction. *Human Reproduction*, 1997; 12 Suppl 1:26-32. doi:10.1093/humrep/12.suppl_1.26.
- Santoro N, Lasley B, McConnell D, et al. Body size and ethnicity are associated with menstrual cycle alterations in women in the early menopausal transition: The Study of Women's Health across the Nation (SWAN) Daily Hormone Study. *Journal of Clinical Endocrinology and Metabolism*, 2004; 89(6):2622-2631. doi:10.1210/jc.2003-031578.
- Purcell SH, Moley KH. The impact of obesity on egg quality. *Journal of Assisted Reproduction and Genetics*, 2011; 28(6):517-524. doi:10.1007/s10815-011-9592-y.
- Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. *New England Journal of Medicine*, 1999; 341(12):879-884. doi:10.1056/nejm199909163411204.
- Jungheim ES, Schoeller EL, Marquardt KL, et al. Diet-induced obesity model: abnormal oocytes and persistent growth abnormalities in the offspring. *Endocrinology*, 2010; 151(8):4039-4046. doi:10.1210/en.2010-0098.
- Luzzo KM, Wang Q, Purcell SH, et al. High fat diet induced developmental defects in the mouse: oocyte meiotic aneuploidy and fetal growth retardation/brain defects. *PloS One*, 2012; 7(11):e49217. doi:10.1371/journal.pone.0049217.
- Duggal PS, Van Der Hoek KH, Milner CR, et al. The in vivo and in vitro effects of exogenous lep-

- tin on ovulation in the rat. *Endocrinology*, 2000; 141(6):1971-1976. doi:10.1210/endo.141.6.7509.
24. van Swieten EC, van der Leeuw-Harmsen L, Badings EA, et al. Obesity and Clomiphene Challenge Test as predictors of outcome of in vitro fertilization and intracytoplasmic sperm injection. *Gynecologic and Obstetric Investigation*, 2005; 59(4):220-224. doi:10.1159/000084347.
25. Salha O, Dada T, Sharma V. Influence of body mass index and self-administration of hCG on the outcome of IVF cycles: a prospective cohort study. *Human Fertility*, 2001; 4(1):37-42. doi:10.1080/1464727012000199241.
26. Matalliotakis I, Cakmak H, Sakkas D, et al. Impact of body mass index on IVF and ICSI outcome: a retrospective study. *Reproductive Biomedicine Online*, 2008; 16(6):778-783. doi:10.1016/s1472-6483(10)60142-3.
27. Bilenka B, Ben-Shlomo I, Cozacov C, et al. Fertility, miscarriage and pregnancy after vertical banded gastroplasty operation for morbid obesity. *Acta Obstetricia et Gynecologica Scandinavica*, 1995; 74(1):42-44. doi:10.3109/00016349509009942.
28. Bastounis EA, Karayannakis AJ, Syrigos K, et al. Sex hormone changes in morbidly obese patients after vertical banded gastroplasty. *European Surgical Research*, 1998; 30(1):43-47. doi:10.1159/000008556.
29. Bellver J, Ayllón Y, Ferrando M, et al. Female obesity impairs in vitro fertilization outcome without affecting embryo quality. *Fertility and Sterility*, 2010; 93(2):447-454. doi:10.1016/j.fertnstert.2008.12.032.
30. Nichols JE, Crane MM, Higdon HL, et al. Extremes of body mass index reduce in vitro fertilization pregnancy rates. *Fertility and Sterility*, 2003; 79(3):645-647. doi:10.1016/s0015-0282(02)04807-0.
31. Wattanakumtornkul S, Damario MA, Stevens Hall SA, et al. Body mass index and uterine receptivity in the oocyte donation model. *Fertility and Sterility*, 2003; 80(2):336-340. doi:10.1016/s0015-0282(03)00595-8.
32. Dokras A, Baredziak L, Blaine J, et al. Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. *Obstetrics and Gynecology*, 2006; 108(1):61-69. doi:10.1097/01.AOG.0000219768.08249.b6.
33. Dechaud H, Anahory T, Reyftmann L, et al. Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, 2006; 127(1):88-93. doi:10.1016/j.ejogrb.2005.12.009.
34. Best D, Bhattacharya S. Obesity and fertility. *Hormone Molecular Biology and Clinical Investigation*, 2015; 24(1):5-10. doi:10.1515/hmbci-2015-0023.
35. Robker RL. Evidence that obesity alters the quality of oocytes and embryos. *Pathophysiology*, 2008; 15(2):115-121. doi:10.1016/j.pathophys.2008.04.004.
36. Leisegang K, Sengupta P, Agarwal A, et al. Obesity and male infertility: Mechanisms and management. *Andrologia*, 2021; 53(1):e13617. doi:10.1111/and.13617.
37. Hammoud AO, Gibson M, Peterson CM, et al. Obesity and male reproductive potential. *Journal of Andrology*, 2006; 27(5):619-626. doi:10.2164/jandrol.106.000125.
38. Katib A. Mechanisms linking obesity to male infertility. *Cent European J Urol*, 2015; 68(1):79-85. doi:10.5173/ceju.2015.01.435.
39. Tsai EC, Matsumoto AM, Fujimoto WY, et al. Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. *Diabetes Care*, 2004; 27(4):861-868. doi:10.2337/diacare.27.4.861.
40. Blache D, Zhang S, Martin GB. Fertility in male sheep: modulators of the acute effects of nutrition on the reproductive axis of male sheep. *Reprod Suppl*, 2003; 61:387-402.
41. Wolfe A, Hussain MA. The Emerging Role(s) for Kisspeptin in Metabolism in Mammals. *Frontiers in Endocrinology*, 2018; 9:184. doi:10.3389/fendo.2018.00184.
42. Clarke H, Dhillo WS, Jayasena CN. Comprehensive Review on Kisspeptin and Its Role in Reproductive Disorders. *Endocrinol Metab (Seoul)*, 2015; 30(2):124-141. doi:10.3803/EnM.2015.30.2.124.
43. Schulster M, Bernie AM, Ramasamy R. The role of estradiol in male reproductive function. *Asian J Androl*, 2016; 18(3):435-440. doi:10.4103/1008-682x.173932.
44. Chimento A, Sirianni R, Casaburi I, et al. Role of estrogen receptors and g protein-coupled estrogen receptor in regulation of hypothalamus-pituitary-testis axis and spermatogenesis. *Frontiers in Endocrinology*, 2014; 5:1. doi:10.3389/fendo.2014.00001.
45. Mounzih K, Lu R, Chehab FF. Leptin treatment rescues the sterility of genetically obese ob/ob males. *Endocrinology*, 1997; 138(3):1190-1193. doi:10.1210/endo.138.3.5024.
46. Bhat GK, Sea TL, Olatinwo MO, et al. Influence of a leptin deficiency on testicular morphology, germ cell apoptosis, and expression levels of apoptosis-related genes in the mouse. *Journal of Andrology*, 2006; 27(2):302-310. doi:10.2164/jandrol.05133.
47. Yamagishi SI, Edelstein D, Du XL, et al. Leptin induces mitochondrial superoxide production and monocyte chemoattractant protein-1 expressi-

- on in aortic endothelial cells by increasing fatty acid oxidation via protein kinase A. *Journal of Biological Chemistry*, 2001; 276(27):25096-25100. doi:10.1074/jbc.M007383200.
48. Ojeda SR, Lomniczi A, Mastronardi C, et al. Minireview: the neuroendocrine regulation of puberty: is the time ripe for a systems biology approach? *Endocrinology*, 2006; 147(3):1166-1174. doi:10.1210/en.2005-1136.
49. Teerds KJ, de Rooij DG, Keijer J. Functional relationship between obesity and male reproduction: from humans to animal models. *Human Reproduction Update*, 2011; 17(5):667-683. doi:10.1093/humupd/dmr017.
50. Page ST, Herbst KL, Amory JK, et al. Testosterone administration suppresses adiponectin levels in men. *Journal of Andrology*, 2005; 26(1):85-92.
51. Zheng D, Zhao Y, Shen Y, et al. Orexin A-mediated stimulation of 3 β -HSD expression and testosterone production through MAPK signaling pathways in primary rat Leydig cells. *Journal of Endocrinological Investigation*, 2014; 37(3):285-292. doi:10.1007/s40618-013-0035-8.
52. Duffy CM, Nixon JP, Butterick TA. Orexin A attenuates palmitic acid-induced hypothalamic cell death. *Molecular and Cellular Neurosciences*, 2016; 75:93-100. doi:10.1016/j.mcn.2016.07.003.
53. Flehmig G, Scholz M, Klöting N, et al. Identification of adipokine clusters related to parameters of fat mass, insulin sensitivity and inflammation. *PloS One*, 2014; 9(6):e99785. doi:10.1371/journal.pone.0099785.
54. Du Plessis SS, Cabler S, McAlister DA, et al. The effect of obesity on sperm disorders and male infertility. *Nat Rev Urol*, 2010; 7(3):153-161. doi:10.1038/nrurol.2010.6.
55. Wang C, Jackson G, Jones TH, et al. Low testosterone associated with obesity and the metabolic syndrome contributes to sexual dysfunction and cardiovascular disease risk in men with type 2 diabetes. *Diabetes Care*, 2011; 34(7):1669-1675. doi:10.2337/dc10-2339.
56. Sinha Hikim AP, Swerdloff RS. Hormonal and genetic control of germ cell apoptosis in the testis. *Reviews of Reproduction*, 1999; 4(1):38-47. doi:10.1530/ror.0.0040038.
57. Garolla A, Torino M, Sartini B, et al. Seminal and molecular evidence that sauna exposure affects human spermatogenesis. *Human Reproduction*, 2013; 28(4):877-885. doi:10.1093/humrep/det020.
58. Jia YF, Feng Q, Ge ZY, et al. Obesity impairs male fertility through long-term effects on spermatogenesis. *BMC Urology*, 2018; 18(1):42. doi:10.1186/s12894-018-0360-5.
59. Li CY, Dong ZQ, Lan XX, et al. [Endoplasmic reticulum stress promotes the apoptosis of testicular germ cells in hyperlipidemic rats]. *Zhonghua Nan Ke Xue*, 2015; 21(5):402-407.
60. Carlsen E, Giwercman A, Keiding N, et al. Evidence for decreasing quality of semen during past 50 years. *BMJ*, 1992; 305(6854):609-613. doi:10.1136/bmj.305.6854.609.
61. Sengupta P, Dutta S, Krajewska-Kulak E. The Disappearing Sperms: Analysis of Reports Published Between 1980 and 2015. *Am J Mens Health*, 2017; 11(4):1279-1304. doi:10.1177/1557988316643383.
62. Sermondade N, Dupont C, Faure C, et al. Body mass index is not associated with sperm-zona pellucida binding ability in subfertile males. *Asian J Androl*, 2013; 15(5):626-629. doi:10.1038/aj.a.2013.10.
63. Jensen TK, Andersson AM, Jørgensen N, et al. Body mass index in relation to semen quality and reproductive hormones among 1,558 Danish men. *Fertility and Sterility*, 2004; 82(4):863-870. doi:10.1016/j.fertnstert.2004.03.056.
64. Kahn BE, Brannigan RE. Obesity and male infertility. *Curr Opin Urol*, 2017; 27(5):441-445. doi:10.1097/mou.0000000000000417.
65. Davidson LM, Millar K, Jones C, et al. deleterious effects of obesity upon the hormonal and molecular mechanisms controlling spermatogenesis and male fertility. *Human Fertility*, 2015; 18(3):184-193. doi:10.3109/14647273.2015.1070438.
66. Bieniek JM, Kashanian JA, Deibert CM, et al. Influence of increasing body mass index on semen and reproductive hormonal parameters in a multi-institutional cohort of subfertile men. *Fertility and Sterility*, 2016; 106(5):1070-1075. doi:10.1016/j.fertnstert.2016.06.041.
67. Chavarro JE, Toth TL, Wright DL, et al. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertility and Sterility*, 2010; 93(7):2222-2231. doi:10.1016/j.fertnstert.2009.01.100.
68. Hammiche F, Laven JS, Boxmeer JC, et al. Sperm quality decline among men below 60 years of age undergoing IVF or ICSI treatment. *Journal of Andrology*, 2011; 32(1):70-76. doi:10.2164/jandrol.109.009647.
69. Agarwal A, Majzoub A, Baskaran S, et al. Sperm DNA Fragmentation: A New Guideline for Clinicians. *World J Mens Health*, 2020; 38(4):412-471. doi:10.5534/wjmh.200128.
70. Sarwer DB, Hanson AJ, Voeller J, et al. Obesity and Sexual Functioning. *Curr Obes Rep*, 2018; 7(4):301-307. doi:10.1007/s13679-018-0319-6.

71. Seftel A. Male hypogonadism. Part II: etiology, pathophysiology, and diagnosis. *International Journal of Impotence Research*, 2006; 18(3):223-228. doi:10.1038/sj.ijir.3901365.
72. Shamloul R, Ghanem H. Erectile dysfunction. *Lancet*, 2013; 381(9861):153-165. doi:10.1016/s0140-6736(12)60520-0.
73. Hammoud AO, Gibson M, Peterson CM, et al. Impact of male obesity on infertility: a critical review of the current literature. *Fertility and Sterility*, 2008; 90(4):897-904. doi:10.1016/j.fertnstert.2008.08.026.
74. Clark AM, Ledger W, Galletly C, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Human Reproduction*, 1995; 10(10):2705-2712. doi:10.1093/oxfordjournals.humrep.a135772.
75. Kiddy DS, Hamilton-Fairley D, Bush A, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clinical Endocrinology*, 1992; 36(1):105-111. doi:10.1111/j.1365-2265.1992.tb02909.x.
76. Sim KA, Partridge SR, Sainsbury A. Does weight loss in overweight or obese women improve fertility treatment outcomes? A systematic review. *Obesity Reviews*, 2014; 15(10):839-850. doi:10.1111/obr.12217.
77. Sneed ML, Uhler ML, Grotjan HE, et al. Body mass index: impact on IVF success appears age-related. *Human Reproduction*, 2008; 23(8):1835-1839. doi:10.1093/humrep/den188.