

BÖLÜM 20

Azospermi Yönetimi

Ünal ÖZTEKİN¹

Emin KAYMAK²

Mehmet CANIKLİOĞLU³

GİRİŞ

İnfertilite, 12 ay veya daha uzun süre düzenli ve korunmasız cinsel ilişkiden sonra gebelik elde edilememesi ile tanımlanan erkek veya kadın üreme sisteminin bir hastalığıdır (1). İnfertilite, dünya çapında üreme çağındaki milyonlarca insanı etkiler ve onların aileleri ve toplulukları üzerinde etkisi vardır (2). Çiftlerin yaklaşık yüzde 15'i infertildir ve bu çiftler arasında yaklaşık olarak erkek faktörü infertilitenin % 50'sinden sorumludur. Erkek infertilitesi, çok çeşitli bozuklukları kapsayan çok faktörlü bir sendromdur. İnfertil erkeklerin yarısından fazlasında kısırlığın nedeni bilinmemektedir (idiyopatik) ve doğuştan veya sonradan kazanılmış olabilir. Erkeklerde infertilite, başlangıçta semen analizi ile teşhis edilebilir. Dünya çapında erkeklerin yaklaşık %4'ü kısırlıktan muzdariptir. Bu erkeklerin yüksek bir yüzdesinde infertilite etiyolojisi, spermatozoanın kon-santrasyonu, motilitesi ve/veya morfolojisi gibi temel semen analizinin klasik parametrelerindeki değişikliklerle yakından ilişkilidir (3). Mevcut tahmin, infertilite kliniğinde yardım arayan erkeklerin yaklaşık yüzde 30'unun etiyolojisi bilinmeyen oligozoospermii veya azoospermiiye sahip olduğu yönündedir (4, 5). Azospermi infertile erkeklerin % 15'ine kadar bulunmaktadır (6).

¹ Doç. Dr., Özel System Hospital Üroloji Kliniği, dr_unal@hotmail.com

² Dr. Öğr. Üyesi, Yozgat Bozok Üniversitesi Tıp Fakültesi Histoloji ve Embriyoji AD., e_kaymak@hotmail.com

³ Dr. Öğr. Üyesi, Yozgat Bozok Üniversitesi, Tip Fakültesi, Üroloji AD., dr.mehmetcaniklioglu@gmail.com

KAYNAKLAR

1. (WHO). WHO. International Classification of Diseases, 11th Revision (ICD-11) Geneva: . 2018.
2. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS medicine*. 2012;9 (12):e1001356.
3. Guzick DS, Overstreet JW, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, et al. Sperm morphology, motility, and concentration in fertile and infertile men. *The New England journal of medicine*. 2001;345 (19):1388-93.
4. Poongothai J, Gopenath TS, Manonayaki S. Genetics of human male infertility. *Singapore medical journal*. 2009;50 (4):336-47.
5. Sinclair S. Male infertility: nutritional and environmental considerations. *Alternative medicine review : a journal of clinical therapeutic*. 2000;5 (1):28-38.
6. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. *The Journal of urology*. 1989;142 (1):62-5.
7. World Health O. WHO laboratory manual for the examination and processing of human semen. 5th ed ed. Geneva: World Health Organization; 2010.
8. Schlegel PN. Causes of azoospermia and their management. *Reproduction, fertility, and development*. 2004;16 (5):561-72.
9. Jaffe TM, Kim ED, Hoekstra TH, Lipshultz LI. Sperm pellet analysis: a technique to detect the presence of sperm in men considered to have azoospermia by routine semen analysis. *The Journal of urology*. 1998;159 (5):1548-50.
10. Cocuzza M, Alvarenga C, Pagani R. The epidemiology and etiology of azoospermia. *Clinics (Sao Paulo, Brazil)*. 2013;68 Suppl 1 (Suppl 1):15-26.
11. Jungwirth A, Giwercman A, Tournaye H, Diemer T, Kopa Z, Dohle G, et al. European Association of Urology guidelines on Male Infertility: the 2012 update. *European urology*. 2012;62 (2):324-32.
12. Dimitriadis F, Adonakis G, Kaponis A, Mamoulakis C, Takenaka A, Sofikitis N. Pre-Testicular, Testicular, and Post-Testicular Causes of Male Infertility. In: Simoni M, Huhtaniemi IT, editors. *Endocrinology of the Testis and Male Reproduction*. Cham: Springer International Publishing; 2017. p. 981-1027.
13. Hoffman AR, Crowley WF, Jr. Induction of puberty in men by long-term pulsatile administration of low-dose gonadotropin-releasing hormone. *The New England journal of medicine*. 1982;307 (20):1237-41.
14. Vicari E, Mongioi A, Calogero AE, Moncada ML, Sidoti G, Polosa P, et al. Therapy with human chorionic gonadotrophin alone induces spermatogenesis in men with isolated hypogonadotropic hypogonadism--long-term follow-up. *International journal of andrology*. 1992;15 (4):320-9.
15. Finkel DM, Phillips JL, Snyder PJ. Stimulation of spermatogenesis by gonadotropins in men with hypogonadotropic hypogonadism. *The New England journal of medicine*. 1985;313 (11):651-5.

16. Burgués S, Calderón MD. Subcutaneous self-administration of highly purified follicle stimulating hormone and human chorionic gonadotrophin for the treatment of male hypogonadotropic hypogonadism. Spanish Collaborative Group on Male Hypogonadotropic Hypogonadism. *Human reproduction* (Oxford, England). 1997;12 (5):980-6.
17. Sussman EM, Chudnovsky A, Niederberger CS. Hormonal evaluation of the infertile male: has it evolved? *The Urologic clinics of North America*. 2008;35 (2):147-55, viii.
18. Bhagavath B, Podolsky RH, Ozata M, Bolu E, Bick DP, Kulharya A, et al. Clinical and molecular characterization of a large sample of patients with hypogonadotropic hypogonadism. *Fertility and sterility*. 2006;85 (3):706-13.
19. Krausz C. Male infertility: pathogenesis and clinical diagnosis. *Best practice & research Clinical endocrinology & metabolism*. 2011;25 (2):271-85.
20. Georgopoulos NA, Koika V, Varnavas P, Efthymiadou A, Marioli DJ, Mantagos S, et al. Can Kallmann syndrome be occasionally diagnosed during childhood? Genetic diagnosis in a child with associated renal agenesis and mirror movements. *Asian journal of andrology*. 2009;11 (4):521-3.
21. Huhtaniemi I, Alevizaki M. Mutations along the hypothalamic-pituitary-gonadal axis affecting male reproduction. *Reproductive biomedicine online*. 2007;15 (6):622-32.
22. Sykiotis GP, Plummer L, Hughes VA, Au M, Durrani S, Nayak-Young S, et al. Oligogenic basis of isolated gonadotropin-releasing hormone deficiency. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107 (34):15140-4.
23. Burris AS, Clark RV, Vantman DJ, Sherins RJ. A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism after gonadotropin therapy. *Fertility and sterility*. 1988;50 (2):343-7.
24. Ma X, Dong Y, Matzuk MM, Kumar TR. Targeted disruption of luteinizing hormone beta-subunit leads to hypogonadism, defects in gonadal steroidogenesis, and infertility. *Proceedings of the National Academy of Sciences of the United States of America*. 2004;101 (49):17294-9.
25. Sokol RZ. Endocrinology of male infertility: evaluation and treatment. *Seminars in reproductive medicine*. 2009;27 (2):149-58.
26. Cocuzza M, Agarwal A. Nonsurgical treatment of male infertility: specific and empiric therapy. *Biologics : targets & therapy*. 2007;1 (3):259-69.
27. Gilbaugh JH, 3rd, Lipshultz LI. Nonsurgical treatment of male infertility. An update. *The Urologic clinics of North America*. 1994;21 (3):531-48.
28. Bhasin S, Ma K, Sinha I, Limbo M, Taylor WE, Salehian B. The genetic basis of male infertility. *Endocrinology and metabolism clinics of North America*. 1998;27 (4):783-805, viii.
29. Aiman J, Griffin JE, Gazak JM, Wilson JD, MacDonald PC. Androgen insensitivity as a cause of infertility in otherwise normal men. *The New England journal of medicine*. 1979;300 (5):223-7.
30. Clarke BG. Incidence of Varicocele in Normal Men and Among Men of Different Ages. *Jama*. 1966;198 (10):1121-2.
31. Gorelick JI, Goldstein M. Loss of fertility in men with varicocele. *Fertility and sterility*. 1993;59 (3):613-6.
32. Marmar JL, Agarwal A, Prabakaran S, Agarwal R, Short RA, Benoff S, et al. Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis. *Fertility and sterility*. 2007;88 (3):639-48.
33. Czaplicki M, Bablok L, Janczewski Z. Varicocelectomy in patients with azoospermia. *Archives of andrology*. 1979;3 (1):51-5.

34. Matthews GJ, Matthews ED, Goldstein M. Induction of spermatogenesis and achievement of pregnancy after microsurgical varicocelectomy in men with azoospermia and severe oligoasthenospermia. *Fertility and sterility*. 1998;70 (1):71-5.
35. Kim ED, Leibman BB, Grinblat DM, Lipshultz LI. Varicocele repair improves semen parameters in azoospermic men with spermatogenic failure. *The Journal of urology*. 1999;162 (3 Pt 1):737-40.
36. Pasqualotto FF, Lucon AM, Hallak J, Góes PM, Saldanha LB, Arap S. Induction of spermatogenesis in azoospermic men after varicocele repair. *Human reproduction* (Oxford, England). 2003;18 (1):108-12.
37. Hutson JM, Balic A, Nation T, Southwell B. Cryptorchidism. *Seminars in pediatric surgery*. 2010;19 (3):215-24.
38. Toppari J, Kaleva M. Maldescendus testis. *Hormone research*. 1999;51 (6):261-9.
39. Bay K, Main KM, Toppari J, Skakkebæk NE. Testicular descent: INSL3, testosterone, genes and the intrauterine milieus. *Nature reviews Urology*. 2011;8 (4):187-96.
40. Grasso M, Buonaguidi A, Lania C, Bergamaschi F, Castelli M, Rigatti P. Postpubertal cryptorchidism: review and evaluation of the fertility. *European urology*. 1991;20 (2):126-8.
41. <EAU-Guidelines-Paediatric-Urology-2016-1.pdf>.
42. Raman JD, Schlegel PN. Testicular sperm extraction with intracytoplasmic sperm injection is successful for the treatment of nonobstructive azoospermia associated with cryptorchidism. *The Journal of urology*. 2003;170 (4 Pt 1):1287-90.
43. Bartsch G, Frank S, Marberger H, Mikuz G. Testicular torsion: late results with special regard to fertility and endocrine function. *The Journal of urology*. 1980;124 (3):375-8.
44. Anim JT, Kehinde EO, Prasad A, Varghese R. Morphological responses of the rabbit testis to ischemic/reperfusion injury due to torsion. *Urologia internationalis*. 2005;75 (3):258-63.
45. Visser AJ, Heyns CF. Testicular function after torsion of the spermatic cord. *BJU international*. 2003;92 (3):200-3.
46. Daehlin L, Ulstein M, Thorsen T, Høisaeter PA. Follow-up after torsion of the spermatic cord. *Scandinavian journal of urology and nephrology Supplementum*. 1996;179:139-42.
47. Sharp VJ, Kieran K, Arlen AM. Testicular torsion: diagnosis, evaluation, and management. *American family physician*. 2013;88 (12):835-40.
48. Davis NF, McGuire BB, Mahon JA, Smyth AE, O'Malley KJ, Fitzpatrick JM. The increasing incidence of mumps orchitis: a comprehensive review. *BJU international*. 2010;105 (8):1060-5.
49. Werner CA. Mumps orchitis and testicular atrophy; a factor in male sterility. *Annals of internal medicine*. 1950;32 (6):1075-86.
50. Werner CA. Mumps orchitis and testicular atrophy; occurrence. *Annals of internal medicine*. 1950;32 (6):1066-74.
51. Nudell DM, Monoski MM, Lipshultz LI. Common medications and drugs: how they affect male fertility. *The Urologic clinics of North America*. 2002;29 (4):965-73.
52. Toth A. Male infertility due to sulphasalazine. *Lancet (London, England)*. 1979;2 (8148):904.
53. Tournaye H, Staessen C, Liebaers I, Van Assche E, Devroey P, Bonduelle M, et al. Testicular sperm recovery in nine 47,XXY Klinefelter patients. *Human reproduction* (Oxford, England). 1996;11 (8):1644-9.
54. Pandiyan N, Jequier AM. Mitotic chromosomal anomalies among 1210 infertile men. *Human reproduction* (Oxford, England). 1996;11 (12):2604-8.

55. Mendez HM, Opitz JM. Noonan syndrome: a review. *American journal of medical genetics.* 1985;21 (3):493-506.
56. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet (London, England).* 2013;381 (9863):333-42.
57. Van Assche E, Bonduelle M, Tournaye H, Joris H, Verheyen G, Devroey P, et al. Cytogenetics of infertile men. *Human reproduction (Oxford, England).* 1996;11 Suppl 4:1-24; discussion 5-6.
58. Graham JM, Jr., Bashir AS, Stark RE, Silbert A, Walzer S. Oral and written language abilities of XXY boys: implications for anticipatory guidance. *Pediatrics.* 1988;81 (6):795-806.
59. Schiff JD, Palermo GD, Veeck LL, Goldstein M, Rosenwaks Z, Schlegel PN. Success of testicular sperm extraction [corrected] and intracytoplasmic sperm injection in men with Klinefelter syndrome. *The Journal of clinical endocrinology and metabolism.* 2005;90 (11):6263-7.
60. Van der Auwera B, Van Roy N, De Paepe A, Hawkins JR, Liebaers I, Castedo S, et al. Molecular cytogenetic analysis of XX males using Y-specific DNA sequences, including SRY. *Human genetics.* 1992;89 (1):23-8.
61. Weidler EM, Pearson M, van Leeuwen K, Garvey E. Clinical management in mixed gonadal dysgenesis with chromosomal mosaicism: Considerations in newborns and adolescents. *Seminars in pediatric surgery.* 2019;28 (5):150841.
62. Denes FT, Cocuzza MA, Schneider-Monteiro ED, Silva FA, Costa EM, Mendonca BB, et al. The laparoscopic management of intersex patients: the preferred approach. *BJU international.* 2005;95 (6):863-7.
63. Tilford CA, Kuroda-Kawaguchi T, Skaletsky H, Rozen S, Brown LG, Rosenberg M, et al. A physical map of the human Y chromosome. *Nature.* 2001;409 (6822):943-5.
64. Navarro-Costa P. Sex, rebellion and decadence: the scandalous evolutionary history of the human Y chromosome. *Biochimica et biophysica acta.* 2012;1822 (12):1851-63.
65. Vogt PH, Edelmann A, Kirsch S, Henegariu O, Hirschmann P, Kiesewetter F, et al. Human Y chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. *Human molecular genetics.* 1996;5 (7):933-43.
66. Skaletsky H, Kuroda-Kawaguchi T, Minx PJ, Cordum HS, Hillier L, Brown LG, et al. The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature.* 2003;423 (6942):825-37.
67. Kraus MR, Schäfer A, Bentink T, Scheurlen M, Weissbrich B, Al-Taie O, et al. Sexual dysfunction in males with chronic hepatitis C and antiviral therapy: interferon-induced functional androgen deficiency or depression? *The Journal of endocrinology.* 2005;185 (2):345-52.
68. Hopps CV, Mielnik A, Goldstein M, Palermo GD, Rosenwaks Z, Schlegel PN. Detection of sperm in men with Y chromosome microdeletions of the AZFa, AZFb and AZFc regions. *Human reproduction (Oxford, England).* 2003;18 (8):1660-5.
69. Repping S, Skaletsky H, Lange J, Silber S, Van Der Veen F, Oates RD, et al. Recombination between palindromes P5 and P1 on the human Y chromosome causes massive deletions and spermatogenic failure. *American journal of human genetics.* 2002;71 (4):906-22.
70. Reijo R, Alagappan RK, Patrizio P, Page DC. Severe oligozoospermia resulting from deletions of azoospermia factor gene on Y chromosome. *Lancet (London, England).* 1996;347 (9011):1290-3.
71. Saxena R, de Vries JW, Repping S, Alagappan RK, Skaletsky H, Brown LG, et al. Four DAZ genes in two clusters found in the AZFc region of the human Y chromosome. *Genomics.* 2000;67 (3):256-67.

72. Dorfman DM, Genest DR, Reijo Pera RA. Human DAZL1 encodes a candidate fertility factor in women that localizes to the prenatal and postnatal germ cells. *Human reproduction* (Oxford, England). 1999;14 (10):2531-6.
73. The management of infertility due to obstructive azoospermia. *Fertility and sterility*. 2008;90 (5 Suppl):S121-4.
74. Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C. Male infertility: role of genetic background. *Reproductive biomedicine online*. 2007;14 (6):734-45.
75. McCallum T, Milunsky J, Munarriz R, Carson R, Sadeghi-Nejad H, Oates R. Unilateral renal agenesis associated with congenital bilateral absence of the vas deferens: phenotypic findings and genetic considerations. *Human reproduction* (Oxford, England). 2001;16 (2):282-8.
76. Kerem B, Kerem E. The molecular basis for disease variability in cystic fibrosis. *European journal of human genetics : EJHG*. 1996;4 (2):65-73.
77. Lu S, Cui Y, Li X, Zhang H, Liu J, Kong B, et al. Association of cystic fibrosis transmembrane-conductance regulator gene mutation with negative outcome of intracytoplasmic sperm injection pregnancy in cases of congenital bilateral absence of vas deferens. *Fertility and sterility*. 2014;101 (5):1255-60.
78. Tournaye H. Surgical sperm recovery for intracytoplasmic sperm injection: which method is to be preferred? *Human reproduction* (Oxford, England). 1999;14 Suppl 1:71-81.
79. Matsuda T, Horii Y, Yoshida O. Unilateral obstruction of the vas deferens caused by childhood inguinal herniorrhaphy in male infertility patients. *Fertility and sterility*. 1992;58 (3):609-13.
80. Shin D, Lipshultz LI, Goldstein M, Barmé GA, Fuchs EF, Nagler HM, et al. Herniorrhaphy with polypropylene mesh causing inguinal vasal obstruction: a preventable cause of obstructive azoospermia. *Annals of surgery*. 2005;241 (4):553-8.
81. Dohle GR, Colpi GM, Hargreave TB, Papp GK, Jungwirth A, Weidner W. EAU guidelines on male infertility. *European urology*. 2005;48 (5):703-11.
82. Handelsman DJ, Conway AJ, Boylan LM, Turtle JR. Young's syndrome. Obstructive azoospermia and chronic sinopulmonary infections. *The New England journal of medicine*. 1984;310 (1):3-9.
83. Hendry WF, AHern RP, Cole PJ. Was Young's syndrome caused by exposure to mercury in childhood? *BMJ (Clinical research ed)*. 1993;307 (6919):1579-82.
84. Meschede D, Dworniczak B, Behre HM, Kliesch S, Claustres M, Nieschlag E, et al. CFTR gene mutations in men with bilateral ejaculatory-duct obstruction and anomalies of the seminal vesicles. *American journal of human genetics*. 1997;61 (5):1200-2.
85. Hopps CV, Goldstein M, Schlegel PN. The diagnosis and treatment of the azoospermic patient in the age of intracytoplasmic sperm injection. *The Urologic clinics of North America*. 2002;29 (4):895-911.
86. Burrows PJ, Schrepferman CG, Lipshultz LI. Comprehensive office evaluation in the new millennium. *The Urologic clinics of North America*. 2002;29 (4):873-94.
87. Esteves SC, Miyaoka R, Agarwal A. An update on the clinical assessment of the infertile male. [corrected]. *Clinics (Sao Paulo, Brazil)*. 2011;66 (4):691-700.
88. Bettinger HF, Robinson B. The Klinefelter-Reifenstein-Albright syndrome. *The Medical journal of Australia*. 1946;2 (13):446-9.
89. Lipshultz LI, Corriere JN, Jr. Progressive testicular atrophy in the varicocele patient. *The Journal of urology*. 1977;117 (2):175-6.
90. Schoor RA, Elhanbly S, Niederberger CS, Ross LS. The role of testicular biopsy in the modern management of male infertility. *The Journal of urology*. 2002;167 (1):197-200.

91. Kim HH, Schlegel PN. Endocrine manipulation in male infertility. *The Urologic clinics of North America.* 2008;35 (2):303-18, x.
92. Sigman M, Jarow JP. Endocrine evaluation of infertile men. *Urology.* 1997;50 (5):659-64.
93. Schlegel PN. Causes of azoospermia and their management. *Reproduction, fertility, and development.* 2004;16 5:561-72.
94. <examination-and-processing-of-human-semen-5ed-eng.pdf>.
95. Castilla JA, Alvarez C, Aguilar J, González-Varea C, Goncalvo MC, Martínez L. Influence of analytical and biological variation on the clinical interpretation of seminal parameters. *Human reproduction (Oxford, England).* 2006;21 (4):847-51.
96. Schlegel PN. Testicular sperm extraction: microdissection improves sperm yield with minimal tissue excision. *Human reproduction (Oxford, England).* 1999;14 (1):131-5.
97. Shiraishi K, Ohmi C, Shimabukuro T, Matsuyama H. Human chorionic gonadotrophin treatment prior to microdissection testicular sperm extraction in non-obstructive azoospermia. *Human reproduction (Oxford, England).* 2012;27 (2):331-9.
98. Reifsnyder JE, Ramasamy R, Husseini J, Schlegel PN. Role of optimizing testosterone before microdissection testicular sperm extraction in men with nonobstructive azoospermia. *The Journal of urology.* 2012;188 (2):532-6.
99. Palermo G, Joris H, Devroey P, Van Steirteghem AC. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. *Lancet (London, England).* 1992;340 (8810):17-8.
100. Devroey P, Liu J, Nagy Z, Goossens A, Tournaye H, Camus M, et al. Pregnancies after testicular sperm extraction and intracytoplasmic sperm injection in non-obstructive azoospermia. *Human reproduction (Oxford, England).* 1995;10 (6):1457-60.
101. Saccà A, Pastore AL, Roscigno M, Naspro R, Pellucchi F, Fuschi A, et al. Conventional testicular sperm extraction (TESE) and non-obstructive azoospermia: is there still a chance in the era of microdissection TESE? Results from a single non-academic community hospital. *Andrology.* 2016;4 (3):425-9.
102. Kahraman S, Ozgür S, Alataş C, Aksoy S, Balaban B, Evrenkaya T, et al. High implantation and pregnancy rates with testicular sperm extraction and intracytoplasmic sperm injection in obstructive and non-obstructive azoospermia. *Human reproduction (Oxford, England).* 1996;11 (3):673-6.
103. Westlander G. Utility of micro-TESE in the most severe cases of non-obstructive azoospermia. *Upsala journal of medical sciences.* 2020;125 (2):99-103.
104. Eken A, Gulec F. Microdissection testicular sperm extraction (micro-TESE): Predictive value of preoperative hormonal levels and pathology in non-obstructive azoospermia. *The Kaohsiung journal of medical sciences.* 2018;34 (2):103-8.