

Bölüm 7

Amenore

Dr. Ülkü ÖZMEN

TANIM: Düzenli menstrüel döngüsü üreme çağındaki tüm kadınlar için fiziksel ve zihinsel iyilik halinin bir göstergesidir. Kadınlarda menstrasyon döngüsü 21 ila 35 gün arası sürer ve iki faza ayrılır: proliferatif faz ve sekrtetuar faz. Yaklaşık 12 ila 49 yaş arasındaki üreme çağındaki kadınlarda menstrasyonun yokluğu amenore olarak bilinir. Amenore primer ve sekonder nedenleri vardır. Primer amenore, adetlerin başlamasının olmamasıdır ve sekonder amenore, daha önce normal adet gören bir kadında adetlerin olmamasıdır. Amenore en sık nedeni gebeliktir, böyle bir hasta araştırılırken ekarte edilmesi gereken ilk şeydir (1). Nispeten sık görülen bir klinik durumdur ve hayatı tehdit eden bir durum olmamasına rağmen kadınları özellikle primer ise her açıdan olumsuz etkilemektedir, sebebine bağlı olarak ve tedavi seçenekleri farklılık göstermekte ve üreme üzerindeki etkileri değişmektedir. Primer ya da sekonder amenore menarşın varlığına göre belirlenir ve çoğunlukla sebepleri benzerdir. Primer amenore bütün amenoreli kadınlarda %5 oranında gözlenir. Sekonder seksüel gelişimi olanlarda 15 yaşa kadar; meme gelişimi 10 yaşından önce başlayan hastalarda ise meme gelişimi sonrası 5 yıl içinde menstrasyon beklenir yoksa primer amenore nedenleri için ayırıcı tanı yapılmalıdır (2). Meme gelişiminin 13 yaşına kadar olmaması araştırılması gereken bir durumdur(2). Normal sıklusa sahip kadınlarda 1 haftalık geçikmelerde gebelik testi yapılmalıdır. Daha önce adet görmüş kadınlarda üç aydan uzun süren amenore ve ya da bir yıl içinde dokuzdan az menstrasyon sayısı sekonder amenoreyi düşündürür

ve tanıya ihtiyaç duyar (3).Gebelik, laktasyon ve menopoz halleri dışında amenorenin insidansı yaklaşık %3-4 dür (3).

Sekonder amenorenin birçok sebebi olmasına rağmen çoğunlukla hastalarda polikistik over sendromu, hiperprolaktinemi, hipotalamik amenore veya ovaryen başarısızlık nedeniyle olur. Sekonder amenorede erişkin kadınların yaklaşık %3-5 inde gözlenir, fonksiyonel hipotalamik amenore sekonder amonerenin yaklaşık %20-30 kısmını oluşturur. (4)

Dünya sağlık örgütü(WHO) nedenleri şu şekilde özetlemiştir: WHO grup I de endojen östrojen üretimi yoktur, normal yada düşük seviyede FSH vardır, normal prolaktin seviyeleri bulunur ve hipotalamik-pitüiter lezyon yoktur, WHO grup II de östrojen üretimi ve normal seviyede prolaktin ve FSH (folliküler stimüle edici hormon) vardır, WHO grup III de yüksek FSH ın bulunduğu gonadal başarısızlık vardır(5). Amenore bazen ambiguous genitalya ve virilizasyon ile görülebilir, sebepleri ayrıntılı araştırılmalıdır(6).

MENSTRUEL SIKLUS: Menstrasyonun varlığı için en önemli şart kanamanın görülmesidir. Bunun için genital bölgenin anatomik olarak normal olması gereklidir. Uterine kavite, endoserviks,vajinal kanal ve vajinal orifisin bağlantısının kesintisiz olması gerekmektedir. Overdeki folikül siklusuna ve seks hormonlarına yanıt verebilecek fonksiyon gören bir endometriyumun olması gerekmektedir. Overin anterior hipofiz bezinden salınan gonadotropinler; FSH ve Lutinize edici hormona(LH) yanıt

yon testi), non klasik kongenital adrenal hiperplazi(KAH) (folliküler fazda sabah erken 17 hydroxy progesterone testi) ve androjen üreten adrenal vey ovaryan tümörler. Non klasik KAH PKOS a çok benzeyen nispeten sık görülen bir durumdur. Bazal 17OHP seviyesi >6 nmol/L ise, cosyntropin ile stimulasyon yapıp 17OHP seviyelerine bakmak gerekir(108).

Adölosanta PKOS tanısı koymak zordur, çünkü adölosanda fizyolojik bulguların bir kısmı PKOS'da da vardır. Adölosanda HA, menstruel düzensizlik ve /veya PCOM bulgularının olması gerekir. Adölosana ait menstruel düzensizliklerin değerlendirmesinin menarş yılına göre nasıl yapılacağı iyi bilinmelidir. Eksik tanıda uzun dönemde ortaya çıkabilecek metabolik, üreme, psikoemosyonel komplikasyonlar gibi komorbiteler gözden kaçabilir, fazladan tanı konulduğunda ise aile ve adölosanda anksiyeteye sebep olunabilir. Tedavide birinci seçenek hayat tarzı değişiklikleridir. Adölosanda erişkinlerde olduğu gibi obesite normal popülasyona göre daha fazladır. Hormonal tedavilerde ve antiandrojenik ilaçlarda meme ve kemik yoğunluğuna olumsuz etkiler akıldatutulmalı menarştan 3 yıl sonra başlanmalıdır. Uygun tedavi seçeneği hastanın kliniğine ve şikâyetlerine göre belirlenmelidir. Primer amonereli kızlar yada menstruel sıklığı >90 gün olanlar PKOS açısından dikkatle değerlendirilip takip edilmelidir.

Kaynaklar

1. Stedman's Medical Dictionary. 27th ed. Philadelphia: Lippincott Williams & Wilkins, 2000:p56.
2. Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, BhapkarMV, Koch GG, et al. Secondary sexual characteristics and menses in young girls seen in office practice: a study from the Pediatric Research in Office Settings network. *Pediatrics* 1997;99:505–12.
3. Current evaluation of amenorrhea. The Practice Committee of the American Society for Reproductive Medicine 2006 ;86(5):S148-55.
4. Qian-Hui Zhou, Ping Chen, Hong Peng, Ruo-Yun Ouyang, Dai-Qiang Li. Secondary Amenorrhea in a Patient with Common Variable Immunodeficiency *Chinese Medical Journal* | May 20, 2017 | Volume 130 | Issue 10
5. Inslar V. Gonadotophin therapy: new trends and insights. *Int J Fertil* 1988;33:85–97.
6. Doody KM, Carr BR. Amenorrhea. *Obstet Gynecol Clin North Am*1990;17:361– 87.
7. Marshall JC, Dalkin AC, Haisenleder DJ, Griffin ML, Kelch RP.GnRH pulses--the regulators of human reproduction. *Trans Am Clin Climatol Assoc.* 1993;104:31-46.
8. Souzana Choussein, Dimitrios Nasioudis,Dimitrios Schizas,Konstantinos P. Economopoulos. Mullerian dysgenesis: a critical review of the literature. *Arch Gynecol Obstet* (2017) 295:1369–1381.
9. Wilson JD. Syndromes of androgen resistance. *Biol Reprod* 1992;46:168–73.
10. Lobo RA. Primary and secondary amenorrhea. In: Fraser IS, Jansen R, Lobo RA, Whitehead M, eds. *Estrogens and progestogens in clinical practice*. London: Churchill Livingstone, 1998.
11. Fiaschetti V, Taglieri A, Gisone V, Coco I, Simonetti GJ. Mayer-Rokitansky-Kuster-Hauser syndrome diagnosed by magnetic resonance imaging. Role of imaging to identify and evaluate the uncommon variation in development of the female genital tract. *Radiol Case Rep.* 2012 Apr;6(4):17-24.
12. Fontana L., Gentilin B., Fedele L., Gervasini C., Miozzo M. Genetics ofMayer–Rokitansky–Küster–Hauser (MRKH)Syndrome.*Clin Genet* 2017: 91: 233–246
13. Padmanabhan Elamparidhi, Rudrappa Ramesh Kumar, Selvakkalanjiyam Sivaranjnie, Rajakumar Sibhithran. Mullerian Agenesis Associated With Turner's Syndrome. *Journal Of Clinical And Diagnostic Research.* 2017 Feb, Vol-11(2): Td01-Td02
14. Sun Kim,Yeong Seok Lee,Dong Hyun Kim,Aram Yang,Tack Lee,Seun Deuk Hwang,Dae Gyu Kwon, Ji Eun Lee. Long-term follow-up on MURCS (Müllerian duct, renal, cervical somite dysplasia) association and a review of the literature. *Ann Pediatr Endocrinol Metab* 2019;24:207-211.
15. Reid RL. Amenorrhea. In: Copeland LJ, ed. *Textbook of gynecology*. 2nd ed. Philadelphia: WB Saunders, 1996.
16. Gungor Ugurlucan F, Bastu E, Gulsen G, et al. OH-VIRAsyndrome presenting with acute abdomen: a case report and review of the literature. *Clin Imaging* 2014; 38(3): 357–359..
17. Asherman J. Amenorrhea traumatica (atretica) *J Obstet Gynaecol Br Emp.* 1948;55:23–7.
18. Fedele L, Bianchi S, Frontino G. Septums and synchiae: approaches to surgical correction. *Clin Obstet Gynecol* 2006;49:767–88.
19. Chason RJ, Levens ED, Yauger BJ, Payson MD, Cho K, Larsen FW Balloon fluoroscopy as treatment for intrauterine adhesions: a novel approach. *Fertil Steril.* 2008 ;90(5):2005.e15-7
20. Raditya Perdhana, Sutrisno Sutrisno, Yani Jane Sugiri, Siti Candra Windu Baktiyani, Arsana Wiyasa. Patients with secondary amenorrhea due to tuberculosis endometritis towards the induced anti-tuber-

- culosis drug category. *Pan African Medical Journal*. 2016; 24:121
21. Hughes IA, Deeb A. Androgen resistance. *Best Pract Res Clin Endocrinol Metab* 2006;20(4):577e98.
 22. Boehmer AL, Brinkmann AO, van Assendelft C, Otten BJ, Verleun-Mooijman MCT, Niermeijer MF, et al. Genotype versus phenotype in families with androgen insensitivity syndrome. *J Clin Endocrinol Metab* 2001;86:4151e60.
 23. Melo KF, Mendonca BB, Billerbeck AE, Costa EM, Ina'cio M, Silva FA, et al. Clinical, hormonal, behavioural, and genetic characteristics of androgen insensitivity syndrome in a Brazilian cohort: five novel mutations in the androgen receptor gene. *J Clin Endocrinol Metab* 2003;88:3241e50.
 24. Bouvattier C. Androgen receptor defects: syndromes of androgen insensitivity. Disorders of sex development: endocrine aspects. In: Gearhart, Rink, Mouriquand, eds. *Pediatric urology*. 2nd ed. Philadelphia: Saunders Elsevier; 2010. p. 472e3.
 25. Turner's syndrome. *West J Med* 1982;137:32–44.
 26. Kota SK, Gayatri K, Pani JP, Kota SK, Meher LK, Modi KD. Dysgerminoma in a female with Turner syndrome and Y chromosome material: A case-based review of literature. *Indian J Endocrinol Metab*. 2012 ;16(3):436–40.
 27. Mortensen KH, Andersen NH, Gravholt CH. Cardiovascular phenotype in Turner syndrome—integrating cardiology, genetics, and endocrinology. 2012 ;33(5):677–714
 28. Fritz MA, Speroff L. Amenorrhea. In: Fritz, Speroff eds. *Clinical Gynecologic Endocrinology and Infertility*. 8th ed. Philadelphia : Lippincott Williams & Wilkins ; 2011 .p.435–493
 29. Toledo SP, Brunner HG, Kraaij R, Post M, Dahia PL, Hayashida CY, et al. An inactivating mutation of the luteinizing hormone receptor causes amenorrhea in a 46,XX female. *J Clin Endocrinol Metab* 1996; 81:3850–4.
 30. Aittomaki K, Lucena JL, Pakarinen P, Sistonen P, Tapanainen J, Gromoll J, et al. Mutation in the follicle-stimulating hormone receptor gene causes hereditary hypergonadotropic ovarian failure. *Cell* 1995; 82:959–68.
 31. Allingham-Hawkins DJ, Babul-Hirji R, Chitayat D, Holden JJ, Yang KT, Lee C, et al. Fragile X premutation is a significant risk factor for premature ovarian failure: the International Collaborative POF in Fragile X study—preliminary data. *Am J Med Genet* 1999;83: 322–5.
 32. Laml T, Preyer O, Umek W, Hengstschlager M, Hanzal H. Genetic disorders in premature ovarian failure. *Hum Reprod Update* 2002;8: 483–91.
 33. Morishima A, Grumbach MM, Simpson ER, Fisher C, Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *J Clin Endocrinol Metab* 1995;80:3689–98.
 34. Nguyen HH, Wong P, Strauss BJ, Jones G, Ebeling PR, Milat F, Vincent A. Delay in estrogen commencement is associated with lower bone mineral density in Turner syndrome. *Climacteric*. 2017 May 19:1–6.
 35. Kallirroi Chaloutsou, Pantelis Aggelidis, Andreas Pampanos, Eleni Theochari, Lina Michala. Premature Ovarian Insufficiency: An Adolescent Series. *Journal of Pediatric and Adolescent Gynecology*
 36. Shelling AN. Premature ovarian failure. *Reproduction* (2010) 140 633–641.
 37. Ayesha, Vandana Jha, Deepti Goswami. Premature Ovarian Failure: An Association with Autoimmune Diseases. *Journal of Clinical and Diagnostic Research*. 2016 Oct, Vol-10(10): QC10–QC12
 38. Sorahia Domenice, Aline Zamboni Machado, Frederico Moraes Ferreira, Bruno Ferraz-de-Souza, Antonio Marcondes Lerario, Lin Lin, Mirian Yumie Nishi, Nathalia Lisboa Gomes, Thatiana Evelin da Silva, Rosana Barbosa Silva, Rafaela Vieira Correa, Luciana Ribeiro Montenegro, Amanda Narciso, Elaine Maria Frade Costa, John C Achermann, Berenice Bilharinho Mendonca. Wide Spectrum of NR5A1-Related Phenotypes in 46,XY and 46,XX Individuals. *BIRTH DEFECTS RESEARCH (PART C)* 108:309–320 (2016)
 39. Jensen JR, Morbeck DE, Coddington III CC. Fertility Preservation. *Mayo Clin Proc*. 2011;86(1):45–9
 40. Persani L, Rossetti R, Cacciatori C & Bonomi M. 2009 Primary ovarian insufficiency: X chromosome defects and autoimmunity. *Journal of Autoimmunity* 33 35–41.
 41. Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. *Endocr Rev* 1997;18:107–34.
 42. Rebar RW, Connolly HV. Clinical features of young women with hypergonadotropic amenorrhea. *Fertil Steril* 1990;53:804–10.
 43. Kirshenbaum M, Orvieto R. Premature ovarian insufficiency (POI) and autoimmunity—an update appraisal. *J Assist Reprod Genet*. 2019 Nov;36(11):2207–2215.
 44. Jessica H Knight, Penelope P Howards, Jessica B Spencer, Katina C Tsagaris, Sam S Lim. Characteristics related to early secondary amenorrhoea and pregnancy among women diagnosed with systemic lupus erythematosus: an analysis using the GOAL study. *Lupus Science & Medicine* 2016;3.
 45. Beck-Peccoz P, Persani L. Premature ovarian failure. *Orphanet Journal of Rare Diseases* 2006, 1:9
 46. Bidet M, Bachelot A & Touraine P. Premature ovarian failure: predictability of intermittent ovarian function and response to ovulation induction agents. *Current Opinion in Obstetrics and Gynecology*. 2008 ; 20 :416–20.

47. Oktay K, Cil AP, Bang H. Efficiency of oocyte cryopreservation: a metaanalysis. *Fertil Steril*. 2006;86(1):70-80.
48. Partridge AH. Ovarian Suppression for Prevention of Premature Menopause and Infertility: Empty Promise or Effective Therapy? *Journal of Clinical Oncology* .30; (5) 2012: 479-81.
49. Badawy A, Elnashar A, El-Ashry M, Shahat M. Gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage: prospective randomized study. *Fertil Steril*. 2009;91(3):694-7.
50. A. Dezellus, P. Barriere, M. Campone, C. Lemanski, L. Vanlemmens, L. Mignot, T. Delozier, C. Levy, C. Bendavid, M. Debled, T. Bachelot, C. Jouannaud, C. Loustalot, M.A. Mouret-Reynier, A. Gallais-Umbert, D. Masson, T. Freour. Prospective evaluation of serum anti-Müllerian hormone dynamics in 250 women of reproductive age treated with chemotherapy for breast cancer. *European Journal of Cancer* 79 (2017) 72-80
51. Ghahremani-Nasab M, Ghanbari E, Jahanbani Y, Mehdizadeh A, Yousefi M. Premature ovarian failure and tissue engineering. *J Cell Physiol*. 2019 Oct 29.
52. Minji Choo, Hana Park, Kyong Wook Yi . Complete vaginal outlet stenosis in a patient with Sheehan's syndrome. *Obstet Gynecol Sci* 2016;59(6):559-561.
53. Miyako Yoshizawa, Yasuhiko Ieki, Eisuke Takazakura, Kaori Fukuta, Takao Hidaka, Takanobu Wakasugi, Akira Shimatsu Successful Pregnancies and Deliveries in a Patient With Evolving Hypopituitarism due to Pituitary Stalk Transection Syndrome: Role of Growth Hormone Replacement. *Intern Med* 56: 527-530, 2017.
54. Ammirati M, Wei L, Ciric I. Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2012;0:1-7.
55. Touraine P, Plu-Bureau G, Beji C, Mauvais-Jarvis P, Kuttenn F. Longterm follow-up of 246 hyperprolactinemic patients. *Acta Obstet Gynecol Scand* 2001;80:162– 8.
56. Shelly S, Boaz M, Orbach H . Prolactin and autoimmunity .*Autoimmunity Reviews*. 2012; 11: A465–A470.
57. Schlechte J, Dolan K, Sherman B, Chapler F, Luciano A. The natural history of untreated hyperprolactinemia: a prospective analysis. *J Clin Endocrinol Metab* 1989;68:412– 8.
58. Qijing Bo, Fang Dong, Xianbin Li, Zhimin Wang, Xin Ma, Chuanyue Wang Prolactin related symptoms during risperidone maintenance treatment: results from a prospective, multicenter study of schizophrenia *BMC Psychiatry* (2016) 16:386.
59. Wang AT, Mullan RJ, Lane MA, Hazem A, Prasad C, Gathaiya NW, et al. Treatment of hyperprolactinemia: a systematic review and meta-analysis. *Syst Rev*. 2012 Jul 24;1(1):33.
60. Hoffmann A, Adelman S, Lohle K, Claviez A, Muller HL. Pediatric prolactinoma: initial presentation, treatment, and long-term prognosis. *Eur J Pediatr* 2018; 177: 125-132.
61. Matalliotakis M, Koliarakis I, Matalliotaki C, Trivli A, Hatzidaki E. Clinical manifestations, evaluation and management of hyperprolactinemia in adolescent and young girls: a brief review. *Acta Biomed* 2019; Vol. 90, N. 1: 149-157.
62. Marshall JC, Eagleson CA, McCartney CR. Hypothalamic dysfunction. *Mol Cell Endocrinol* 2002;183:29–32.
63. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. A nomogram to predict the probability of live birth after clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *Fertil Steril* 2002;77: 91–7.
64. Kaplan JR, Manuck SB. Ovarian dysfunction, stress, and disease: a primate continuum. *ILAR J*. 2004; 45: 89–115.
65. Qijing Bo, Fang Dong, Xianbin Li, Zhimin Wang, Xin Ma, Chuanyue Wang Prolactin related symptoms during risperidone maintenance treatment: results from a prospective, multicenter study of schizophrenia *BMC Psychiatry* (2016) 16:386.
66. Frisch RE, McArthur JW. Menstrual cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. *Science* 1974;185:949–51.
67. Lucas AR, Crowson CS, O'Fallon WM, Melton LJ 3rd. The ups and downs of anorexia nervosa. *Int J Eat Disord* 1999;26:397– 405.
68. Chou SH, Chamberland JP, Liu X, Matarese G, Gao C, Stefanakis R, et.al. Leptin is an effective treatment for hypothalamic amenorrhea. *Proc Natl Acad Sci USA*. 2011;108(16):6585- 90.
69. Uher R, Rutter M. Classification of feeding and eating disorders: review of evidence and proposals for ICD-11. *World Psychiatry*. 2012 Jun;11(2):80-92.
70. Winkler LA. *Dan Med J*. 2017 Jun;64(6). Funen Anorexia Nervosa Study - a follow-up study on outcome, mortality, quality of life and body composition.
71. Karountzos V, Lambrinou I, Tsitsika A, Deligeorgiou E. The role of total body fat mass and trunk fat mass, combined with other endocrine factors, in menstrual recovery and psychopathology of adolescents with Anorexia Nervosa. *Gynecol Endocrinol*. 2017 May 31:1-6.
72. Flora Bacopoulou, George I. Lambrou, Maria-Evangelia Rodanaki, Evgenia Stergioti, Vasiliki Efthymiou, Efthymios Deligeorgiou, Sophia L. Markantonis. Serum kisspeptin concentrations are negatively correlated with body mass index in adolescents with

- anorexia nervosa and amenorrhea. *Hormones* 2017; 16(1):33-41
73. Miller KK, Lawson EA, Mathur V, Wexler TL, Meenaghan E, Misra M, et al. Androgens in women with anorexia nervosa and normal-weight women with hypothalamic amenorrhea. *J Clin Endocrinol Metab.* 2007 Apr;92(4):1334-9.
 74. Kotani M, Katagiri F, Hirai T, Kagawa J, Tanaka I. Plasma kisspeptin levels in lactational amenorrhea. *Gynecol Endocrinol.* 2017 May 11:1-3.
 75. Pauli SA, Berga SL. Athletic amenorrhea: energy deficit or psychogenic challenge? *Ann N Y Acad Sci.* 2010 ;1205:33- 8.
 76. Warren MP, Goodman LR. Exercise-induced endocrine pathologies. *J Endocrinol Invest* 2003;26:873-8.
 77. Bethea CL, Pau FK, Fox S, Hess DL, Berga SL, Cameron JL. Sensitivity to stress-induced reproductive dysfunction linked to activity of the serotonin system. *Fertil Steril.* 2005; 83:148-55.
 78. Welt CK, Chan JL, Bullen J, Murphy R, Smith P, DePaoli AM, et al. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med* 2004;351(10):987-97
 79. Giles DE, Berga SL. Cognitive and psychiatric correlates of functional hypothalamic amenorrhea: a controlled comparison. *Fertil Steril.* 1993; 60:486-92.
 80. Alessandro D, Genazzani, Giulia Despini, Adam Czyzyk, Agnieszka Podfigurna, Tommaso Simoncini & Blazej Meczekalski. Modulatory effects of l-carnitine plus l-acetyl-carnitine on neuroendocrine control of hypothalamic functions in functional hypothalamic amenorrhea (FHA) *Gynecol Endocrinol.* 2017 Jun 2:1-5.
 81. A Lania, LGianotti, I Gagliardi, M Bondanelli, W Vena, M R. Ambrosio.. Functional hypothalamic and drug-induced amenorrhea: an overview. *Journal of Endocrinological Investigation* (2019) 42:1001-1010.
 82. Rosenfield RL. Clinical review 6: diagnosis and management of delayed puberty. *J Clin Endocrinol Metab* 1990;70:559-62.
 83. David Prokai and Sarah L. Berga. Neuroprotection via Reduction in Stress: Altered Menstrual Patterns as a Marker for Stress and Implications for Long-Term Neurologic Health in Women. *Int. J. Mol. Sci.* 2016, 17, 2147.
 84. Caronia LM, Martin C, Welt CK, Sykiotis GP, Quinton R, Thambundit A, et al. A Genetic Basis for Functional Hypothalamic Amenorrhea *N Engl J Med.* 2011 ; 364(3): 215-25.
 85. Hall JE. Physiologic and genetic insights into the pathophysiology and management of hypogonadotropic hypogonadism. *Ann Endocrinol* 1999;60:93-101.
 86. Vaaralahti K, Raivio T, Koivu R, Valanne L, Laitinen EM, Tommiska J. Genetic Overlap between Holoprosencephaly and Kallmann Syndrome. *Mol Syndromol.* 2012 Jun;3(1):1-5.
 87. Layman LC, McDonough PG, Cohen DP, Maddox M, Tho SP, Reindollar RH. Familial gonadotropin-releasing hormone resistance and hypogonadotropic hypogonadism in a family with multiple affected individuals. *Fertil Steril* 2001;75:1148 -55.
 88. Cohen A, Fleischer J, Freeby MJ, McMahon DJ, Irani D, Shane E. Clinical characteristics and medication use among premenopausal women with osteoporosis and low BMD: the experience of an osteoporosis referral center. *J Womens Health (Larchmt).* 2009 ;18(1):79-84.
 89. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med.* 1999; 341:549-55.
 90. Moran C, Azziz R, Carmina E, Dewailly D, Fruszetti F, Ibanez L, et al. 21-Hydroxylase-deficient nonclassic adrenal hyperplasia is a progressive disorder: a multicenter study. *Am J Obstet Gynecol* 2000;183:1468-74
 91. ACOG Practice Bulletin No. 108: Polycystic ovary syndrome. ACOG Committee on Practice Bulletins--Gynecology. *Obstet Gynecol.* 2009 Oct;114(4):936-49.
 92. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, Carmina E, Chang J, Yildiz BO, Laven JS, Boivin J, Petraglia F, Wijeyeratne CN, Norman RJ, Dunaif A, Franks S, Wild RA, Dumesic D, Barnhart K. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril.* 2012 ;97(1):28-38.e25.
 93. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004; 81:19-25.
 94. Dewailly et al., Dewailly, D., Gronier, H., Poncelet, E., Robin, G., Leroy, M., Pigny, P., Duhamel, A., Catteau-Jonard, S., 2011. Diagnosis of polycystic ovary syndrome (PCOS): revisiting the threshold values of follicle count on ultrasound and of the serum AMH level for the definition of polycystic ovaries. *Hum. Reprod.* 26, 3123-3129.
 95. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999;84:165-9.

96. Grundy SM, Cleeman JL, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. American Heart Association, National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735–52
97. Hart, R. et al. (2015) The potential implication of a PCOS diagnosis on a woman's long-term health using data linkage. *J. Clin. Endocrinol. Metab.* 100, 911–919
98. Zhu, L. et al. (2015) Confocal microscopic analysis of the spindle and chromosome configurations of in vitro-matured oocytes from different types of polycystic ovary syndrome patients. *Gynecol. Obstet. Invest.* 80, 179–186
99. Kjær MM, Madsbad S, Hougaard DM, Cohen AS, Nilas L. The impact of gastric bypass surgery on sex hormones and menstrual cycles in premenopausal women. *Gynecol Endocrinol.* 2017 Feb;33(2):160–163.
100. Legro RS, Arslanian SA, Ehrmann DA, et al.: Diagnosis and treatment of polycystic ovary syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2013, 98:4565–4592. 10.1210/jc.2013-2350.
101. Selma F. Witchela, Anne Claire Burghardb, Rachel H. Taob, and Sharon E. Oberfield. The diagnosis and treatment of PCOS in adolescents: an update. *Curr Opin Pediatr* 2019, 31:562–569.
102. Spritzer PM, Motta AB. Adolescence and polycystic ovary syndrome: Current concepts on diagnosis and treatment. *Int J Clin Pract.* 2015;69(11):1236–46.
103. Fahimeh Ramezani Tehrani and Mina Amiri. Polycystic Ovary Syndrome in Adolescents: Challenges in Diagnosis and Treatment *Int J Endocrinol Metab.* 2019 July; 17(3):e91554.,
104. Rosenfield RL. The diagnosis of polycystic ovary syndrome in adolescents. *Pediatrics.* 2015;136(6):1154–65.
105. Witchel SF, Oberfield S, Rosenfield RL, Codner E, Bonny A, Ibanez L, et al. The diagnosis of polycystic ovary syndrome during adolescence. *Horm Res Paediatr.* 2015 Apr 1.
106. Thompson IR, Kaiser UB. GnRH pulse frequency-dependent differential regulation of LH and FSH gene expression. *Mol Cell Endocrinol* 2014;385:28e35.
107. Dabadghao P. Polycystic ovary syndrome in adolescents.. *Best Pract Res Clin Endocrinol Metab.* 2019 Apr 13:101272
108. Selma Feldman Witchel, Sharon E. Oberfield, and Alexia S. Peña. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. 8 *Journal of the Endocrine Society.* August 2019 | Vol. 3, Iss. | 1545–1573.