

Bölüm 3

MİGREN VE KADIN

Selcen DURAN¹

1. GİRİŞ

Migren, 4-72 saat süren fotofobi ve fonofobinin eşlik ettiği ve genellikle bulantı ve bazı durumlarda kusma ile seyreden bir primer baş ağrısıdır (1). Aura, kademeli olarak gelişen ve genellikle baş ağrısı fazından önce gelen görsel, duyuşsal, konuşma ve/veya motor semptomları içeren tamamen geri dönüşümlü fokal nörolojik semptomdur ve her dört migren hastasından biri auralı migrendir (2, 3). Daha yaygın olarak izlenen ise auranın görülmediği aurasız migren alt tipidir (2). Migren hafif özürülükten çalışamamaya kadar deęişken şekilde dizabiliteye neden olur ve dizabilitenin önde gelen ikinci sırada sebebidir (4).

Son yıllarda, migrenin altında yatan mekanizmalara ilişkin bilgiler gelişerek; fonksiyonel sinir ağlarının aktivasyonu, vasküler deęişiklikler, hipereksitabilite, nörotransmitter ve nöropeptid sinyalizasyonunu içeren karmaşık bir dizi süreci ortaya çıkarmıştır (5). Migren patofizyolojisinde kilit rol oynayan trigeminovasküler sistem; nosisepsiyonu, meninksler ve serebral arterlerden beyin sapı trigeminoservikal kompleksine (trigeminal nükleus kaudalis ve üst servikal dorsal boynuzdan oluşur), ardından hipotalamus, talamus ve kortikal bölgelere ileten fonksiyonel bir yoldur (5). Çok sayıda kanıt, östrojenin merkezi ağrı ağlarında nosiseptif girdinin işlenmesini modüle ettiğini göstermiştir (6). Kadın cinsiyet hormonları (özellikle östrojen) seviyelerindeki dalgalanmaların, farklı üreme dönemlerinde, trigeminovasküler sistemdeki kalsitonin geniyle ilişkili peptidi (CGRP) modüle ettiği gösterilmiştir (7). CGRP'yi inhibe eden ilaçların başarılı bir şekilde piyasaya sürülmesi, migren patofizyolojisine ve yeni tedavilerin geliştirilmesine olan ilgiyi artırsa da, özellikle kadınlarda migren tedavisini iyileştirmek için migren mekanizmaları üzerindeki hormonal ve genetik etkilerin daha iyi anlaşılması gerekmektedir (8).

¹ Dr. Öğr. Üyesi, Kırşehir Ahi Evran Üniversitesi Tıp Fakültesi Nöroloji AD, drselcenduran@gmail.com, ORCID iD: 0000-0001-7553-2034

8. SONUÇ

Migren, kadın cinsiyette daha sık görülen ve daha şiddetli klinik bulgulara neden olan bir primer baş ağrısıdır. Migren, yaşam boyu süren bir hastalıktır ve hormonal durumlarındaki dalgalanmalar migrenin kötüleşmesine veya iyileşmesine neden olur. Kadının yaşam döngüsündeki özel durumlarda migren kötüleşebilir ve verilecek tedavi uygulamada zorluklara yol açabilir. Klinisyenlerin, hormonal tedavilerin migren üzerindeki etkileri yanı sıra, auralı migreni veya diğer vasküler risk faktörleri olan bir kadında hormon kullanımına ilişkin endişeler de dahil olmak üzere, bu son derece yaygın ve özürleyici durum hakkında iyi bilgi sahibi olmaları gerekir. Migren ve kadın alanında daha fazla bilimsel çalışmaya ihtiyaç vardır.

KAYNAKLAR:

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
2. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol. 2017;16(1):76-87.
3. Lucas C. Migraine with aura. Rev Neurol (Paris). 2021;177(7):779-84.
4. Todd C, Lagman-Bartolome AM, Lay C. Women and Migraine: the Role of Hormones. Curr Neurol Neurosci Rep. 2018;18(7):42.
5. Ahmad SR, Rosendale N. Sex and Gender Considerations in Episodic Migraine. Curr Pain Headache Rep. 2022;26(7):505-16.
6. Amandusson Å, Blomqvist A. Estrogenic influences in pain processing. Front Neuroendocrinol. 2013;34(4):329-49.
7. Labastida-Ramírez A, Rubio-Beltrán E, Villalón CM, MaassenVanDenBrink A. Gender aspects of CGRP in migraine. Cephalalgia. 2019;39(3):435-44.
8. Krause DN, Warfvinge K, Haanes KA, Edvinsson L. Hormonal influences in migraine - interactions of oestrogen, oxytocin and CGRP. Nat Rev Neurol. 2021;17(10):621-33.
9. Vetvik KG, MacGregor EA. Menstrual migraine: a distinct disorder needing greater recognition. The Lancet Neurology. 2021;20(4):304-15.
10. Burch R. Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review. Headache. 2020;60(1):200-16.
11. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-9.
12. Nappi RE, Tiranini L, Sacco S, De Matteis E, De Icco R, Tassorelli C. Role of Estrogens in Menstrual Migraine. Cells. 2022;11(8).
13. Lagman-Bartolome AM, Lay C. Migraine in Women. Neurol Clin. 2019;37(4):835-45.
14. Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. Cephalalgia. 2003;23(7):519-27.

15. Sacco S, Ricci S, Degan D, Carolei A. Migraine in women: the role of hormones and their impact on vascular diseases. *J Headache Pain*. 2012;13(3):177-89.
16. Nappi RE, Sances G, Detaddei S, Ornati A, Chiovato L, Polatti F. Hormonal management of migraine at menopause. *Menopause Int*. 2009;15(2):82-6.
17. Boese AC, Kim SC, Yin KJ, Lee JP, Hamblin MH. Sex differences in vascular physiology and pathophysiology: estrogen and androgen signaling in health and disease. *Am J Physiol Heart Circ Physiol*. 2017;313(3):H524-h45.
18. Laflamme N, Nappi RE, Drolet G, Labrie C, Rivest S. Expression and neuropeptidergic characterization of estrogen receptors (ERalpha and ERbeta) throughout the rat brain: anatomical evidence of distinct roles of each subtype. *J Neurobiol*. 1998;36(3):357-78.
19. Warfvinge K, Krause DN, Maddahi A, Edvinsson JCA, Edvinsson L, Haanes KA. Estrogen receptors α , β and GPER in the CNS and trigeminal system - molecular and functional aspects. *J Headache Pain*. 2020;21(1):131.
20. Messlinger K, Russo AF. Current understanding of trigeminal ganglion structure and function in headache. *Cephalalgia*. 2019;39(13):1661-74.
21. Marciszewski KK, Meylakh N, Di Pietro F, Mills EP, Macefield VG, Macey PM, et al. Changes in Brainstem Pain Modulation Circuitry Function over the Migraine Cycle. *J Neurosci*. 2018;38(49):10479-88.
22. Martin VT, Behbehani M. Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis--part I. *Headache*. 2006;46(1):3-23.
23. Gundlach C, Pecins-Thompson M, Schutzer WE, Bethea CL. Ovarian steroid effects on serotonin 1A, 2A and 2C receptor mRNA in macaque hypothalamus. *Brain Res Mol Brain Res*. 1999;63(2):325-39.
24. Smith YR, Stohler CS, Nichols TE, Bueller JA, Koeppe RA, Zubieta JK. Pronociceptive and antinociceptive effects of estradiol through endogenous opioid neurotransmission in women. *J Neurosci*. 2006;26(21):5777-85.
25. Özge A, Uludüz D, Karadaş Ö, Bozkurt MM. Mekanizma Temelli Migren Tedavisinde Erenumab. *Turk J Neurol*. 2021;27:229-39.
26. Cetinkaya A, Kilinc E, Camsari C, Ogun MN. Effects of estrogen and progesterone on the neurogenic inflammatory neuropeptides: implications for gender differences in migraine. *Exp Brain Res*. 2020;238(11):2625-39.
27. Frederiksen SD, Bekker-Nielsen Dunbar M, Snoer AH, Deen M, Edvinsson L. Serotonin and Neuropeptides in Blood From Episodic and Chronic Migraine and Cluster Headache Patients in Case-Control and Case-Crossover Settings: A Systematic Review and Meta-Analysis. *Headache*. 2020;60(6):1132-64.
28. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol*. 2010;11(5):373-84.
29. Rustichelli C, Bellei E, Bergamini S, Monari E, Baraldi C, Castro FL, et al. Serum levels of allopregnanolone, progesterone and testosterone in menstrually-related and postmenopausal migraine: A cross-sectional study. *Cephalalgia*. 2020;40(12):1355-62.
30. Shields LBE, Seifert T, Shelton BJ, Plato BM. Testosterone levels in men with chronic migraine. *Neurol Int*. 2019;11(2):8079.

31. Glaser R, Dimitrakakis C, Trimble N, Martin V. Testosterone pellet implants and migraine headaches: a pilot study. *Maturitas*. 2012;71(4):385-8.
32. Tzabazis A, Kori S, Mechanic J, Miller J, Pascual C, Manering N, et al. Oxytocin and Migraine Headache. *Headache*. 2017;57 Suppl 2:64-75.
33. Warfvinge K, Krause D, Edvinsson L. The distribution of oxytocin and the oxytocin receptor in rat brain: relation to regions active in migraine. *J Headache Pain*. 2020;21(1):10.
34. Crawford MJ, Lehman L, Slater S, Kabbouche MA, LeCates SL, Segers A, et al. Menstrual migraine in adolescents. *Headache*. 2009;49(3):341-7.
35. Mattsson P. Hormonal factors in migraine: a population-based study of women aged 40 to 74 years. *Headache*. 2003;43(1):27-35.
36. Vetvik KG, Macgregor EA, Lundqvist C, Russell MB. Prevalence of menstrual migraine: a population-based study. *Cephalalgia*. 2014;34(4):280-8.
37. Loder E. Menstrual Migraine. *Curr Treat Options Neurol*. 2001;3(2):189-200.
38. Mihm M, Gangooly S, Muttukrishna S. The normal menstrual cycle in women. *Anim Reprod Sci*. 2011;124(3-4):229-36.
39. Cupini LM, Corbelli I, Sarchelli P. Menstrual migraine: what it is and does it matter? *J Neurol*. 2021;268(7):2355-63.
40. Paredes S, Cantillo S, Candido KD, Knezevic NN. An Association of Serotonin with Pain Disorders and Its Modulation by Estrogens. *Int J Mol Sci*. 2019;20(22).
41. Tan PMM, Kriterleri A. MENSTRÜEL MİGREN PATOGENEZİ.
42. Sutherland HG, Champion M, Plays A, Stuart S, Haupt LM, Frith A, et al. Investigation of polymorphisms in genes involved in estrogen metabolism in menstrual migraine. *Gene*. 2017;607:36-40.
43. Rodriguez-Acevedo AJ, Smith RA, Roy B, Sutherland H, Lea RA, Frith A, et al. Genetic association and gene expression studies suggest that genetic variants in the SYNE1 and TNF genes are related to menstrual migraine. *J Headache Pain*. 2014;15(1):62.
44. Downie J, Poyser NL, Wunderlich M. Levels of prostaglandins in human endometrium during the normal menstrual cycle. *J Physiol*. 1974;236(2):465-72.
45. Mannix LK. Menstrual-related pain conditions: dysmenorrhea and migraine. *J Womens Health (Larchmt)*. 2008;17(5):879-91.
46. Mattsson P. Serum levels of androgens and migraine in postmenopausal women. *Clin Sci (Lond)*. 2002;103(5):487-91.
47. Ornello R, De Matteis E, Di Felice C, Caponnetto V, Pistoia F, Sacco S. Acute and Preventive Management of Migraine during Menstruation and Menopause. *J Clin Med*. 2021;10(11).
48. Lay CL, Broner SW. Migraine in women. *Neurol Clin*. 2009;27(2):503-11.
49. Nierenburg Hdcl C, Ailani J, Malloy M, Siavoshi S, Hu NN, Yusuf N. Systematic Review of Preventive and Acute Treatment of Menstrual Migraine. *Headache*. 2015;55(8):1052-71.
50. Maasumi K, Tepper SJ, Kriegler JS. Menstrual Migraine and Treatment Options: Review. *Headache*. 2017;57(2):194-208.

51. MacGregor EA. Menstrual and perimenopausal migraine: A narrative review. *Maturitas*. 2020;142:24-30.
52. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology*. 2006;67(12):2159-63.
53. Ho TW, Ho AP, Ge YJ, Assaid C, Gottwald R, MacGregor EA, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for prevention of headache in women with perimenstrual migraine. *Cephalalgia*. 2016;36(2):148-61.
54. Facchinetti F, Sances G, Borella P, Genazzani AR, Nappi G. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. *Headache*. 1991;31(5):298-301.
55. Massiou H, MacGregor EA. Evolution and treatment of migraine with oral contraceptives. *Cephalalgia*. 2000;20(3):170-4.
56. Macgregor EA, Hackshaw A. Prevention of migraine in the pill-free interval of combined oral contraceptives: a double-blind, placebo-controlled pilot study using natural oestrogen supplements. *J Fam Plann Reprod Health Care*. 2002;28(1):27-31.
57. Li L, Yang X, Tran D, Seo SK, Lu Y. Combined Oral Contraceptives As Victims of Drug Interactions. *Drug Metab Dispos*. 2023;51(6):718-32.
58. Calhoun AH, Batur P. Combined hormonal contraceptives and migraine: An update on the evidence. *Cleve Clin J Med*. 2017;84(8):631-8.
59. Calhoun AH. Hormonal Contraceptives and Migraine With Aura-Is There Still a Risk? *Headache*. 2017;57(2):184-93.
60. ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. *Obstet Gynecol*. 2010;115(1):206-18.
61. MacGregor EA. Migraine, menopause and hormone replacement therapy. *Post Reprod Health*. 2018;24(1):11-8.
62. Allais G, Chiarle G, Sinigaglia S, Mana O, Benedetto C. Migraine during pregnancy and in the puerperium. *Neurol Sci*. 2019;40(Suppl 1):81-91.
63. van Casteren DS, van den Brink AM, Terwindt GM. Migraine and other headache disorders in pregnancy. *Handb Clin Neurol*. 2020;172:187-99.
64. Frederick IO, Qiu C, Enquobahrie DA, Aurora SK, Peterlin BL, Gelaye B, et al. Lifetime prevalence and correlates of migraine among women in a pacific northwest pregnancy cohort study. *Headache*. 2014;54(4):675-85.
65. Robbins MS, Farmakidis C, Dayal AK, Lipton RB. Acute headache diagnosis in pregnant women: a hospital-based study. *Neurology*. 2015;85(12):1024-30.
66. Sandoe CH, Lay C. Secondary Headaches During Pregnancy: When to Worry. *Curr Neurol Neurosci Rep*. 2019;19(6):27.
67. Amundsen S, Nordeng H, Nezvalová-Henriksen K, Stovner LJ, Spigset O. Pharmacological treatment of migraine during pregnancy and breastfeeding. *Nature Reviews Neurology*. 2015;11(4):209-19.
68. Airola G, Allais G, Castagnoli Gabellari I, Rolando S, Mana O, Benedetto C. Non-pharmacological management of migraine during pregnancy. *Neurol Sci*. 2010;31 Suppl 1:S63-5.
69. Rayhill M. Headache in Pregnancy and Lactation. *Continuum (Minneapolis)*. 2022;28(1):72-92.

70. Black E, Khor KE, Kennedy D, Chutatape A, Sharma S, Vancaillie T, et al. Medication Use and Pain Management in Pregnancy: A Critical Review. *Pain Pract.* 2019;19(8):875-99.
71. Turankar T, Sorte A, Wanjari MB, Chakole S, Sawale S. Relation and Treatment Approach of Migraine in Pregnancy and Breastfeeding. *Cureus.* 2023;15(3):e36828.
72. Marchenko A, Etwel F, Olutunfese O, Nickel C, Koren G, Nulman I. Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis. *Headache.* 2015;55(4):490-501.
73. Cohen F, Yuan H, DePoy EMG, Silberstein SD. The Arrival of Anti-CGRP Monoclonal Antibodies in Migraine. *Neurotherapeutics.* 2022;19(3):922-30.
74. Govindappagari S, Grossman TB, Dayal AK, Grosberg BM, Vollbracht S, Robbins MS. Peripheral nerve blocks in the treatment of migraine in pregnancy. *Obstet Gynecol.* 2014;124(6):1169-74.
75. Nezvalová-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *European journal of clinical pharmacology.* 2011;67:1253-61.
76. Wells RE, Turner DP, Lee M, Bishop L, Strauss L. Managing Migraine During Pregnancy and Lactation. *Curr Neurol Neurosci Rep.* 2016;16(4):40.
77. ACE inhibitors, angiotensin II receptor blockers and pregnancy: fetal renal impairment. *Prescrire Int.* 2013;22(142):243.
78. Doyle LW, Anderson PJ, Haslam R, Lee KJ, Crowther C. School-age outcomes of very preterm infants after antenatal treatment with magnesium sulfate vs placebo. *Jama.* 2014;312(11):1105-13.
79. Badell ML, Rimawi BH, Rao AK, Jamieson DJ, Rasmussen S, Meaney-Delman D. Botulism During Pregnancy and the Postpartum Period: A Systematic Review. *Clin Infect Dis.* 2017;66(suppl_1):S30-s7.
80. Calhoun AH. Migraine Treatment in Pregnancy and Lactation. *Curr Pain Headache Rep.* 2017;21(11):46.
81. Parikh SK. Unique Populations with Episodic Migraine: Pregnant and Lactating Women. *Curr Pain Headache Rep.* 2018;22(12):80.
82. Hoshiyama E, Tatsumoto M, Iwanami H, Saisu A, Watanabe H, Inaba N, et al. Postpartum migraines: a long-term prospective study. *Intern Med.* 2012;51(22):3119-23.
83. Hutchinson S, Marmura MJ, Calhoun A, Lucas S, Silberstein S, Peterlin BL. Use of common migraine treatments in breast-feeding women: a summary of recommendations. *Headache.* 2013;53(4):614-27.
84. Townsend RJ, Benedetti TJ, Erickson SH, Cengiz C, Gillespie WR, Gschwend J, et al. Excretion of ibuprofen into breast milk. *Am J Obstet Gynecol.* 1984;149(2):184-6.
85. Pringsheim T, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci.* 2012;39(2 Suppl 2):S1-59.
86. Davanzo R, Bua J, Paloni G, Facchina G. Breastfeeding and migraine drugs. *Eur J Clin Pharmacol.* 2014;70(11):1313-24.
87. Valproic Acid. *Drugs and Lactation Database (LactMed®)*. Bethesda (MD): National Institute of Child Health and Human Development; 2006.

Güncel Nöroloji Çalışmaları IV

88. Ibrahimi K, Couturier EG, MaassenVanDenBrink A. Migraine and perimenopause. *Maturitas*. 2014;78(4):277-80.
89. Bernstein C, O'Neal MA. Migraine and menopause - a narrative review. *Menopause*. 2020;28(1):96-101.
90. Allais G, Chiarle G, Bergandi F, Benedetto C. Migraine in perimenopausal women. *Neurol Sci*. 2015;36 Suppl 1:79-83.
91. Oldenhave A, Jaszmann LJ, Everaerd WT, Haspels AA. Hysterectomized women with ovarian conservation report more severe climacteric complaints than do normal climacteric women of similar age. *Am J Obstet Gynecol*. 1993;168(3 Pt 1):765-71.
92. Misakian AL, Langer RD, Bensenor IM, Cook NR, Manson JE, Buring JE, et al. Postmenopausal hormone therapy and migraine headache. *J Womens Health (Larchmt)*. 2003;12(10):1027-36.
93. Aegidius KL, Zwart JA, Hagen K, Schei B, Stovner LJ. Hormone replacement therapy and headache prevalence in postmenopausal women. The Head-HUNT study. *Eur J Neurol*. 2007;14(1):73-8.
94. Facchinetti F, Nappi RE, Tirelli A, Polatti F, Nappi G, Sances G. Hormone supplementation differently affects migraine in postmenopausal women. *Headache*. 2002;42(9):924-9.