BÖLÜM 21

GEBELİĞE ÖZGÜ KARACİĞER HASTALIKLARI

Ayşegül ÖZEL[1]

GİRİŞ

Gebeliğe özgü karaciğer hastalıkları farklı isimlerde, farklı klinik ve laboratuvar özelliklerde karşımıza çıkmaktadır.Bu hastalıklar başlıca Gebeliğin Akut Yağli Karaciğeri (GAYK), Gebelikte İntrahepatik Kolestaz (İHK), Hiperemesis Gravidarum (HG), Preeklampsi ve HELLP Sendromu olarak değerlendirilmektedir.

GEBELİĞİN AKUT YAĞLI KARACİĞERİ

Tanım, Tarihçe ve Genel Bilgiler

Gebeliği komplike eden, mikrovesiküler yağ infiltrasyonu ile giden, ilk akut karaciğer yetmezliği olgusu 1857'de Tarnier tarafından sunulmuşsa da, hastalığın patolojik tanımlanması 1940'da Sheehan tarafından yapılmıştır (1). 1800'lerin ortalarından 1940'lara dek gebelikte görülen akut karaciğer yetmezliği hastalığının bir anestezik ajan olarak kullanılan kloroform ile ilişkili iyatrojenik olarak veya fulminant seyirli viral hepatit nedeni ile ortaya çıktığı fikri kabul görüyorken, Sheehan' ın sunduğu olgular bunların hiçbiri ile ilişkili değildi. O, karaciğerdeki bu durumu 'obstetrik akut sarı atrofi' olarak tanımladı. Bugün bildiğimiz şekli ile GAYK hastalığını ise ilk kez 1982'de Burroughs ve arkadaşları, sundukları 12 olgu ile literatüre kazandırmışlardır (2). Gebeliklerinin üçüncü trimesterinde olan bu kadınların kardinal semptomları tekrarlayan bulantı, kusma iken 7 hastada sarılık belirmeden önce ortaya çıkan proteinuri, periferik ödem ve hipertansiyon olmuştur. Biyopsi bulguları ise hepatositlerin şişmesine neden olan yaygın mikrovesiküler yağ infilrasyonu, minimal nekroz ve kolestazdır. Bu kadınlarda akut karaciğer hasarı ile ilişkili ensefelopati, ciddi metabollik asidoz, 3 olguda diyaliz gereksinimi olan akut böbrek yetmezliği gelişmiştir. Koagulopati nedeni ile hemoraji, trombositopeni, dolaşımda dev megakaryositler, hemoliz ilişkili normoblastlar yaygın görülen hematolojik bulgular olmuştur.

Epidemiyoloji

GAYK hastalığı insidansı 1/7000-1/20.000 arasında değişmektedir (9-11). Populasyon bazlı çalışmalar yetersiz de olsa, etnik ve coğrafi farklılıkların hastalığın insidansını çok etkilemediği düşünülmektedir. Vakaların çoğu üçüncü trimesterde ortaya çıkmakla birlikte ikinci trimesterde de görülebilir (12).

GAYK hastalığı ile ilişkili risk faktörleri, yağ asidi oksidasyon defektlerinden başka çoğul gebelik, erkek fetus, önceki gebeliğinde GAYK öyküsü, obezite, düşük vücut kitle indeksi, diyabet gibi metabolik hastalıklar, intrahepatik kolestaz, pre-

[1] Doç. Dr. Ayşegül ÖZEL, SBÜ. Ümraniye Eğitim ve Araştırma Hastanesi, Perinatoloji Bölümü, ozelaysegul@hotmail.com

HG tedavisinde non-farmakolojik ve farmakolojik yöntemlerden faydalanılmaktadır.

Preeklampsi; hipertansiyon ile karakterize, multiorgan disfonksiyonuna neden olabilen, gebeliklerin yaklaşık %2-8'inde ortaya çıkan bir hastalıktır. Tüm dünyada maternal morbidite ve mortalitenin önde gelen nedenleri arasında yer alır. Primiparite, çoğul gebelikler, erken ve geç doğurganlık yaşı risk faktörleri arasındadır. Sadece insanlara özgü olan bu hastalığın patofizyolojisi hala tam olarak anlaşılamamıştır. Temelde bir plasentasyon problemi olup spiral arterlerin gebeliğe uyumlu bir şekilde 'remodelling' inin sağlanamaması ile ortaya çıkan uteroplasental hipoperfüzyondur. Oluşan oksidatif stress ile plasentadan salınan serbest radikaller, sitokinler, prostaglandinler ve endotelin, maternal dolaşıma salınarak sistemik vasküler endotelyal disfonksiyona neden olur. Bu durum bazı vakalarda multi organ tutulumuna sebep olur. HELLP (hemolysis, elevated liver enzymes, low platelet) sendromu karaciğerin tutulumu ile karakterize olan bir patoloji olup hepatik iskemi neticesinde subkapsüler hematom, parankimal hemoraji ve hepatik rüptüre kadar varabilen sonuçları ile preeklampsi spekturumunun ciddi seyirli bir hastalığıdır. Gerek preeklampsi gerekse de HELLP sendromunda tek ve kesin tedavi ise; doğumun gerçekleştirilerek plasentanın ortadan kaldırılmasıdır.

KAYNAKLAR

1. David B. Nelson, John J. Byrne, and F. Gary Cunningham.Acute fatty liver of pregnancy. Clinical Obstetrics and Gynecology ,2019; volume 63, number 1, 152–164
2. Burroughs AK, Seong NH, Dojcinov DM, et al. Idiopathic acute fatty liver of pregnancy in 12 patients. Q J Med. 1982;51:481–497.
3. Schoeman MN, Batey RG, Wilcken B: Recurrent acute fatty liver of pregnancy associated with a fatty-acid oxidation defect in the offspring. Gastroenterology 100: 544-548, 1991
4. Strauss AW, Bennett MJ, Rinaldo P, et al. Inherited deficiency and a fetal-maternal interaction complications. Semin Perinatol. 1999;23:100–112.
5. Browning MF, Levy HL, Wilkins-Haug LE, et al. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. Obstet Gynecol. 2006;107:115–120.
6. Tyni T , Ekholm E , Pihko H . Pregnancy complications are frequent in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase defi ciency . Am J Obstet Gynecol 1998 ; 178 : 603 – 8
7. Mansouri A , Fromenty B , Durand F et al. Assessment of the prevalence of genetic metabolic defects in acute fatty liver of pregnancy . J Hepatol 1996 ; 25 : 781.
8. Fukushima K , Ueno Y , Inoue J et al. Lack of common mutation in the alfasubunit of the mitochondrial trifunctional protein and the polymorphism of CYP2E1 in three Japanese women with acute fatty liver of pregnancy/ HELLP syndrome . Hepatol Res 2004 ; 30 : 226 – 31
9. Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. Am J Obstet Gynecol. 2013;209:456.e1–456.e7.
10. Castro MA, Fassett MJ, Reynolds TB, et al. Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. Am J Obstet Gynecol. 1999;18:389–395.
11. Knight M, Nelson-Piercy C, Kurinczuk JJ, et al. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;57:951–956.
12. Monga M, Katz AR. Acute fatty liver in the second trimester. Obstet Gynecol. 1999;93:811–813.
13. Lui J, Ghaziani TT, Wolf JL. Acute fatty liver disease of pregnancy: updates in pathogenesis, diagnosis, and management. Am J Gastroenterol. 2017;112:838–846.
14. Vigil-De Gracia P . Acute fatty liver and HELLP syndrome: two distinct pregnancy disorders . Int J Gynaecol Obstet 2001 ; 73 : 215 – 20 .
15. Ch'ng CL, Morgan M, Hainsworth I, et al. Prospective study of liver dysfunction in pregnancy in Southwester Wales. Gut. 2002;51:876–880.
16. Critical care in pregnancy. ACOG Practice Bulletin No. 211. American College of Obstetricians and Gynecologists. Obstet Gynecol. 2019;133:e303–e319.
17. American College of Obstetricians and Gynecologists: Hypertension in Pregnancy. Report of the American college of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122:1122–1131.
18. Wu Z, Huang P, Gong Y, et al. Treating acute fatty liver of pregnancy with artificial liver support therapy: systematic review. Medicine (Baltimore).2018;97:e12473.
19. Martin JN, Briery NM, Rose CH, et al. Postpartum plasma exchange as adjunctive therapy for severe acute fatty liver of pregnancy. J Clin Apher. 2008;47:113–115.
20. Yu CB, Chen JJ, Du WB, et al. Effects of plasma exchange combined with continuous renal replacement therapy on acute fatty liver of pregnancy. Hepatobiliary Pancreat Dis Int. 2014;13:179–183.
21. Kushner T, Tholey D, Dodge J, et al. Outcomes of liver transplantation for acute fatty liver disease of pregnancy. Am J Transplant. 2019;19:2101–2107.
22. de Naeyer S, Ysebaert D, van Utterbeeck M, et al. Acute fatty liver of pregnancy and molecular absorbent recirculating system (MARS)- therapy: a case report. J Matern Fetal Neonatal Med. 2008;21:587–589.
23. Kenyon AP, Piercy CN, Girling J, et al. Obstetric cholestasis, outcome with active management: a series of 70 cases. BJOG An Int J Obstet Gynaecol. 2002;109:282–288.
24. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol. 2014;124:120–133.
25. Devin D. Smith, Kara M. Rood, Intrahepatic Cholestasis

of Pregnancy Clinical Obstetrics and Gynecology 2019; Volume 63, Number 1, 134–151
26. Fisk NM, Storey GN. Fetal outcome in obstetric cholestasis. Br J Obstet Gynaecol. 1988;95:1137–1143.
27. Alsulyman OM, Ouzounian JG, Ames-Castro M, et al. Intrahepatic cholestasis of pregnancy: perinatal outcome associated with expectant management. Am J Obstet Gynecol. 1996;175 (pt 1):957–960.
28. Reyes H, Gonzalez MC, Ribalta J, et al. Prevalence Chile. Ann Intern Med. 1978;88:487–493.
29. Said HM. Physiology of the Gastrointestinal Tract, Sixth Edition. 2018:1–2.
30. Abu-Hayyeh S, Papacleovoulou G, Lövgren-Sandblom A, et al. Intrahepatic cholestasis of pregnancy levels of sulfated progesterone metabolites inhibit farnesoid X receptor resulting in a cholestatic phenotype. Hepatology. 2013;57:716–726.
31. Chen Y, Vasilenko A, Song X, et al. Estrogen and estrogen receptor-α-mediated transrepression of bile salt export pump. Mol Endocrinol. 2015;29: 613–626.
32. Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancy-current achievements and unsolved problems. World J Gastroenterol. 2008;14: 5781–5788.
33. Wasmuth HE, Glantz A, Keppeler H, et al. Intrahepatic cholestasis of pregnancy: the severe form is associated with common variants of the hepatobiliary phospholipid transporter ABCB4 gene. Gut. 2007;56:265–270.
34. Barnes S, Gallo GA, Trash DB, et al. Diagnostic value of serum bile acid estimations in liver disease. J Clin Pathol. 1975;28:506–509.
35. Glantz A, Marschall HU, Mattsson LÅ. Intrahepatic cholestasis of pregnancy: relationships between bile acid levels and fetal complication rates. Hepatology. 2004;40:467–474.
36. Ovadia C, Seed PT, Sklavounos A, et al. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet. 2019;393:899–909.
37. Bergasa NV. The pruritus of cholestasis. Semin Cutan Med Surg. Available at: https://doi.org/10. 1002/hep.27582.
38. Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2009;15: 2049–2066.
39. Wikström Shemer E, Marschall HU, Ludvigsson JF, et al. Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study. BJOG An Int J Obstet Gynaecol. 2013;120:717–723.
40. Marschall HU, Wikström Shemer E, Ludvigsson JF, et al. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population-based cohort study. Hepatology. 2013. Available at: https://doi.org/10.1002/hep.26444.
41. Williamson C, Miragoli M, Sheikh Abdul Kadir S, et al. Bile acid signaling in fetal tissues: Implications for intrahepatic cholestasis of pregnancy. Dig Dis. 2011;29:58–61.
42. Geenes V, Chappell LC, Seed PT, et al. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology. 2014;59:1482–1491.
43. Zecca E, De Luca D, MarrasM, et al. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome. Pediatrics. 2006;117:1669–1672.
44. Snape WJ, Shiff S, Cohen S. Effect of deoxycholic acid on colonic motility in the rabbit. Am J Physiol Liver Physiol. 1980;1:321–325.
45. Bacq Y, Sentilhes L, Reyes HB, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology. 2012;143:1492–1501.
46. Gurung V, Stokes M, Middleton P, et al. Interventions for treating cholestasis in pregnancy. Cochrane Database Syst Rev. 2013. Available at: https://doi.org/10.1002/14651858.CD000493. pub2.
47. Kong X, Kong Y, Zhang F, et al. Evaluating the effectiveness and safety of ursodeoxycholic acid in treatment of intrahepatic cholestasis of pregnancy: a meta-analysis (a prisma-compliant study). Med (United States). 2016. Available at: https://doi.org/10.1097/MD.0000000000004949.
48. Chappell LC, Bell JL, Smith A, et al. Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial. Lancet. 2019;394:849–860.
49. Prince MI, Burt AD, Jones DEJ.Hepatitis and liver dysfunction with rifampicin therapy for pruritus in primary biliary cirrhosis. Gut. 2002;50:436–439.
50. Puljic A, Kim E, Page J, et al. The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. Am J Obstet Gynecol. 2015;212:667.e1–667.e
51. ACOG Committee Opinion. Medically indicated late-preterm and early-term deliveries. Obstet Gynecol.2019. Available at: https://doi.org/10.1097/AOG.0000000000003083.
52. Fairweather, D. V. Nausea and vomiting in pregnancy. Am. J. Obstet. Gynecol. 1968;102: 135–175.
53. Fejzo MS, Trovik J, Grooten IJ, Sridharan K, Roseboom TJ, Vikanes A, Painter RC, Mullin PM. Nausea and vomiting of pregnancy and hyperemesis gravidarum. Nat Rev Dis Primers. 2019 Sep 12;5(1):62. doi: 10.1038/s41572-019-0110-3.
54. Lacroix, R., Eason, E., Melzack, R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and patterns of change. Am. J. Obstet. Gynecol. 2000;182: 931–937.
55. Källén, B. Hyperemesis during pregnancy and delivery outcome: a registry study. Eur. J. Obstet. Gynecol. Reprod. Biol. 1987;26: 291–302.
56. Zhang, J., Cai, W. W. Severe vomiting during pregnancy: antenatal correlates and fetal outcomes.Epidemiology 1991;2, 454–457.
57. Grjibovski, A. M., Vikanes, A., Stoltenberg, C., Magnus, P. Consanguinity and the risk of hyperemesis gravidarum in Norway. Acta Obstet. Gynecol. Scand. 2008;87, 20–25.
58. Smith JA, Fox KA, Clark SM. Nausea and vomiting of pregnancy: Clinical findings and evaluation. UpToDate 2020; Jul.
59. Bustos, M., Venkataramanan, R.,Caritis, S. Nausea and

vomiting of pregnancy - what's new? Auton. Neurosci. 2017;202, 62–72.
60. Corey LA, Berg K, Solaas MH, Nance WE. The epidemiology of pregnancy complications and outcome in a Norwegian twin population. Obstet Gynecol. 1992; 80:989–994.
61. Vikanes, A. et al. Recurrence of hyperemesis gravidarum across generations: population based cohort study. BMJ 2010;340, c2050.
62. Fejzo, M. S. et al. Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum. Nat. Commun.2018; 9:1178.
63. Niemeijer, M. N. et al. Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis. Am. J. Obstet. Gynecol.2014; 211:150.e1-15.
64. Grooten, I. J. et al. Helicobacter pylori infection:a predictor of vomiting severity in pregnancy and adverse birth outcome. Am. J. Obstet. Gynecol.2017; 216:512.e1–512.e9.
65. Lacasse A, Rey E, Ferreira E, Morin C, Bérard A. Validity of a modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) scoring index to assess severity of nausea and vomiting of pregnancy. Am J Obstet Gynecol 2008;198:71.e1-71.e7
66. Tian, R., MacGibbon, K., Martin, B., Mullin, P., Fejzo, M. Analysis of pre- and post- pregnancy issues in women with hyperemesis gravidarum. Auton. Neurosci. 2017;202: 73–78.
67. Oudman, E. et al. Wernicke's encephalopathy in hyperemesis gravidarum: a systematic review. Eur. J. Obstet. Gynecol. Reprod. Biol. 2019;236: 84–93.
68. Lane, A. S., Stallworth, J. L., Eichelberger, K. Y.,Trofatter, K. F. Vitamin K deficiency embryopathy from hyperemesis gravidarum. Case Rep. Obstet. Gynecol. 2015;2015:324173.
69. Fejzo, M. S., Magtira, A., Schoenberg, F. P.,Macgibbon, K., Mullin, P. M. Neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum. Eur. J. Obstet. Gynecol. Reprod. Biol.2015;189: 79–84.
70. Fejzo, M., Kam, A., Laguna, A., MacGibbon, K., Mullin, P. Analysis of neurodevelopmental delay in children exposed in utero to hyperemesis gravidarum reveals increased reporting of autism spectrum. Reprod Toxicol. 2019 Mar;84:59-64.
71. Roman, E. et al. Perinatal and reproductive factors: a report on haematological malignancies from the UKCCS. Eur. J. Cancer 2005;41:749–759.
72. Committee on Practice Bulletins- Obstetrics. ACOG practice bulletin No. 189: nausea and vomiting of pregnancy. Obstet. Gynecol. 2018;131:e15–e30.
73. Matthews A, Haas DM, O'Mathuna DP, Dowswell T. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2015; 9:CD007575.
74. Skuladottir H, Wilcox AJ, Ma C, Lammer EJ, Rasmussen SA, Werler MM, Shaw GM, Carmichael SL. Corticosteroid use and risk of orofacial clefts. Birth Defects Res A Clin Mol Teratol. 2014; 100:499–506.
75. Gill SK, Maltepe C, Mastali K, Koren G. The effect of acid-reducing pharmacotherapy on the severity of nausea and vomiting of pregnancy. Obstet Gynecol Int. 2009;2009:585269.
76. Steegers EA, von Dadelszen P, Duvekot JJ, et al. Pre-eclampsia. Lancet.2010;376:631–644.
77. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33:130–137.
78. ACOG Practice Bulletin No. 202: gestational hypertension and preeclampsia. Obstet Gynecol. 2019;133:e1–e25.
79. Payne B, Magee LA, von Dadelszen P Assessment, surveillance and prognosis in pre-eclampsia. Best Pract Res Clin Obstet Gynaecol. 2011 Aug;25(4):449-62.
80. Visintin C, Mugglestone MA, Almerie MQ, Nherera LM, James D, Walkinshaw S, Guideline Development Group Management of hypertensive disorders during pregnancy: summary of NICE guidance. BMJ. 2010;341:c2207.
81. Bartsch E, Medcalf KE, Park AL, Ray JG, High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353:i1753
82. Sircar M, Thadhani R, Karumanchi SA. Pathogenesis of preeclampsia. Curr Opin Nephrol Hypertens. 2015;24:131–138.
83. Myatt L. Role of placenta in preeclampsia. Endocrine. 2002;19(1):103.
84. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. Semin Nephrol.2011;31(1):33
85. LisonkovaS,JosephKS. Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease. Am J Obstet Gynecol. 2013 Dec;209(6):544.e1-544.e12.
86. Mifsud W, Sebire NJ. Placental pathology in early-onset and late-onset fetal growth restriction. Fetal Diagn Ther. 2014;36(2):117-28. Epub 2014 2 21.
87. FrankWolf M, Peleg D, Kariv Silberstein N, et al. Correlation between changes in liver stiffness and preeclampsia as shown by transient elastography. Hypertens Pregnancy. 2016;35:536–541.
88. Chandrasekaran S, Simon R. Hepatic Complications in Preeclampsia. Clin Obstet Gynecol. 2020 Mar;63(1):165-174.
89. Alese MO, Moodley J, Naicker T. Preeclampsia and HELLP syndrome, the role of the liver. J Matern Fetal Neonatal Med. 2019;31:1–7.
90. Morton A. Imitators of preeclampsia: a review. Pregnancy Hypertens. 2016;6:1–9.
91. Sibai BM. Imitators of severe preeclampsia. Pregnancy Hypertens. 2011;1:238–9.
92. Vigil-De Gracia P . Acute fatty liver and HELLP syndrome: two distinct pregnancy disorders . Int J Gynaecol Obstet 2001 ; 73 : 215 – 20 .
93. Ditisheim A, Sibai BM. Diagnosis and management of HELLP syndrome complicated by liver hematoma. Clin Obstet Gynecol. 2017;60:190–7.