

## BÖLÜM 14

# Doğum Eylemi ve Doğumla İlgili Mikrobiyom

Holly Jenkins ve Matthew Hyde

Çeviren: Hacer Yalnız Dilcen

### Giriş

İnsan vücudundan yaşayan mikroorganizma popülasyonunu temsil etmek için verilen bir terim olan insan mikrobiyomu, uzun zamandır sağlık ve hastalık ile ilişkilendirilmiştir.<sup>1</sup> İnsan mikrobiyomlarının en büyüğü ve en çok araştırılanı bağırsak mikrobiyomudur. Bağırsak mikrobiyomu, temel koruyucu, yapısal, metabolik ve immüโนlojik işlevleri yerine getirmek için konakçıyla ortak yaşam geliştiren karmaşık bir mikrobiyal topluluktur.<sup>2</sup>

Mikrobiyomda yapılan değişiklikler patolojik olabilir ve sağlıklı bir bağırsak mikrobiyomunun nasıl geliştirilip sürdürülüğünü anlamak önemlidir.

Bu bölüm, yaşamın erken dönemlerinde bağırsak mikrobiyotasının (belirlenmiş bir ortamda bulunan mikroorganizmalar) gelişimi hakkında bilinenlere ve özellikle doğum eylemi ve doğum sürecinin etkisine odaklanacaktır.<sup>3</sup>

### Bağırsak mikrobiyotasının kökenleri

Bakteri kolonizasyonunun nasıl ve ne zaman başladığı hâlâ tartışılmaktadır. Daha önceki çalışmalar amniyotik sıvıda, göbek kordonu kanında, plasenta dokusunda, fetal membranlarda ve mekonyumda bakteri varlığına dair kanıt sağlamıştır.<sup>4-8</sup> Örneğin Aagard vd. (2014) tarafından yapılan bir çalışma, plasentanın patojenik olmayan benzersiz bakteri türlerini barındırdığını ortaya koymuştur.<sup>9</sup> Bununla birlikte, bu bulgular, plasenta numunelerini negatif kontrollerden ayırmayı başaramayan diğer gruplar tarafından ağır bir şekilde eleştirilmiştir.<sup>10,11</sup> Benzer şekilde, Lim vd. (2018), sağlıklı term gebeliklerden alınan amniyotik sıvının saptanabilir bakteri türleri barındımadığını göstermiştir.<sup>12</sup> Buna karşılık, mekonyumun *Bacilli* ve *Firmicutes* türleri tarafından karakterize edildiği gösterilmiştir.<sup>3,7,9</sup> Tespit edilen bakterilerin canlı

## Kaynaklar

1. Manor O, Borenstein E. Systematic Characterization and Analysis of the Taxonomic Drivers of Functional Shifts in the Human Microbiome. *Cell Host Microbe*. 2017;21(2): 254–267.
2. Kinross JM, Darzi AW, Nicholson JK. Gut microbiome-host interactions in health and disease. *Gen Med*. 2011;3(3): 14.
3. Marchesi JR, Ravel J. The vocabulary of microbiome research: a proposal. *Microbiome*. 2015;3(1): 31.
4. Ardisson AN, de la Cruz DM, Davis-Richardson AG, Rechcigl KT, Li N, Drew JC, et al. Meconium Microbiome Analysis Identifies Bacteria Correlated with Premature Birth. *PLoS ONE*. 2014;9(3): e90784.
5. Neu J, Rushing J. Cesarean versus Vaginal Delivery: Long term infant outcomes and the Hygiene Hypothesis. *Clin Perinatol*. 2011;38(2): 321–331.
6. Watts DH, Krohn MA, Hillier SL, Eschenbach DA. The association of occult amniotic fluid infection with gestational age and neonatal outcome among women in preterm labor. *Obstet Gynecol*. 1992;79(3): 351–357.
7. Gritz EC, Bhandari V. The Human Neonatal Gut Microbiome: A Brief Review. *Front Pediatr*. 2015;3.
8. Rodriguez JM, Murphy K, Stanton C, Ross RP, Kober OI, Juge N, et al. The composition of the gut microbiota throughout life, with an emphasis on early life. *Microb Ecol Health Dis*. 2015;26: 26050.
9. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J versalovic J. The placenta harbors a unique microbiome. *Sci Transl Med*. 2014;6(237): 237ra65.
10. Lauder AP, Roche AM, Sherrill-Mix S, Bailey A, Laughlin AL, Bittinger K, et al. Comparison of placenta samples with contamination controls does not provide evidence for a distinct placenta microbiota. *Microbiome*. 2016;4(1): 29.
11. Leiby JS, McCormick K, Sherrill-Mix S, Clarke EL, Kessler LR, Taylor LJ, et al. Lack of detection of a human placenta microbiome in samples from preterm and term deliveries. *Microbiome*. 2018;6(1): 196.
12. Lim ES, Rodriguez C, Holtz LR. Amniotic fluid from healthy term pregnancies does not harbor a detectable microbial community. *Microbiome*. 2018;6(1): 87.
13. Romano-Keeler J, Weitkamp J-H. Maternal influences on fetal microbial colonization and immune development. *Pediatr Res*. 2015;77(1–2): 189–195.
14. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome development: mom matters. *Trends Mol Med*. 2015;21(2): 109–117.
15. Jost T, Lacroix C, Braegger CP, Chassard C. New Insights in Gut Microbiota Establishment in Healthy Breast Fed Neonates. *PLoS ONE*. 2012;7(8): e44595.
16. Fujimura KE, Slusher NA, Cabana MD, Lynch S V. Role of the gut microbiota in defining human health. *Expert Rev Anti Infect Ther*. 2010;8(4): 435–454.
17. Guaraldi F, Salvatori G. Effect of Breast and Formula Feeding on Gut Microbiota Shaping in Newborns. *Frontiers in Cellular and Infection Microbiology*. 2012;2: 94.
18. Miclat NN, Hodgkinson R, Marx GF. Neonatal gastric pH. *Anesth Analg*. 1978;57(1): 98–101.
19. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA*. 2010;107(26): 11971–11975.
20. Shin H, Pei Z, Martinez KA, Rivera-Vinas JI, Mendez K, Cavallin H, et al. The first microbial environment of infants born by C-section: the operating room microbes. *Microbiome*. 2015;3(1): 59.
21. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, et al. Factors Influencing the Composition of the Intestinal Microbiota in Early Infancy. *Pediatrics*. 2006;118(2): 511–521.
22. Biasucci G, Rubini M, Riboni S, Morelli L, Bessi E, Retetangos C. Mode of delivery affects the bacterial community in the newborn gut. *Early Hum Dev*. 2010;86(1): 13–15.
23. Fanaro S, Chierici R, Guerrini P, Vigi V. Intestinal microflora in early infancy: composition and development. *Acta Paediatr Suppl*. 2003;91(441): 48–55.

24. Madan J, Hoen A, Lundgren S, Al E. Association of cesarean delivery and formula supplementation with the intestinal microbiome of 6-week-old infants. *JAMA Pediatr.* 2016;170(3): 212–219.
25. Hyde MJ, Mostyn A, Modi N, Kemp PR. The health implications of birth by Caesarean section. *Biol Rev Camb Philos Soc.* 2012;87(1): 229–243.
26. Hyde MJ, Griffin JL, Herrera E, Byrne CD, Clarke L, Kemp PR. Delivery by Caesarean section, rather than vaginal delivery, promotes hepatic steatosis in piglets. *Clin Sci (Lond).* 2009;118(1): 47–59.
27. Pistiner M, Gold DR, Abdulkirim H, Hoffman E, Celedon JC. Birth by cesarean section, allergic rhinitis, and allergic sensitization among children with a parental history of atopy. *J Allergy Clin Immunol.* 2008;122(2): 274–279.
28. Huh SY, Rifas-Shiman SL, Zera CA, Edwards JWR, Oken E, Weiss ST, et al. Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study. *Arch Dis Child.* 2012;97(7): 610–616.
29. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy.* 2008;38(4): 629–633.
30. Riiser A. The human microbiome, asthma, and allergy. *Allergy Asthma Clin Immunol.* 2015;11: 35.
31. Chu DM, Ma J, Prince AL, Antony KM, Seferovic MD, Aagaard KM. Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. *Nat Med.* 2017;23(3): 314–326.
32. Stewart CJ, Embleton ND, Clements E, Luna PN, Smith DP, Fofanova TY, et al. Cesarean or Vaginal Birth Does Not Impact the Longitudinal Development of the Gut Microbiome in a Cohort of Exclusively Preterm Infants. *Front Microbiol.* 2017;8: 1008.
33. Gregory KE, Samuel BS, Houghteling P, Shan G, Ausubel FM, Sadreyev RI, et al. Influence of maternal breast milk ingestion on acquisition of the intestinal microbiome in preterm infants. *Microbiome.* 2016;4(1): 68.
34. Rodriguez JM. The Origin of Human Milk Bacteria: Is There a Bacterial Enter-Mammary Pathway during Late Pregnancy and Lactation? *Adv Nutr.* 2014;5(6): 779–784.
35. Rodriguez JM. The Origin of Human Milk Bacteria: Is There a Bacterial Enter-Mammary Pathway during Late Pregnancy and Lactation? *Adv Nutr.* 2014;5(6): 779–784.
36. Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: A review on its composition and bioactivity. *Early Hum Dev.* 2015;91(11): 629–635.
37. Meier P, Patel A, Esquerra-Zwiers A. Donor Human Milk Update: Evidence, Mechanisms and Priorities for Research and Practice. *J Pediatr.* 2017;180: 15–21.
38. Gale C, Logan KM, Santhakumaran S, Parkinson JR, Hyde MJ, Modi N. Effect of breastfeeding compared with formula feeding on infant body composition: a systematic review and meta-analysis. *Am J Clin Nutr.* 2012;95(3): 656–669.
39. Fallani M, Young D, Scott J, Norin E, Amarri S, Adam R, et al. Intestinal microbiota of 6-week-old infants across Europe: geographic influence beyond delivery mode, breast-feeding, and antibiotics. *J Pediatr Gastroenterol Nutr.* 2010;51(1): 77–84.
40. Groer MW, Luciano AA, Dishaw LJ, Ashmeade TL, Miller E, Gilbert JA. Development of the preterm infant gut microbiome: a research priority. *Microbiome.* 2014;2: 38.
41. Prior E, Santhakumaran S, Gale C, Philippis LH, Modi N, Hyde MJ. Breastfeeding after cesarean delivery: a systematic review and meta-analysis of world literature. *Am J Clin Nutr.* 2012;95(5): 1113–1135.
42. NICE Guidelines. *Caesarean Section (update).* 2012. Available from <https://www.nice.org.uk/guidance/cg132> [Accessed Feb 2017].
43. Azad M, Konya T, Persaud R, Guttman D, Chari R, Field C, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG.* 2015;123(6): 983–93.
44. Arboleya S, Sánchez B, Milani C, Duranti S, Solís G, Fernández N, et al. Intestinal microbiota development in preterm neonates and effect of perinatal antibiotics. *J Pediatr.* 2015;166(3): 538–544.
45. Jauréguy F, Carton M, Panel P, Foucaud P, Butel M-J, Doucet-Populaire F. Effects of Intrapar-

- tum Penicillin Prophylaxis on Intestinal Bacterial Colonization in Infants. *J Clin Microbiol.* 2004;42(11): 5184–5188.
- 46. NICE Guidelines (2012) *Neonatal infection : antibiotics for prevention and treatment*. Available from <https://www.nice.org.uk/guidance/cg149> [Accessed Feb 2017].
  - 47. Munyaka PM, Eissa N, Bernstein CN, Khafipour E, Ghia J-E. Antepartum Antibiotic Treatment Increases Offspring Susceptibility to Experimental Colitis: A Role of the Gut Microbiota. *PLoS ONE.* 2015;10(11): e0142536.
  - 48. Gibson MK, Crofts TS, Dantas G. Antibiotics and the developing infant gut microbiota and resistome. *Curr Opin Microbiol.* 2015;27: 51–56.
  - 49. Westerbeek EAM, van den Berg A, Lafeber HN, Knol J, Fetter WPF, van Elburg RM. The intestinal bacterial colonisation in preterm infants: A review of the literature. *Clinl Nutr.* 2006;25(3): 361–368.
  - 50. Alexander VN, Northrup V, Bizzarro MJ. Antibiotic Exposure in the Newborn Intensive Care Unit and the Risk of Necrotizing Enterocolitis. *J Pediatr.* 2011;159(3): 392–397.
  - 51. Brooks B, Firek BA, Miller CS, Sharon I, Thomas BC, Baker R, et al. Microbes in the neonatal intensive care unit resemble those found in the gut of premature infants. *Microbiome.* 2014;2(1): 1.
  - 52. Schwierz A, Gruhl B, Lobitz M, Michel P, Radke M, Blaut M. Development of the intestinal bacterial composition in hospitalized preterm infants in comparison with breast-fed, full-term infants. *Pediatr Res.* 2003;54(3): 393–399.
  - 53. Unger S, Stintzi A, Shah P, Mack D, O'Connor DL. Gut microbiota of the very-low-birth-weight infant. *Pediatr Res.* 2015;77(1–2): 205–213.
  - 54. Delnord M, Blondel B, Drewniak N, Klungsøyr K, Bolumar F, Mohangoo A, et al. Varying gestational age patterns in cesarean delivery: an international comparison. *BMC Preg Childbirth.* 2014;14(1): 321.
  - 55. Magne F, Abely M, Boyer F, Morville P, Pochart P, Suau A. Low species diversity and high interindividual variability in faeces of preterm infants as revealed by sequences of 16S rRNA genes and PCR-temporal temperature gradient gel electrophoresis profiles. *FEMS Microbiol Ecol.* 2006;57(1): 128–138.
  - 56. Aujoulat F, Roudière L, Picaud J-C, Jacquot A, Filleron A, Neveu D, et al. Temporal dynamics of the very premature infant gut dominant microbiota. *BMC Microbiol.* 2014;14(1): 325.
  - 57. Combellick JL, Shin H, Shin D, Cai Y, Hagan H, Lacher C, et al. Differences in the fecal microbiota of neonates born at home or in the hospital. *Sci Rep.* 2018;8(1): 15660.
  - 58. Fehervary P, Lauinger-Lorsch E, Hof H, Melchert F, Bauer L, Zieger W. Water birth: microbiological colonisation of the newborn, neonatal and maternal infection rate in comparison to conventional bed deliveries. *Arch Gynecol Obstet.* 2004;270(1): 6–9.
  - 59. Stewart CJ, Skeath T, Nelson A, Fernstad SJ, Marrs ECL, Perry JD, et al. Preterm gut microbiota and metabolome following discharge from intensive care. *Sci Rep.* 2015;5: 17141.
  - 60. Goedert JJ, Hua X, Yu G, Shi J. Diversity and Composition of the Adult Fecal Microbiome Associated with History of Cesarean Birth or Appendectomy: Analysis of the American Gut Project. *EBioMedicine.* 2014;1(2–3): 167–172.
  - 61. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev Immunol.* 2009;9(5): 313–323.
  - 62. Belkaid Y, Hand T. Role of the Microbiota in Immunity and inflammation. *Cell.* 2014;157(1): 121–141.
  - 63. Ngoc PL, Gold DR, Tzianabos AO, Weiss ST, Celedon JC. Cytokines, allergy, and asthma. *Curr Opin Allergy Clin Immunol.* 2005;5(2): 161–166.
  - 64. Fujimura KE, Sitari AR, Havstad S, Lin DL, Levan S, Fadrosh D, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med.* 2016;22(10): 1187–1191.
  - 65. Paun A, Danska JS. Modulation of type 1 and type 2 diabetes risk by the intestinal microbiome. *Pediatr Diabetes.* 2016;17(7): 469–477.
  - 66. Needell JC, Zipris D. The Role of the Intestinal Microbiome in Type 1 Diabetes Pathogenesis. *Curr Diab Rep.* 2016;16(10): 89.

67. Garcia-Mantrana I, Collado MC. Obesity and overweight: Impact on maternal and milk microbiome and their role for infant health and nutrition. *Mol Nutr Food Res.* 2016;60(8): 1865–1875.
68. Knoll RL, Forslund K, Kultima JR, Meyer CU, Kullmer U, Sunagawa S, et al. Gut microbiota differs between children with Inflammatory Bowel Disease and healthy siblings in taxonomic and functional composition - a metagenomic analysis. *Am J Physiol Gastro Liver Physiol.* 2016; ajpgi.00293.2016.
69. Van den Abbeele P verstraete W, El Aidy S, Geirnaert A, Van de Wiele T. Prebiotics, faecal transplants and microbial network units to stimulate biodiversity of the human gut microbiome. *Microbl Biotech.* 2013;6(4): 335–340.
70. Rohlke F, Stollman N. Fecal microbiota transplantation in relapsing Clostridium difficile infection. *Therap Adv Gastroenterol.* 2012;5(6): 403–420.
71. Mullish BH, Marchesi JR, Thiersz MR, Williams HRT. Microbiome manipulation with faecal microbiome transplantation as a therapeutic strategy in Clostridium difficile infection. *QJM.* 2015;108(5): 355–359.
72. Juul FE, Garborg K, Brethauer M, Skudal H, Øines MN, Wiig H, et al. Fecal Microbiota Transplantation for Primary Clostridium difficile Infection. *NEJM.* 2018;378(26): 2535–2536.
73. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, Cox LM, Amir A, Gonzalez A, et al. Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer. *Nat Med.* 2016;22(3): 250–253.
74. Cunnington AJ, Sim K, Deierl A, Kroll JS, Brannigan E, Darby J. ‘Vaginal Seeding’ of infants born by caesarean section. *BMJ.* 2016;352.
75. Stinson LF, Payne MS, Keelan JA. A Critical Review of the Bacterial Baptism Hypothesis and the Impact of Cesarean Delivery on the Infant Microbiome. *Front Med.* 2018;5: 135.