Korean J Gastroenterol Vol. 78 No. 1, 3-8
https://doi.org/10.4166/kjg.2021.408
pISSN 1598-9992 eISSN 2233-6869

SPECIAL ARTICLE

유아기 성장환경과 장내미생물총 발달

정수진
차의과학대학교 분당차병원 소아청소년과

Early Life Events and Development of Gut Microbiota in Infancy

SuJin Jeong
Division of Gastroenterology and Nutrition of Pediatrics, CHA Bundang Medical Center, CHA University, Seongnam, Korea

With its dynamic composition and function, the gut microbiome plays a key role in human development and long-term health. The first 2 years of life are crucial to the early establishment of the gut microbiome. During early life, the gut microbial composition rapidly changes and multiple factors influence the initial colonization, development, and function of the neonatal gut microbiome. In addition, alterations in early-life gut microbial composition linked to necrotizing enterocolitis in infancy, as well as some chronic diseases in later, including obesity, inflammatory bowel disease, cancer, allergies, asthma, and neurological diseases associated with the gut-brain axis. In this review, we focus on both maternal and infant factors known to influence early-life gut colonization. **(Korean J Gastroenterol 2021;78:3-8)**

Key Words: Gut microbiome; Chronic diseases; Maternal factors; Infant factors

INTRODUCTION

The human gut is a vast and diverse community of bacteria, fungi, archaea, and viruses collectively known as the gut microbiota.[1] The gut microbiota assists with essential nutrient synthesis and absorption,[2,3] generates short-chain fatty acids that serve as an energy source for colonocytes,[4-6] maintains the intestinal mucosal barrier and protects against pathogenic bacteria and endotoxin translocation, stimulates immune-system maturation,[7] provides anti-inflammatory signals to the host,[8] during a critical developmental window in early life.[9] Markedly, multiple studies of mother-infant have indicated the existence of vertical transmission of microbes from mother to infant that can contribute to colonizing microbiota.[10,11] During early life, the gut microbial composition rapidly changes by maternal microbiota composition, delivery mode, infant feeding mode, antibiotic usage, and various environmental factors, such as the presence of pets and siblings.[12] Disruption in the gut microbiota (ie, gut dysbiosis) has been linked to necrotizing enterocolitis in infancy, as well as some chronic diseases in later, including obesity, diabetes, inflammatory bowel disease, cancer, allergies, asthma,[13] and

Received March 15, 2021. **Revised** April 2, 2021. **Accepted** April 6, 2021.

교신저자: 정수진, 13496, 성남시 분당구 야탑로 59, 차의과학대학교 분당차병원 소아청소년과
Correspondence to: SuJin Jeong, Division of Gastroenterology and Nutrition of Pediatrics, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea. Tel: +82-31-780-5230, Fax: +82-31-780-5239, E-mail: jinped@cha.ac.kr, **ORCID:** https://orcid.org/0000-0002-7388-8368

Financial support: None. Conflict of interest: None.

*이 종설은 2021 대한소화기학회 춘계학술대회 강의록에 기초하였으며, 대한소화기학회 편집위원회에서 대한소화기학회지에 특별기고로 게재하는 것에 동의함(This manuscript is based on 2021 Spring Seminar of the Korean Society of Gastroenterology. The Editorial Board of Korean J Gastroenterol agreed to publish this manuscript to Korean J Gastroenterol as a special article).

neurological diseases associated with the gut-brain axis.[14] This review will focus on the process of early colonization, understanding the factors influencing microbial colonization of the infant gut.

MAIN BODY

1. Colonization of fetus gut

Basically, the uterus and fetus are considered sterile environments unless clinical infection occurs, such as in chorioamnionitis; however, growing body of evidence indicates that the intrauterine environment is not sterile, but that maternal-fetal transmission of microbiota occurs during pregnancy. Nonpathogenic bacteria are detected in the placenta, umbilical cord,[15,16] and the meconium of the healthy newborns, independent of birth mode of delivery,[17] and its composition is associated with the gestational age. Intrauterine infection has been reported to be associated with a leaky gut, confirmed by finding maternal gut microbes in the amniotic fluid of women with premature membrane rupture.[18] This suggests microbial translocation from a maternal leaky gut to the uterus and placenta. But this hypothesis remains controversial up to this day. Certainly, debate will continue on whether or not microbial colonization occurs in utero and well controlled, large cohort studies are essential to ensure that the data produced is robust and reliable.

2. Maternal obesity and nutrition Influencing early colonization

Obesity is characterized with an imbalance in the *Firmicutes*-to-*Bacteroidetes* ratio in the gut.[19,20] Birth cohort studies disclose that infants born from overweight or obese mothers were profusely colonized with the bacterial genera belonging to the phyla *Firmicutes*, mainly of the *Lachnospiraceae* family, and three times more likely to be overweight by 1 year of age, which increases to 5 times in infants born by cesarean section (C-section).[21] Weight gain during pregnancy is a normal physiological response, however, excessive gestational weight gain (defined as 16 kg or above for women with BMI 19.8-25 or above 11.5 for women with BMI >25) has been shown to result in the increased relative expansion of *Bacteroides*,[22] *Enterobacteriaceae*, and *E. coli* and a reduction in *Bifidobacterium* and *Akkermansia muciniphila*.[23] Moreover, metagenomics analysis has shown that gestational weight gain impacts on the function of the infant microbiome[24] by significant reduction in the community of bacteria involved in metabolic signaling and energy regulation, including *Enterococcus*, *Acinetobacter*, *Pseudomonas*, and *Hydrogenophilus*. Infant gut dysbiosis associated with maternal obesity has been shown to increase gut permeability and directly initiate pathways of nonalcoholic fatty liver disease.[25] C-section–delivered infants from overweight mothers are at higher risk of becoming overweight later in life than infants born vaginally to overweight or obese mothers.[21,26]

Maternal weight status also might affect maternal milk composition.[27,28] Cabrera-Rubio et al.[29] noticed higher total bacterial counts, expansion of *Staphylococcus* and *Lactobacillus*, and reduced levels of *Bifidobacterium* in the milk of obese compared with normal weight women during the first 6 months of lactation. It suggested an additional mechanism explaining the intensified obesity risk in infants born to obese and overweight mothers.

Longitudinal cohort data showed that a maternal high-fat diet altered early bacterial colonization independent of maternal obesity.[30] In association with a maternal high-fat diet, the neonatal meconium microbiome varied with a significant relative depletion in *Bacteroides* immediately, which persisted until 6 weeks of age.[30] A maternal high-fat diet rather than just maternal obesity profoundly impact on shaping the gut microbiota early in life.[31] A combination of a high-fat/high-sugar diet led to gut dysbiosis in mice[32] and dietary intake of refined sugars modulate the gut microbial composition to that of an inflammatory-type microbiota.[33] Since maternal milk microbiota is hypothesized to originate from maternal gut microbiota, the gut dysbiosis associated with the maternal diet might be transferred to maternal milk and further exacerbate dysbiosis seen in the early gut microbiome in breastfed infants. However, research investigating long-term impact of maternal lifestyle and health status during gestation and lactation on the infant's gut microbiota is lacking.

3. Delivery mode

Mode of delivery is generally accepted as a major factor determining initial colonization.[34] Infant born by C-section can have altered immune development and are at a higher risk for numerous non communicable diseases such as obesity, allergy, asthma, and atopy.[35] Infants delivered vaginally are colonized with bacteria present in the maternal vagina,[34]

whereas those delivered by C-section are colonized with bacteria similar to maternal skin and oral cavity.[36,37] Although most vaginal and skin bacteria do not seem to take hold in the infant gut, their presence may differentially affect the colonization abilities of other bacteria. Longer period studies that have followed microbiota composition in infants during the first 2 years of life have confirmed an association of C-section with delayed colonization of the *Bacteroidetes phylum*, and with lower total microbial diversity up to 2 years of age.[38] Also, differences between the microbiotas of C-section and vaginally born infants have been detected in analyses performed at 7 years of age.[39] C-section delivery impacts on microbiota through several means: 1) the lack of exposure to the vaginal and fecal microbes of the mother will alter the type and diversity of the microbes that colonize the gut at birth; 2) the different starting points in terms of microbial exposure and immune environment will mark the course of microbiota.[40] The microbial origin in C-section born infants is distinct between infants born by elective or emergency C-section. The source of the gut microbiota in infants born by emergency C-section is supposed to be the skin and vagina, whereas the skin was thought to be the predominant microbial origin of the gut microbiota in infants born by elective C-section.[41] These differences may be due to fetal membrane rupture which commonly occurs before emergency C-section leading to infiltration by vaginal microbe.

4. Feeding

1) Maternal milk–commensal microbes

Recent studies support that human milk is not sterile and is a primary and main factor that drives the acquisition and evolution of the gut microbiota in early life.[42,43] Mother-to-child transmission studies support that bacterial transfer from mother to infant occurs via breast milk.[44-46] Breast milk contributes significantly to the metabolism, development of gut integrity, and maturation of the immune and neuroendocrine systems.[47,48] Breastfeeding confers protection against respiratory and gastrointestinal infections and decreases the risk of sudden infant death syndrome and certain inflammatory diseases such as dermatitis, asthma, obesity, type 1 and 2 diabetes.[49,50] Breast milk itself is also a source of commensal bacteria that are naturally present in this secretory fluid. It has been estimated that a breast feeding infant ingests between 1×10^4 and 1×10^6 bacteria daily (Table 1).[51,52] *Streptococci* (mitis and salivarius groups) and coagulase negative *Staphylococci* are potentially able to compete with the establishment of undesired pathogens (eg, *Staphylococcus aureus*) in the infant gut. *Propionibacterium* acnes can prevent the growth of S aureus.[53] *Bifidobacterium* and *Lactobacillus spp* in breast milk are noted to activate IgA-producing plasma cells in the neonatal gut. An association was shown between low levels of intestinal *Bifidobacterium* microbiota during infancy and an increased risk of atopy later in life.[54-56] As with the composition of breast milk itself, its associated microbiome changes during the lactation period. Different factors are thought to be responsible for its composition and diversity, such as gestational age, lactation stage, environmental exposures, geographical location, daily breastfeeding practices, infant gender, and maternal factors (BMI, parity, and delivery mode).[57-60] As previously discussed, obesity influences the maternal gut microbiota but it also affects the milk microbiota.[29,61] Breast milk microbial alterations might be attributed to the physiological stress and/or hormonal changes that occur with labor or an emergency C-section. Indeed, breast milk dysbiosis was only observed in mothers who underwent an elective C-section not emergency C-section. Vaginal delivery might induce intestinal permeability and enhance the bacterial translocation from the gut to the mammary gland and breast milk.[62] Human milk contains human milk oligosaccharides, a type of prebiotic. Human milk oligosaccharides promote the growth of specific *Bifidobacteria*, supporting an early *Bifidobacteria*-dominated gut microbiome.[63] Over 200 different oligosaccharides have been identified in human milk.[64]

Table 1. Microbes Identified in Human Milk

Staphylococci
Streptococci
Corynebacteria
Propionibacteria
Lactobacillus spp
Bifidobacterium spp

5. Antibiotic usage

Antibiotic administration is another major factor that interferes with the composition of the GI microbiome. Especially antibiotic exposure within 1 month of birth alters the balanced development of the microbiome momentarily but also persistently.[65] Resistance of some gut microbes to antibiotic

agents may also occur, and these resistant genes can possibly be transferred to pathogens. The immune homeostasis will be challenged, disrupting the T-reg/Th balance.[66] Therefore, antibiotic administration increases the risk of developing immune-mediated diseases, such as cow milk protein allergy, diabetes, and asthma. The younger, the more frequent, and the larger the spectrum of antibiotic agents administered, the stronger the association with overweight status.[67]

CONCLUSIONS

The composition and development of infant gut microbiota can be influenced by maternal and infant factors. Microbial colonization primarily occurs after birth but there may be some colonization in utero, although this remains highly controversial. Maternal factors during pregnancy that can affect the infant microbiota include maternal diet, weight, gestational weight gain, and antibiotic usage but overall, their impact is low in comparison to that of birth mode, infant diet, and antibiotic treatment. Microbes are passed from mother to infant during and after birth. Delivery mode, breastfeeding, and intrapartum and early life antibiotic treatment have the largest effects on microbial composition in early life.

The early life gut microbiome plays an important role in the development of the immune system and metabolism. Emerging data demonstrating the importance of early-life gut microbiome development as a protective factor against gut dysbiosis–related diseases later in life support the rationale for targeted therapies to restore early-life gut microbiome.

Therefore, understanding the impact of maternal-to-infant transfer of dysbiotic microbes and then modifying infant early colonization or correcting early-life gut dysbiosis might be a potential strategy to overcome chronic health conditions.

REFERENCES

1. Arrieta MC, Stiemsma LT, Amenyogbe N, Brown EM, Finlay B. The intestinal microbiome in early life: health and disease. Front Immunol 2014;5:427.
2. Flint HJ, Scott KP, Duncan SH, Louis P, Forano E. Microbial degradation of complex carbohydrates in the gut. Gut Microbes 2012;3:289-306.
3. LeBlanc JG, Milani C, de Giori GS, Sesma F, van Sinderen D, Ventura M. Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr Opin Biotechnol 2013;24:160-168.
4. Blanton LV, Charbonneau MR, Salih T, et al. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. Science 2016;351:aad3311.
5. Charbonneau MR, O'Donnell D, Blanton LV, et al. Sialylated milk oligosaccharides promote microbiota-dependent growth in models of infant undernutrition. Cell 2016;164:859-871.
6. Davis JC, Lewis ZT, Krishnan S, et al. Growth and morbidity of gambian infants are influenced by maternal milk oligosaccharides and infant gut microbiota. Sci Rep 2017;7:40466.
7. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nat Rev Immunol 2009;9:313-323.
8. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science 2016;352:539-544.
9. Ganal-Vonarburg SC, Duerr CU. The interaction of intestinal microbiota and innate lymphoid cells in health and disease throughout life. Immunology 2020;159:39-51.
10. Ferretti P, Pasolli E, Tett A, et al. Mother-to-infant microbial transmission from different body sites shapes the developing infant gut microbiome. Cell Host Microbe 2018;24:133-145.e5.
11. Bäckhed F, Roswall J, Peng Y, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe 2015;17:690-703.
12. O'Neill IJ, Sanchez Gallardo R, Saldova R, et al. Maternal and infant factors that shape neonatal gut colonization by bacteria. Expert Rev Gastroenterol Hepatol 2020;14:651-664.
13. Young VB. The intestinal microbiota in health and disease. Curr Opin Gastroenterol 2012;28:63-69.
14. Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. J Neuroinflammation 2019;16:53.
15. Lauder AP, Roche AM, Sherrill-Mix S, et al. Comparison of placenta samples with contamination controls does not provide evidence for a distinct placenta microbiota. Microbiome 2016;4:29.
16. de Goffau MC, Lager S, Sovio U, et al. Human placenta has no microbiome but can contain potential pathogens. Nature 2019;572:329-334.
17. Jiménez E, Marín ML, Martín R, et al. Is meconium from healthy newborns actually sterile?. Res Microbiol 2008;159:187-193.
18. DiGiulio DB, Romero R, Kusanovic JP, et al. Prevalence and diversity of microbes in the amniotic fluid, the fetal inflammatory response, and pregnancy outcome in women with preterm pre-labor rupture of membranes. Am J Reprod Immunol 2010;64:38-57.
19. Kozyrskyj AL, Kalu R, Koleva PT, Bridgman SL. Fetal programming of overweight through the microbiome: boys are disproportionately affected. J Dev Orig Health Dis 2016;7:25-34.
20. Kumari M, Kozyrskyj AL. Gut microbial metabolism defines host metabolism: an emerging perspective in obesity and allergic inflammation. Obes Rev 2017;18:18-31.
21. Tun HM, Bridgman SL, Chari R, et al. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. JAMA Pediatr 2018;172:368-377.
22. Collado MC, Isolauri E, Laitinen K, Salminen S. Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. Am J Clin Nutr 2008;88:894-899.
23. Santacruz A, Collado MC, García-Valdés L, et al. Gut microbiota

composition is associated with body weight, weight gain and biochemical parameters in pregnant women. Br J Nutr 2010;104: 83-92.
24. Baumann-Dudenhoeffer AM, D'Souza AW, Tarr PI, Warner BB, Dantas G. Infant diet and maternal gestational weight gain predict early metabolic maturation of gut microbiomes. Nat Med 2018;24:1822-1829.
25. Soderborg TK, Clark SE, Mulligan CE, et al. The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD. Nat Commun 2018;9:4462.
26. Christopher MM, Jacob EF. Maternal modifiers of the infant gut-microbiota: metabolic consequences. Journal of Endocrinology 2017;235:R1-R12.
27. Fields DA, George B, Williams M, et al. Associations between human breast milk hormones and adipocytokines and infant growth and body composition in the first 6 months of life. Pediatr Obes 2017;12 Suppl 1:78-85.
28. Whitaker KM, Marino RC, Haapala JL, et al. Associations of maternal weight status before, during, and after pregnancy with inflammatory markers in breast milk. Obesity (Silver Spring) 2017;25:2092-2099.
29. Cabrera-Rubio R, Collado MC, Laitinen K, Salminen S, Isolauri E, Mira A. The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery. Am J Clin Nutr 2012;96:544-551.
30. Chu DM, Antony KM, Ma J, et al. The early infant gut microbiome varies in association with a maternal high-fat diet. Genome Med 2016;8:77.
31. Ma J, Prince AL, Bader D, et al. High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. Nat Commun 2014;5:3889.
32. Martinez-Medina M, Denizot J, Dreux N, et al. Western diet induces dysbiosis with increased E coli in CEABAC10 mice, alters host barrier function favouring AIEC colonisation. Gut 2014;63: 116-124.
33. Spreadbury I. Comparison with ancestral diets suggests dense acellular carbohydrates promote an inflammatory microbiota, and may be the primary dietary cause of leptin resistance and obesity. Diabetes Metab Syndr Obes 2012;5:175-189.
34. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 2010;107:11971-11975.
35. Sandall J, Tribe RM, Avery L, et al. Short-term and long-term effects of caesarean section on the health of women and children. Lancet 2018;392:1349-1357.
36. Bäckhed F, Roswall J, Peng Y, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. Cell Host Microbe 2015;17:852.
37. MacIntyre DA, Chandiramani M, Lee YS, et al. The vaginal microbiome during pregnancy and the postpartum period in a European population. Sci Rep 2015;5:8988.
38. Bokulich NA, Chung J, Battaglia T, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Sci Transl Med 2016;8:343ra82.
39. Penders J, Gerhold K, Thijs C, et al. New insights into the hygiene hypothesis in allergic diseases: mediation of sibling and birth mode effects by the gut microbiota. Gut Microbes 2014;5:239-244.
40. Francino MP. Birth mode-related differences in gut microbiota colonization and immune system development. Ann Nutr Metab 2018;73 Suppl 3:12-16.
41. 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;23:314-326.
42. Kumar H, du Toit E, Kulkarni A, et al. Distinct patterns in human milk microbiota and fatty acid profiles across specific geographic locations. Front Microbiol 2016;7:1619.
43. Pannaraj PS, Li F, Cerini C, et al. Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. JAMA Pediatr 2017;171:647-654.
44. Asnicar F, Manara S, Zolfo M, et al. Studying vertical microbiome transmission from mothers to infants by strain-level metagenomic profiling. mSystems 2017;2:e00164-16.
45. Duranti S, Lugli GA, Mancabelli L, et al. Maternal inheritance of bifidobacterial communities and bifidophages in infants through vertical transmission. Microbiome 2017;5:66.
46. Murphy K, Curley D, O'Callaghan TF, et al. The composition of human milk and infant faecal microbiota over the first three months of life: a pilot study. Sci Rep 2017;7:40597.
47. Fernández L, Langa S, Martín V, et al. The human milk microbiota: origin and potential roles in health and disease. Pharmacol Res 2013;69:1-10.
48. Jost T, Lacroix C, Braegger C, Chassard C. Impact of human milk bacteria and oligosaccharides on neonatal gut microbiota establishment and gut health. Nutr Rev 2015;73:426-437.
49. Fitzstevens JL, Smith KC, Hagadorn JI, Caimano MJ, Matson AP, Brownell EA. Systematic review of the human milk microbiota. Nutr Clin Pract 2017;32:354-364.
50. Eidelman AI, Schanler RJ. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827-e841.
51. Heikkilä MP, Saris PE. Inhibition of Staphylococcus aureus by the commensal bacteria of human milk. J Appl Microbiol 2003;95: 471-478.
52. Kapourchali FR, Cresci GAM. Early-life gut microbiome-the importance of maternal and infant factors in its establishment. Nutr Clin Pract 2020;35:386-405.
53. Shu M, Wang Y, Yu J, et al. Fermentation of Propionibacterium acnes, a commensal bacterium in the human skin microbiome, as skin probiotics against methicillin-resistant Staphylococcus aureus. PLoS One 2013;8:e55380.
54. Stsepetova J, Sepp E, Julge K, Vaughan E, Mikelsaar M, de Vos WM. Molecularly assessed shifts of Bifidobacterium ssp. and less diverse microbial communities are characteristic of 5-year-old allergic children. FEMS Immunol Med Microbiol 2007; 51:260-269.
55. Kalliomäki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol 2001;107:129-134.
56. Suzuki S, Shimojo N, Tajiri Y, Kumemura M, Kohno Y. Differences in the composition of intestinal Bifidobacterium species and the

development of allergic diseases in infants in rural Japan. Clin Exp Allergy 2007;37:506-511.
57. Toscano M, De Grandi R, Peroni DG, et al. Impact of delivery mode on the colostrum microbiota composition. BMC Microbiol 2017; 17:205.
58. Fujita M, Roth E, Lo YJ, Hurst C, Vollner J, Kendell A. In poor families, mothers' milk is richer for daughters than sons: a test of Trivers-Willard hypothesis in agropastoral settlements in Northern Kenya. Am J Phys Anthropol 2012;149:52-59.
59. Michaelsen KF, Skafte L, Badsberg JH, Jørgensen M. Variation in macronutrients in human bank milk: influencing factors and implications for human milk banking. J Pediatr Gastroenterol Nutr 1990;11:229-239.
60. Moossavi S, Sepehri S, Robertson B, et al. Composition and variation of the human milk microbiota are influenced by maternal and early-life factors. Cell Host Microbe 2019;25:324-335.e4.
61. Gohir W, Ratcliffe EM, Sloboda DM. Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. Pediatr Res 2015;77:196-204.
62. Hermansson H, Kumar H, Collado MC, Salminen S, Isolauri E, Rautava S. Breast milk microbiota is shaped by mode of delivery and intrapartum antibiotic exposure. Front Nutr 2019;6:4.
63. Vandenplas Y, Berger B, Carnielli VP, et al. Human milk oligosaccharides: 2'-fucosyllactose (2'-FL) and lacto-N-neotetraose (LNnT) in infant formula. Nutrients 2018;10:1161.
64. Urashima T, Taufik E, Fukuda K, Asakuma S. Recent advances in studies on milk oligosaccharides of cows and other domestic farm animals. Biosci Biotechnol Biochem 2013;77:455-466.
65. Zeissig S, Blumberg RS. Life at the beginning: perturbation of the microbiota by antibiotics in early life and its role in health and disease. Nat Immunol 2014;15:307-310.
66. Francino MP. Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. Front Microbiol 2016;6: 1543.
67. Miller SA, Wu RKS, Oremus M. The association between antibiotic use in infancy and childhood overweight or obesity: a systematic review and meta-analysis. Obes Rev 2018;19:1463-1475.