

Microbiome, autoimmunity, allergy, and helminth infection: The importance of the pregnancy period

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Pregnancy is a special physical period in reproductive age women, which has a beneficial influence on the course of certain autoimmune diseases. It has been recently suggested that the microbiome undergoes profound changes during pregnancy that are associated with host physiological and immunological adaptations. The maternal microbiome remodeling during pregnancy is an active response of the mother, possibly to alter immune system status and to facilitate metabolic and immunological adaptations, which are needed for a successful pregnancy. In this review, we attempt to discuss (i) the role of maternal microbiome in pregnancy outcomes known to adversely influence neonatal and infant health, including preterm birth, cardiometabolic complications of pregnancy, and gestational weight gain; (ii) the association of microbiome with autoimmunity, allergy diseases, and asthma during pregnancy; and (iii) the impact of helminth infection during pregnancy.

KEYWORDS

allergy, autoimmunity, helminth infection, microbiome, pregnancy

1 | INTRODUCTION

The human microbiome is the community of microorganisms that live on and in the human body, which consists of upwards of 100 trillion cells.¹ The human microbiome is estimated to outnumber human cells by an order of magnitude, and human genome by two orders of magnitude.² Immediately after birth, all mammals are initiated into a lifelong process of colonization by foreign microorganisms that inhabit most environmentally exposed surfaces (such as the skin, mouth, gut, and vagina).³ These bacteria and their genomes are classically identified as commensal, symbiotic, or pathogenic. It seems that certain basic developmental features and functions of mammalian immune system depend on interactions with the human microbiome.⁴ Therefore, the microbiota has the potential to exert both pro- and anti-inflammatory responses, and the composition of the bacterial communities in human body may be intimately linked to the proper functioning of the immune system.

Pregnancy is a specific condition characterized with a transient tolerance for the foreign fetal body. Immune regulation plays an important role in successful pregnancy. Fetal as well as maternal factors

influence the local mucosal immune system so that the fetus is not rejected by the mother.⁵ Furthermore, not only is the fetus growing but also the diversity of gut bacteria changes. Thus, the microbial community as a whole undergoes striking rearrangements. Recently, it has been suggested that the microbiome undergoes profound changes during pregnancy that are associated with host physiological and immunological adaptations.⁶ It also has been proposed that microbiome remodeling during pregnancy is an active response of the mother, possibly to alter immune system status and to facilitate metabolic and immunological adaptations, which are needed for a successful pregnancy.⁷ Furthermore, the profound immunological adaptations during and after pregnancy have an influence on maternal autoimmune diseases in several ways.^{8,9} However, the underlying mechanisms of pregnancy-related microbiome are not well understood. Therefore, we present recent evidence to discuss that the pregnancy outcome, autoimmunity, allergy are influenced by microbiomes during pregnancy, and the impact of helminth infection during pregnancy. We also highlight the mechanisms that mediated host-symbiont interactions that regulate proper immune function.

2 | ALTERATIONS TO THE MICROBIOME DURING PREGNANCY

During a normal and healthy pregnancy, the body undergoes a spectrum of hormonal, immunological, and metabolic changes.^{10,11} These changes are accompanied by concomitant changes in the microbiome, especially in the vagina and gut.^{6,12,13} The gut microbiota which is shaped by the environmental factors, such as diet, host genetics, and the immune system,^{2,14–17} has been reported to play a role in driving metabolic disease, including inflammation, weight gain, and reduced insulin sensitivity.^{15,18}

Recently, Koren et al. have reported on a profound alteration of the gut microbiota changes during pregnancy by characterizing the fecal bacteria of 91 pregnant women which have variable pre-pregnancy body mass index (BMI) and gestational diabetes status and their children.⁶ The gut microbiotas during the first trimester (T1) are similar to one another, but the phylogenetic composition and structure shift substantially over the course of pregnancy. By the third trimester (T3), the between-subject diversity has greatly expanded, although the within-subject diversity is reduced.⁶ As the remodeling of the gut microbiota over the course of pregnancy is not related to diet, the gestational diabetes status, BMI, or treatment with antibiotics, other factors such as the host immune or endocrine systems may contribute to the observed shift.

Another study using 454 pyrosequencing technology revealed that the vaginal microbial community differed in pregnancy by gestational age and proximity to the cervix.¹² Furthermore, although the alpha diversity was reduced in late gestation, the *Lactobacillus* species which play a role in preventing the growth of pathogenic bacteria, helping human digestion, and shaping the host innate and adaptive immune system responses increased among pregnant individuals compared with non-pregnant subjects.¹² Recently, Romero et al. examined the vaginal microbiome longitudinally during pregnancy at the posterior fornix and also found the predominance of *Lactobacillus* species in normal pregnancy, suggesting the relationship between vaginal microbiome and adverse pregnancy outcomes.¹³

When the T1 and T3 microbiotas were transferred into germ-free wild-type mice, levels of inflammation markers were significantly higher in the stool and cecal samples from the T3 sample recipients compared to those of T1 recipients.⁶ Furthermore, the T3 recipients have reduced oral glucose tolerance and more adiposity gains, indicating that the T3 microbiota particularly has the capacity to induce metabolic changes in the host.

3 | THE MICROBIOME AND PREGNANCY OUTCOMES

There is growing evidence that the maternal microbiome plays an important role in pregnancy outcomes including preterm birth, cardiometabolic complications of pregnancy, and gestational weight gain.

3.1 | Preterm birth

The vaginal microbiome influences the risk of preterm birth. The healthy vaginal microbiome plays a role in preventing bacterial vaginosis (BV), which is associated with preterm birth and increased risk for acquiring sexually transmitted infections, urinary tract infections,^{19–22} and human immunodeficiency virus (HIV).^{23,24} Protection is attributed to *Lactobacillus* species that produce lactic acid and H₂O₂.^{25,26} BV is characterized by the deficiency of *Lactobacillus* species.^{27,28} A recent study by Hyman et al.²⁹ has examined the vaginal microbiome in preterm birth and found that the high-risk subjects (previous unexplained preterm birth) has a lower prevalence of lactobacilli when compared with low-risk subjects (all other gravid). Currently, the NGS techniques make it easier to determine the bacterial flora of the “normal” vs “abnormal” vagina through characterizing the vaginal microbiome.

The preterm birth could also be caused by infections not originating in the vaginal cavity. The oral cavity has a characteristic microbiome. A study by Fardini et al. reported that the oral bacteria were capable of hematogenous transmission to colonize the murine placenta, and most of these species had been reported to associate with adverse pregnancy outcomes.³⁰ Arce et al. found that the mice infected with the human periodontal pathogens *Campylobacter rectus* and *Porphyromonas gingivalis* had decreased fecundity and increased resorption.³¹ These studies demonstrate that the oral cavity plays an important role in preterm birth.

The gut microbiome not only influences the host metabolism, but also associates with preterm premature rupture of membranes which causes one-third of preterm births and contributes to significant perinatal morbidity and mortality.^{32,33}

3.2 | Cardiometabolic complications of pregnancy

The gut microbiome could influence on metabolic processes, such as energy harvest, energy expenditure, and fat storage, which contributes to obesity and its comorbidities (such as insulin resistance, diabetes, and cardiovascular disease).³⁴ The gut microbiota may affect host metabolism by altering adipose tissue inflammation since by feeding lipopolysaccharide to mice, the adipose tissue inflammation increased and the insulin sensitivity reduced.¹⁸ The gut microbiome from women who developed gestational diabetes has the least diversity during the T1 of pregnancy.⁶ There is mounting evidence indicating that the gut microbiota may be a target for treating metabolic diseases.³⁵ The therapies can include supplementing the diet with non-digestible food ingredients, or pre-biotics which stimulate the expansion of specific microbes to improve metabolic regulation.

3.3 | Gestational weight gain

The gut microbiota is altered in people who are obese and it can respond to changes in body weight. Differences in gut microbiome between normal and obese pregnant women suggest that the microbiome might be important in weight management during pregnancy.^{36–38} The changes observed in women during T3 of pregnancy with increased

levels of Enterobacteriaceae and reduced bacterial diversity are similar to those of the obesity-associated microbiome shown to be more efficient at energy extraction.³⁹ Furthermore, after transferred the gut microbiome of T3 into bacteria-free mice, the animals developed signs of metabolic syndrome including weight gain, but these changes might be beneficial in expectant women to support the growth of the fetus.⁶

4 | THE MATERNAL MICROBIOME SETS THE OFFSPRING'S MICROBIAL STRUCTURE

The composition of the mother's microbiome and other perinatal factors play an important role in the microbial colonization of the infant gut.^{40,41} The transfer of T3 maternal microbiota may prevent the overgrowth of pathogenic bacteria such as *Ureaplasma urealyticum*, which are related to an increased risk of necrotizing enterocolitis in preterm infants.⁴² Meanwhile, the delivery mode may also shape the acquisition and structure of the initial microbiota in newborns.⁴⁰ The vaginally delivered infants acquire microbes resembling their mother's vaginal microbiome, while cesarean-delivered infants harbor bacterial communities similar to those found on the maternal skin surface.⁴⁰ The size and gestational age of the neonate also influences the composition of the infant microbiome. Compared with the healthy term infants, the preterm infants display a dominance of Proteobacteria but lack two main bacterial genera, which are Bifidobacterium and Lactobacillus.⁴³ The feeding patterns also affect the gut microbiome composition of the infants. The microbiome of breastfed infants is characterized by higher abundance of Bifidobacteria, while for the infants who are exclusively fed formula, *E. coli*, *Clostridium difficile*, *Bacteroides fragilis*, and lactobacilli remain predominant.⁴¹

5 | MICROBIOME AND AUTOIMMUNITY DURING PREGNANCY

Autoimmune diseases include more than 70 different disorders affecting approximately 5% of the population of the Western countries.⁴⁴ Most autoimmune diseases more frequently occur in women than in men. During pregnancy, the levels of estrogen, progesterone, and other hormones have dramatic changes. At the same time, there are profound immunological changes throughout pregnancy and during the post-partum period under the influence of these hormones.⁴⁵ These immunological changes are essential for the growth of fetus to maintain successful pregnancy. Both the hormonal and immunological changes also have significant effects on the course of autoimmune disease, and the nature of the disease determines whether these effects are detrimental or beneficial. In turn, the course and progression of the disease during pregnancy and the underlying immunological and possibly hormonal abnormalities of the disease may affect the pregnancy outcome.^{46,47} An increasing number of evidence demonstrated that autoimmunity can affect every aspect of pregnancy and can contribute to maternal complications and adverse fetal outcomes.^{46,48} However, pregnancy also has a beneficial impact on the course of

certain autoimmune diseases. Pregnancy woman with multiple sclerosis (MS) typically have reduced relapse rate in the latter half of pregnancy, whereas disease activity often returns greater severity after the delivery than in pregnancy.⁴⁹ In the case of rheumatoid arthritis (RA), two-thirds of pregnant women also experience an improvement in their RA disease activity.⁵⁰ For system lupus erythematosus (SLE), the changes in the disease state during pregnancy appear to be more varied.⁵¹ Thus, it can be seen that the relationships between pregnancy and autoimmunity are represented by a bidirectional model.

Recently, it has been reported that the microbiome undergoes profound changes during pregnancy that are associated with host physiological and immunological adaptations.⁷ What is more, it has been proposed that microbiome remodeling during pregnancy is an active response of the mother, possibly to alter immune system status and to facilitate metabolic and immunological adaptations, which are important factors for successful pregnancy.⁷ Fetal as well as maternal factors influence the local mucosal immune system so that the fetus is not rejected by the mother. Furthermore, not only is the fetus growing but also the diversity of gut bacteria changes. Thus, the microbial community as a whole undergoes striking rearrangements.

It has been generally accepted that autoimmune diseases are the results of a complex interaction between genetic and environmental factors, most of which have not been identified.^{52,53} Considerable information has been published that infections have been proposed for a long time as environmental triggers for the induction of autoimmunity, such as EB virus (SLE and other diseases), HCV (autoimmune hepatitis), beta hemolytic streptococci (rheumatic carditis), and *Helicobacter pylori* (autoimmune gastritis).^{54,55} In addition, there is increasing evidence for the critical role of the gut, oral, and skin microbiota in the pathogenesis of systemic and organ-specific autoimmune diseases.^{56–59} Recent studies reported that significant differences can be found in the microbiome of patients with autoimmune diseases such as diabetes types I⁶⁰ and II,⁶¹ SLE,⁶² Crohn's disease,⁶³ psoriasis,⁶⁴ and Behcet's syndrome.⁶⁵ These suggest that the dysbiosis of the human microbiome can drive autoimmune disease. Dysbiosis of the gut is associated with several disease states including inflammatory bowel disease (IBD), in which the loss of mucosal tolerance toward the commensal microbiota results in ulcerative inflammatory responses.⁶⁶ Likewise, dysbiotic intestinal microbiota is associated with RA and is found in genetically RA-susceptible murine models.⁶⁷ Besides, oral commensals are also were found to be associated with RA.⁵⁶ A recent study indicated that psoriasis is also triggered by dysbiotic microbiota.⁶⁸ Although the mechanisms of human microbiome influencing the onset and progression of autoimmune diseases remain to be determined, evidence from animal models of autoimmune diseases demonstrates that local and systemic bidirectional interactions with the microbiome may play a signaling or promoting role through the immune system.⁶⁹ Altogether, the complex interaction between the human body and its microbiome affect our health and disease, as presented here in the context of autoimmunity. Therefore, unraveling the exact mechanisms by which dysbiosis participates in the pathogenesis of autoimmune diseases may facilitate the identification of population at risk, and enable the development of new approaches for patient-tailored early intervention.⁵⁹

6 | MICROBIOME AND ALLERGY DISEASES OR ASTHMA DURING PREGNANCY

Allergy and asthma are one of the most common medical problems to complicated pregnancy. Due to its increased prevalence, and the increased morbidity and mortality from these diseases, allergic diseases and asthma have come to be recognized as a major worldwide public health issue. Many factors are important in pathogenesis of these diseases, such as lifestyle changes, exposure to pollutants, drugs, and changes in nutrition.⁷⁰ Limited microbial exposure in developed countries has also been suggested to underlie the allergy development.^{70,71} Recent studies indicate that a low intestinal microbial diversity during the first month of life is associated with subsequent atopic eczema and asthma.^{72,73} It seems that bacterial diversity might be more important than specific bacteria taxa.

Furthermore, there is a strong evidence suggesting that the maternal microbiota during pregnancy has long-lasting influences on the offspring's microbial structure, and subsequently on its susceptibility to diseases.⁷⁴ Prospective studies indicate that the gut microbiota composition during the first months of life influences allergy development,^{72,75} and support the theory that factors influencing the early maturation of the immune system might be important for subsequent allergic disease.⁷⁶ An experimental piglet model reported that establishment and development of the normal gut microbiota and immune system seem to require continuous microbial exposure during the early stages of life, and that this process is compromised under conditions of excessive hygiene.⁷⁷ Moreover, altering the intestinal microbiota during a critical development window in early life using low-dose antibiotics also induces long-term host metabolic effects in a murine model.⁷⁸ Antibiotic treatment during pregnancy is also associated with asthma in the offspring.⁷⁹ However, recent study demonstrates that prenatal supplementation seems to be even more crucial for the preventive effect of probiotics on infant eczema.^{75,80} Hence, it seems that the pre- and postnatal environment may represent a window of opportunity for allergy and asthma intervention.

Until recently, it has been speculated that the presentation of maternal bacterial components to the fetus during pregnancy is very important for the maturation of the immune system and the induction of oral tolerance to allergens.⁸¹ A study on human newborns shows that bacterial DNA in amniotic fluid and in the placenta can affect TLR gene expression in the fetal intestine collected at elective cesarean section.⁸² Furthermore, exposure to *A. Iwoffii* during gestation resulted in a suppression of TLR expression in placental tissue in a mice asthma model.⁸³ The prenatal programming of the immune system by the maternal bacterial components may be required for a tolerogenic immune response to the abundant bacterial load occurring immediately after birth.

7 | HELMINTH INFECTION DURING PREGNANCY

Approximately one-third of the world's population is infected with helminths, the majority of whom reside in the poorest communities of

the developing world. Chronic helminth infections are characterized by skewing toward a T helper 2 type response as well as regulatory responses, thought to prevent strong immune responses against parasitic worm (helminths), allowing their long-term survival and restricting pathology. Pregnancy is an exceptional physiological state with a Th-2-biased phenomenon promoting tolerance and successful growth of the so-called feto-placental allograft, so pregnancy may increase susceptibility to helminths.⁸⁴ In Entebbe, Uganda, 68.3% pregnant women had at least one helminth infection.⁸⁵

Helminths contribute to iron deficiency anaemia as they feed on blood and cause further bleeding by releasing anticoagulant compounds. They also affect the supply of nutrients and cause anorexia, vomiting, and diarrhea. Pregnancy complicated by maternal hookworm infection poses a serious threat to the health of mothers and their babies, especially in developing countries. Women who are anaemic during pregnancy are more likely to have ill health, give birth prematurely, and have low-birthweight babies with low iron reserves.⁸⁶

In recent years, researchers have become more interested in the effects helminths have on immunoregulation. The possible consequences of this immunoregulation may have for susceptibility to other infections, for vaccine efficacy, and for immunologically mediated conditions such as allergy and autoimmune disease.⁸⁷ At the same time, the consequences of maternal helminth infection on the immune systems of mothers and descendants have been the subject of investigation.

Studies have indicated that the residency of adult schistosomal in the mesenteric vasculature and lodging of eggs in the liver allow for continuous secretion of antigens directly into the blood stream of the host, and these antigens are known to traffic to, and cross, the human placenta, and have been found in fetal circulation.^{88–90} These antigens may have a direct effect on the cells at the maternal-fetal interface. Kurtis JD have reported increased levels of inflammatory cytokines in maternal peripheral (tumor necrosis factor alpha [TNF- α] and interleukin-10 [IL-10]), placental (TNF- α , IL-6, TNF- α receptor II [RII], and IL-1 β), and cord blood (IL-1 β and TNF- α RII) in a population of pregnant women residing in the Philippines. And then they found exposure of first trimester hHT8/SVneo trophoblast cells to schistosome-soluble egg antigens (SEA) exhibited an increased pro-inflammatory cytokine (IL-6, IL-8, MCP-1) and TI-MP-1. These may result in a proinflammatory, antimigration, anti-invasive signature, and then associated with miscarriage, subchorionitis, preeclampsia, preterm delivery, and decreased birthweight.^{91,92}

Epidemiological studies have provided evidence that children born to helminth-infected mothers have more sensitization to helminth antigens⁹³ and have the potential to affect neonatal responses to BCG vaccination as well as TB-specific immunity.⁹⁴ Here is increasing evidence that prenatal T-cell priming occurs via transplacental exposure to antigens and such primary sensitization affects the maturation of the postnatal immune system. The absence of helminth antibodies and a higher total IgE and cross-placental transfer of TB-specific IgG in the cord bloods from helminth-infected mothers are associated with cytokines and Th1/Th2 skews in neonates.^{95,96} Maternal helminth infection can alter the early balance between the CD4⁺T-cell

subsets of the offspring. A study reported by Ulysse et al. who found no significant difference was observed between newborns from infected versus uninfected mothers in the frequencies of total CD4⁺T cells and CD4⁺T cells subsets including CD4⁺Tbet⁺, CD4⁺RORγt⁺ T and CD4⁺CD25^{hi}FOXP3⁺ T cells. However, there was a negative association between CD4⁺CD25^{hi}FOXP3⁺T cells and CD4⁺Tbet⁺ as well as CD4⁺RORγt⁺ T cells in the infected group only. The results suggests that filarial infection during pregnancy leads to an expansion of functionally active regulatory T cells that keep Th1 and Th17 in check.⁹⁷ It also has been demonstrated that cord blood exposure to parasite antigens from the helminth-infected mother induces a Th2-predominant response.⁸⁹ The lack of an optimal Th1 response leads to impaired immunity to helminth and mycobacterial infection.

A study showed an inverse association between helminth parasites at delivery and infantile eczema and hypothesized that maternal helminth infection protects against infantile eczema, and this protection would be modified by deworming.⁹⁸

8 | CONCLUSIONS

The maternal microbiome is being shown to play a critical role in the occurrence of adverse pregnancy outcomes that greatly influence the health of the neonate and infant. Microbiome alterations may contribute to immunological changes during pregnancy. Further complex interaction between the human body and its microbiome affects our health and disease during pregnancy, as presented here in the context of autoimmunity. Physiological development that occurs during pregnancy affects the microbial community, which, in turn, creates a positive feedback loop to stimulate host immune system. Therefore, this suggests that our bodies have coevolved with the microbiota and may actually be using them as a tool to help alter the metabolism of the mother to support growth of the fetus.

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REFERENCES

- Whitman WB, Coleman DC, Wiebe WJ. Prokaryotes: the unseen majority. *Proc Natl Acad Sci USA*. 1998;95:6578–6583.
- Spor A, Koren O, Ley RE. Unravelling the effects of the environment and host genotype on the gut microbiome. *Nat Rev Microbiol*. 2011;9:279–290.
- Ley RE, Peterson DA, Gordon JI. Ecological and evolutionary forces shaping microbial diversity in the human intestine. *Cell*. 2006;124:837–848.
- Macpherson AJ, Harris NL. Interactions between commensal intestinal bacteria and the immune system. *Nat Rev Immunol*. 2004;4:478–485.
- Thellin O, Heinen E. Pregnancy and the immune system: between tolerance and rejection. *Toxicology*. 2003;185:179–184.
- Koren O, Goodrich JK, Cullender TC, et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. *Cell*. 2012;150:470–480.
- Konstantinov SR, van der Woude CJ, Peppelenbosch MP. Do pregnancy-related changes in the microbiome stimulate innate immunity? *Trends Mol Med*. 2013;19:454–459.
- Buyon JP. The effects of pregnancy on autoimmune diseases. *J Leukoc Biol*. 1998;63:281–287.
- Gordon C. Pregnancy and autoimmune diseases. *Best Pract Res Clin Rheumatol*. 2004;18:359–379.
- Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol*. 2010;63:425–433.
- Newbern D, Freemerk M. Placental hormones and the control of maternal metabolism and fetal growth. *Curr Opin Endocrinol Diabetes Obes*. 2011;18:409–416.
- Aagaard K, Riehle K, Ma J, et al. A metagenomic approach to characterization of the vaginal microbiome signature in pregnancy. *PLoS ONE*. 2012;7:e36466.
- Romero R, Hassan SS, Gajer P, et al. The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women. *Microbiome*. 2014;2:4.
- Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011;334:105–108.
- Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science*. 2010;328:228–231.
- Salzman NH, Hung K, Haribhai D, et al. Enteric defensins are essential regulators of intestinal microbial ecology. *Nat Immunol*. 2010;11:76–83.
- Slack E, Hapfelmeier S, Stecher B, et al. Innate and adaptive immunity cooperate flexibly to maintain host-microbiota mutualism. *Science*. 2009;325:617–620.
- Cani PD, Amar J, Iglesias MA, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007;56:1761–1772.
- Donders GG, Bosmans E, Dekeersmaecker A, Vereecken A, Van Bulck B, Spitz B. Pathogenesis of abnormal vaginal bacterial flora. *Am J Obstet Gynecol*. 2000;182:872–878.
- Wiesenfeld HC, Hillier SL, Krohn MA, Landers DV, Sweet RL. Bacterial vaginosis is a strong predictor of Neisseria gonorrhoeae and Chlamydia trachomatis infection. *Clin Infect Dis*. 2003;36:663–668.
- Gupta K, Stapleton AE, Hooton TM, Roberts PL, Fennell CL, Stamm WE. Inverse association of H2O2-producing lactobacilli and vaginal Escherichia coli colonization in women with recurrent urinary tract infections. *J Infect Dis*. 1998;178:446–450.
- Cherpes TL, Meyn LA, Krohn MA, Lurie JG, Hillier SL. Association between acquisition of herpes simplex virus type 2 in women and bacterial vaginosis. *Clin Infect Dis*. 2003;37:319–325.
- Lai SK, Hida K, Shukair S, et al. Human immunodeficiency virus type 1 is trapped by acidic but not by neutralized human cervicovaginal mucus. *J Virol*. 2009;83:11196–11200.
- Martin HL, Richardson BA, Nyange PM, et al. Vaginal lactobacilli, microbial flora, and risk of human immunodeficiency virus type 1 and sexually transmitted disease acquisition. *J Infect Dis*. 1999;180:1863–1868.
- Boskey ER, Cone RA, Whaley KJ, Moench TR. Origins of vaginal acidity: high D/L lactate ratio is consistent with bacteria being the primary source. *Hum Reprod*. 2001;16:1809–1813.
- Kaewsrichan J, Peeyanjarassri K, Kongprasertkit J. Selection and identification of anaerobic lactobacilli producing inhibitory compounds against vaginal pathogens. *FEMS Immunol Med Microbiol*. 2006;48:75–83.
- Klebanoff SJ, Hillier SL, Eschenbach DA, Waltersdorff AM. Control of the microbial flora of the vagina by H2O2-generating lactobacilli. *J Infect Dis*. 1991;164:94–100.
- Voravuthikunchai SP, Bilasoi S, Supamala O. Antagonistic activity against pathogenic bacteria by human vaginal lactobacilli. *Anaerobe*. 2006;12:221–226.

29. Hyman RW, Fukushima M, Jiang H, et al. Diversity of the vaginal microbiome correlates with preterm birth. *Reprod Sci*. 2014;21:32–40.
30. Fardini Y, Chung P, Dumm R, Joshi N, Han YW. Transmission of diverse oral bacteria to murine placenta: evidence for the oral microbiome as a potential source of intrauterine infection. *Infect Immun*. 2010;78:1789–1796.
31. Arce RM, Barros SP, Wacker B, Peters B, Moss K, Offenbacher S. Increased TLR4 expression in murine placentas after oral infection with periodontal pathogens. *Placenta*. 2009;30:156–162.
32. 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.
33. Wardwell LH, Huttenhower C, Garrett WS. Current concepts of the intestinal microbiota and the pathogenesis of infection. *Curr Infect Dis Rep*. 2011;13:28–34.
34. Tremaroli V, Backhed F. Functional interactions between the gut microbiota and host metabolism. *Nature*. 2012;489:242–249.
35. Murphy EF, Cotter PD, Hogan A, et al. Divergent metabolic outcomes arising from targeted manipulation of the gut microbiota in diet-induced obesity. *Gut*. 2013;62:220–226.
36. 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.
37. Aitken JD, Gewirtz AT. Gut microbiota in 2012: toward understanding and manipulating the gut microbiota. *Nat Rev Gastroenterol Hepatol*. 2013;10:72–74.
38. Cox LM, Blaser MJ. Pathways in microbe-induced obesity. *Cell Metab*. 2013;17:883–894.
39. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature*. 2009;457:480–484.
40. 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 USA*. 2010;107:11971–11975.
41. Penders J, Thijs C, Vink C, et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics*. 2006;118:511–521.
42. Okogbule-Wonodi AC, Gross GW, Sun CC, et al. Necrotizing enterocolitis is associated with ureaplasma colonization in preterm infants. *Pediatr Res*. 2011;69:442–447.
43. Barrett E, Kerr C, Murphy K, et al. The individual-specific and diverse nature of the preterm infant microbiota. *Arch Dis Child Fetal Neonatal Ed*. 2013;98:F334–F340.
44. Lleo A, Invernizzi P, Gao B, Podda M, Gershwin ME. Definition of human autoimmunity–autoantibodies versus autoimmune disease. *Autoimmun Rev*. 2010;9:A259–A266.
45. Polese B, Griselet V, Araklioti E, Martens H, Perrier d'Hauterive S, Geenen V. The Endocrine Milieu and CD4 T-Lymphocyte Polarization during Pregnancy. *Front Endocrinol (Lausanne)*. 2014;5:106.
46. Cervera R, Balasch J. Bidirectional effects on autoimmunity and reproduction. *Hum Reprod Update*. 2008;14:359–366.
47. Borchers AT, Naguwa SM, Keen CL, Gershwin ME. The implications of autoimmunity and pregnancy. *J Autoimmun*. 2010;34:J287–J299.
48. Tuohy VK, Altuntas CZ. Autoimmunity and premature ovarian failure. *Curr Opin Obstet Gynecol*. 2007;19:366–369.
49. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. *N Engl J Med*. 1998;339:285–291.
50. Hazes JM, Coulie PG, Geenen V, et al. Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. *Rheumatology (Oxford)*. 2011;50:1955–1968.
51. de Jesus GR, Mendoza-Pinto C, de Jesus NR, et al. Understanding and Managing Pregnancy in Patients with Lupus. *Autoimmune Dis*. 2015;2015:943490.
52. Selmi C, Gershwin ME. The role of environmental factors in primary biliary cirrhosis. *Trends Immunol*. 2009;30:415–420.
53. Burek CL, Talor MV. Environmental triggers of autoimmune thyroiditis. *J Autoimmun*. 2009;33:183–189.
54. Fallarino F, Volpi C, Zelante T, et al. IDO mediates TLR9-driven protection from experimental autoimmune diabetes. *J Immunol*. 2009;183:6303–6312.
55. Zanone MM, Favaro E, Quadri R, et al. Association of cytomegalovirus infections with recurrence of humoral and cellular autoimmunity to islet autoantigens and of type 1 diabetes in a pancreas transplanted patient. *Transpl Int*. 2010;23:333–337.
56. He J, Li Y, Cao Y, Xue J, Zhou X. The oral microbiome diversity and its relation to human diseases. *Folia Microbiol (Praha)*. 2015;60:69–80.
57. Lerner A, Matthias T. Rheumatoid arthritis–celiac disease relationship: joints get that gut feeling. *Autoimmun Rev*. 2015;14:1038–1047.
58. Ma HD, Wang YH, Chang C, Gershwin ME, Lian ZX. The intestinal microbiota and microenvironment in liver. *Autoimmun Rev*. 2015;14:183–191.
59. Shamriz O, Mizrahi H, Werbner M, Shoenfeld Y, Avni O, Koren O. Microbiota at the crossroads of autoimmunity. *Autoimmun Rev*. 2016;15:859–869.
60. Giongo A, Gano KA, Crabb DB, et al. Toward defining the autoimmune microbiome for type 1 diabetes. *ISME J*. 2011;5:82–91.
61. Larsen L, Vogensen FK, van den Berg FW, et al. Gut microbiota in human adults with type 2 diabetes differs from nondiabetic adults. *PLoS ONE*. 2010;5:e9085.
62. Edwards CJ, Costenbader KH. Epigenetics and the microbiome: developing areas in the understanding of the aetiology of lupus. *Lupus*. 2014;23:505–506.
63. Morgan XC, Tickle TL, Sokol H, et al. Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol*. 2012;13:R79.
64. Gao Z, Tseng CH, Strober BE, Pei Z, Blaser MJ. Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. *PLoS ONE*. 2008;3:e2719.
65. Consolandi C, Turroni S, Emmi G, et al. Behcet's syndrome patients exhibit specific microbiome signature. *Autoimmun Rev*. 2015;14:269–276.
66. Fava F, Danese S. Intestinal microbiota in inflammatory bowel disease: friend of foe? *World J Gastroenterol*. 2011;17:557–566.
67. Gomez A, Luckey D, Taneja V. The gut microbiome in autoimmunity: sex matters. *Clin Immunol*. 2015;159:154–162.
68. Fry L, Baker BS, Powles AV, Fahlen A, Engstrand L. Is chronic plaque psoriasis triggered by microbiota in the skin? *Br J Dermatol*. 2013;169:47–52.
69. Yurkovetskiy L, Burrows M, Khan AA, et al. Gender bias in autoimmunity is influenced by microbiota. *Immunity*. 2013;39:400–412.
70. Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. *J Allergy Clin Immunol*. 2013;131:23–30.
71. Holt PG, Sly PD, Bjorksten B. Atopic versus infectious diseases in childhood: a question of balance? *Pediatr Allergy Immunol*. 1997;8:53–58.
72. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. *J Allergy Clin Immunol*. 2012;129:434–440, 440 e431–432.
73. Abrahamsson TR, Jakobsson HE, Andersson AF, Bjorksten B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. *Clin Exp Allergy*. 2014;44:842–850.
74. Romano-Keeler J, Weitkamp JH. Maternal influences on fetal microbial colonization and immune development. *Pediatr Res*. 2015;77:189–195.
75. Ismail IH, Licciardi PV, Tang ML. Probiotic effects in allergic disease. *J Paediatr Child Health*. 2013;49:709–715.

76. Prescott SL. Early origins of allergic disease: a review of processes and influences during early immune development. *Curr Opin Allergy Clin Immunol*. 2003;3:125–132.
77. Schmidt B, Mulder IE, Musk CC, et al. Establishment of normal gut microbiota is compromised under excessive hygiene conditions. *PLoS ONE*. 2011;6:e28284.
78. Cox LM, Yamanishi S, Sohn J, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* 2014;158:705–721.
79. Benn CS, Thorsen P, Jensen JS, et al. Maternal vaginal microflora during pregnancy and the risk of asthma hospitalization and use of antiasthma medication in early childhood. *J Allergy Clin Immunol*. 2002;110:72–77.
80. Jenmalm MC, Duchon K. Timing of allergy-preventive and immunomodulatory dietary interventions - are prenatal, perinatal or postnatal strategies optimal? *Clin Exp Allergy*. 2013;43:273–278.
81. Abrahamsson TR, Wu RY, Jenmalm MC. Gut microbiota and allergy: the importance of the pregnancy period. *Pediatr Res*. 2015;77:214–219.
82. Rautava S, Collado MC, Salminen S, Isolauri E. Probiotics modulate host-microbe interaction in the placenta and fetal gut: a randomized, double-blind, placebo-controlled trial. *Neonatology*. 2012;102:178–184.
83. Conrad ML, Ferstl R, Teich R, et al. Maternal TLR signaling is required for prenatal asthma protection by the nonpathogenic microbe *Acinetobacter lwoffii* F78. *J Exp Med*. 2009;206:2869–2877.
84. Adegnik AA, Agnandji ST, Chai SK, et al. Increased prevalence of intestinal helminth infection during pregnancy in a Sub-Saharan African community. *Wien Klin Wochenschr*. 2007;119:712–716.
85. Woodburn PW, Muhangi L, Hillier S, et al. Risk factors for helminth, malaria, and HIV infection in pregnancy in Entebbe, Uganda. *PLoS Negl Trop Dis*. 2009;3:e473.
86. Salam RA, Haider BA, Humayun Q, Bhutta ZA. Effect of administration of antihelminthics for soil-transmitted helminths during pregnancy. *Cochrane Database Syst Rev*. 2015;6:CD005547.
87. van Riet E, Hartgers FC, Yazdanbakhsh M. Chronic helminth infections induce immunomodulation: consequences and mechanisms. *Immunobiology*. 2007;212:475–490.
88. Siegrist D, Siegrist-Obimpeh P. Schistosoma haematobium infection in pregnancy. *Acta Trop*. 1992;50:317–321.
89. Malhotra I, Ouma J, Wamachi A, et al. In utero exposure to helminth and mycobacterial antigens generates cytokine responses similar to that observed in adults. *J Clin Invest*. 1997;99:1759–1766.
90. Hassan MM, Hassounah OA, Hegab M, Salah K, el-Mahrouky L, Galal N. Transmission of circulating schistosomal antigens from infected mothers to their newborns. *J Egypt Soc Parasitol*. 1997;27:773–780.
91. Kurtis JD, Higashi A, Wu HW, et al. Maternal Schistosomiasis japonica is associated with maternal, placental, and fetal inflammation. *Infect Immun*. 2011;79:1254–1261.
92. McDonald EA, Friedman JF, Sharma S, et al. Schistosoma japonicum soluble egg antigens attenuate invasion in a first trimester human placental trophoblast model. *PLoS Negl Trop Dis*. 2013;7:e2253.
93. Guadalupe I, Mitre E, Benitez S, Chico ME, Nutman TB, Cooper PJ. Evidence for in utero sensitization to *Ascaris lumbricoides* in newborns of mothers with ascariasis. *J Infect Dis*. 2009;199:1846–1850.
94. Malhotra I, Mungai P, Wamachi A, et al. Helminth- and *Bacillus Calmette-Guerin*-induced immunity in children sensitized in utero to filariasis and schistosomiasis. *J Immunol*. 1999;162:6843–6848.
95. Achary KG, Mandal NN, Mishra S, et al. Maternal filarial infection: association of anti-sheath antibody responses with plasma levels of IFN-gamma and IL-10. *Parasitology*. 2013;140:598–603.
96. Gebreegziabher D, Desta K, Desalegn G, Howe R, Abebe M. The effect of maternal helminth infection on maternal and neonatal immune function and immunity to tuberculosis. *PLoS ONE*. 2014;9:e93429.
97. Ateba-Ngoa U, Mombo-Ngoma G, Zettlmeissl E, et al. CD4+CD25hiFOXP3+ cells in cord blood of neonates born from filaria infected mother are negatively associated with CD4+Tbet+ and CD4+RORgammat+ T cells. *PLoS ONE*. 2014;9:e114630.
98. Elliott AM, Mpairwe H, Quigley MA, et al. Helminth infection during pregnancy and development of infantile eczema. *JAMA*. 2005;294:2032–2034.

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