



1.5 ANCC
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Abstract

The gut microbiome is a critical component of an individual's metabolism and overall health. The prenatal period is marked by unique inflammatory and immune changes that alter maternal gut function and bacterial composition as the pregnancy advances. The composition of the maternal gut microbiome contributes to obstetric outcomes with long-term health sequelae for mother and child. Estrogen and progesterone also have an impact on gut function, especially during the prenatal period. These physiologic changes in pregnancy allow for adjustments in maternal metabolism and weight necessary to support the pregnancy. Normal hormonal, metabolic, and immunologic changes to the maternal gut microbiome throughout the prenatal period are reviewed, including relevant implications for nurses providing care for pregnant women.

Key words: Gastrointestinal microbiome; Maternal health; Microbiota; Pregnancy.

THE MATERNAL GUT MICROBIOME DURING PREGNANCY



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An Overview of the Gut Microbiome

The 100 trillion bacteria that reside in the human intestinal tract, referred to as the gut microbiota, are essential to human metabolism and immunity (Power, O'Toole, Stanton, Ross, & Fitzgerald, 2014) (see Table 1 for definitions of terms used in this article). The most recent estimate of the ratio of bacteria to human cells in the adult body is approximately 1:1 (Sender, Fuchs, & Milo, 2016). It is also estimated that the genes contained within the human microbiota, known as the microbiome, are 150-fold greater than those contained within the individual human genome (Power et al.). Development of the human gut microbiome begins before birth and proceeds in a systematic manner, affected by factors including maternal oral microbiome, mode of birth, maternal and infant diet, and environmental exposures (Brown et al., 2013). Development of the microbiome occurs simultaneously with, and plays a key role in neurologic system maturation (Borre et al., 2014). Significant early-life disruptions of the microbiome, such as through major illness or exposure to high-dose, broad-spectrum antibiotics, can lead to chronic disease or mental disorders later in life (Borre et al.). Although the entire gut begins in the mouth and continues to the anus, the gut microbiome describes the intestinal portion alone, given that the intestine harbors the most diverse and abundant microbial community in the body (Backhed et al., 2012). The focus of this review is the gut microbiome as it is commonly defined, limited to the intestines. The state of the science is presented on the maternal gut during pregnancy, related maternal–fetal health implications, and evidence-based nursing care strategies to improve delivery of care and optimize health.

The gut microbiome provides a broad range of functions. Most importantly, it collects indigestible particles from food into fecal waste and assimilates nutritional particles, such as vitamins and minerals (Mayer, Savidge, & Shulman, 2014). It acts with the liver to detoxify and excrete xenobiotics, ubiquitous harmful foreign chemicals present in the environment (Mayer, Savidge, et al., 2014). An individual's systemic and intestinal immune systems depend greatly on the gut microbiome's function of epithelial cell renewal and management of intestinal integrity (Power et al., 2014). Without a healthy intestinal wall, bacteria migrate across the gut into the general

circulation increasing systemic inflammation (Power et al.). This migration occurs through a mechanism of intestinal permeability sometimes referred to as “leaky gut” (Power et al.). With leaky gut, junctions, composed of various proteins that link adjacent intestinal epithelial cells, are weak and fail to act as an integral barrier to migrating pathogens (Power et al.). Increased intestinal permeability is hypothesized to be the mechanism by which a dysbiotic gut is linked with low-grade inflammatory disorders like obesity and its associated conditions, insulin resistance and type 2 diabetes mellitus (Mokkala et al., 2016). High permeability allows the leakage of bacteria, and/or bacterial components like the lipopolysaccharides (LPS) contained in the cell walls of gram-negative bacteria, thus inducing a deleterious systemic inflammatory condition called metabolic endotoxemia (Cani, Osto, Geurts, & Everard, 2012).

Immunologic Changes of the Gut Microbiome in Pregnancy

During pregnancy, inflammatory states vary from higher inflammation at implantation and in labor to lower levels of inflammation in midpregnancy (Trevisanuto et al., 2013). Anti-inflammatory properties exist at the placental bed that protects the fetus from rejection, yet the mucosal surfaces of the gut and other tissues experience a low-grade inflammation with rising levels of proinflammatory cytokines and white cells as the pregnancy advances (Koren et al., 2012). When conditions like maternal obesity, gestational diabetes, or a leaky gut shift the maternal inflammatory state from a physiologic to an

Table 1. Definition of Terms

Term	Definition
Antibiotic	A type of antimicrobial drug used in the prevention or treatment of bacterial infections; some also have antiprotozoal activity
Brain-gut axis (or gut-microbiome-brain axis)	Bidirectional signaling between the gut microbes and the brain via immunological, endocrine, and neural pathways
Dysbiosis	An unhealthy imbalance in microbial composition in a part of the body
Eubiosis	A microbial composition that is balanced and associated with health in a part of the body
Microbial diversity	The range of different kinds of unicellular organisms, bacteria, archaea, protists, and fungi in a particular environment
Microbiota	The microbial community that resides on or within a particular environment, including bacteria, archaea, protists, and fungi
Prebiotic	Selectively fermented dietary ingredients that result in specific changes in the consumption and/or activity of the gastrointestinal microbiota
Probiotic	Live microorganisms which when administered in adequate amounts confer a health effect on the host



Starting in the prenatal period, maternal health and diet play a critical role in the foundation of the child's gut microbiome with long-lasting health implications.

excessive level, vascular dysfunction of the placental tissue can develop leading to deleterious effects such as fetal growth restriction and preeclampsia (Kashtanova et al., 2016; Kim, Romero, Chaemsithong, & Kim, 2015). Gut microbes found in amniotic fluid of women who experienced preterm premature rupture of membranes suggest that the gut microbiome could play a role in intrauterine infections (DiGiulio et al., 2010). Possible mechanisms of microbial translocation have been proposed; either by LPS from gram-negative bacteria that increase inflammatory mediators and prostaglandin production, via ascending inoculation through the vagina, or hematogenous spread of microbes from a leaky gut to the placenta or uterus (Nuriel-Ohayon, Neuman, & Koren, 2016).

Factors That Can Modify the Gut Microbiome

The gut microbiome is also shaped by diet and genetics. The typical Western diet consists of excessive processed foods, dietary fat, and sugars (Morrison & Regnault, 2016). This type of diet promotes excess weight gain and a dysbiotic gut and is associated with adverse maternal and child health outcomes (Dunlop et al., 2015; Morrison & Regnault, 2016; Ma, et al., 2014). Conversely, certain dietary nutrients, namely low-fat protein (for instance beans, skinless chicken, lean beef), organic proteins and produce (which reduces exposure to dietary antibiotics and pesticides), unsaturated fatty acids (for instance in canola and olive oils, flaxseeds, and salmon), whole grains, and certain strains of probiotics have been found to promote a healthy gut microbiome, enhance intestinal integrity, and reduce excessive systemic inflammation (Griffin, 2015; Kashtanova et al., 2016). Short-chain fatty acids (SCFA), such as acetate, propionate, and butyrate, are byproducts of fiber fermentation called prebiotics and serve as an energy source to intestinal epithelial cells and enhance the connections between these cells (David et al., 2014). Short-chain fatty acid production by the gut microbiota is negatively correlated with body mass index (Gomez-Arango et al., 2016a). Increased maternal serum SCFA levels can positively influence metabolic changes seen in pregnancy: maternal weight gain, glucose metabolism, and levels of various metabolic hormones (Koren et al., 2012; Priyadarshini et al., 2014). A recent study to evaluate the relationships among maternal weight, gut microbiome, blood pressure, and plasminogen activator inhibitor-1 (PAI-1) levels in overweight and obese pregnant women found the abundance of butyrate-producing bacteria to be significantly negatively associated with systolic and diastolic blood pressure and PAI-1 levels (Gomez-Arango et al., 2016a). These findings suggest increasing butyrate-producing bacteria may contribute to lower blood pressure in overweight and obese pregnant women. Studies of omega-3 long-chain polyunsaturated fatty acids also suggest protection of the intestinal wall through strengthening of cellular connections (Li et al., 2008). A recent clinical trial examined the effect of 2,000 mg omega-3 supplementation versus placebo in overweight and obese pregnant women (Haghiac et al., 2015). Although the gut microbiome was not evaluated, the primary finding was a significant reduction in the plasma inflammatory marker C-reactive protein (CRP) among the supplemented group (Haghiac et al.). This could prove to be a strategy to reduce the low-grade inflammation and higher obstetric risks suffered by overweight and obese women or those with gestational diabetes.

The rise in estrogen and progesterone during pregnancy alters gut function and microbiome composition, increasing vulnerability to pathogens.



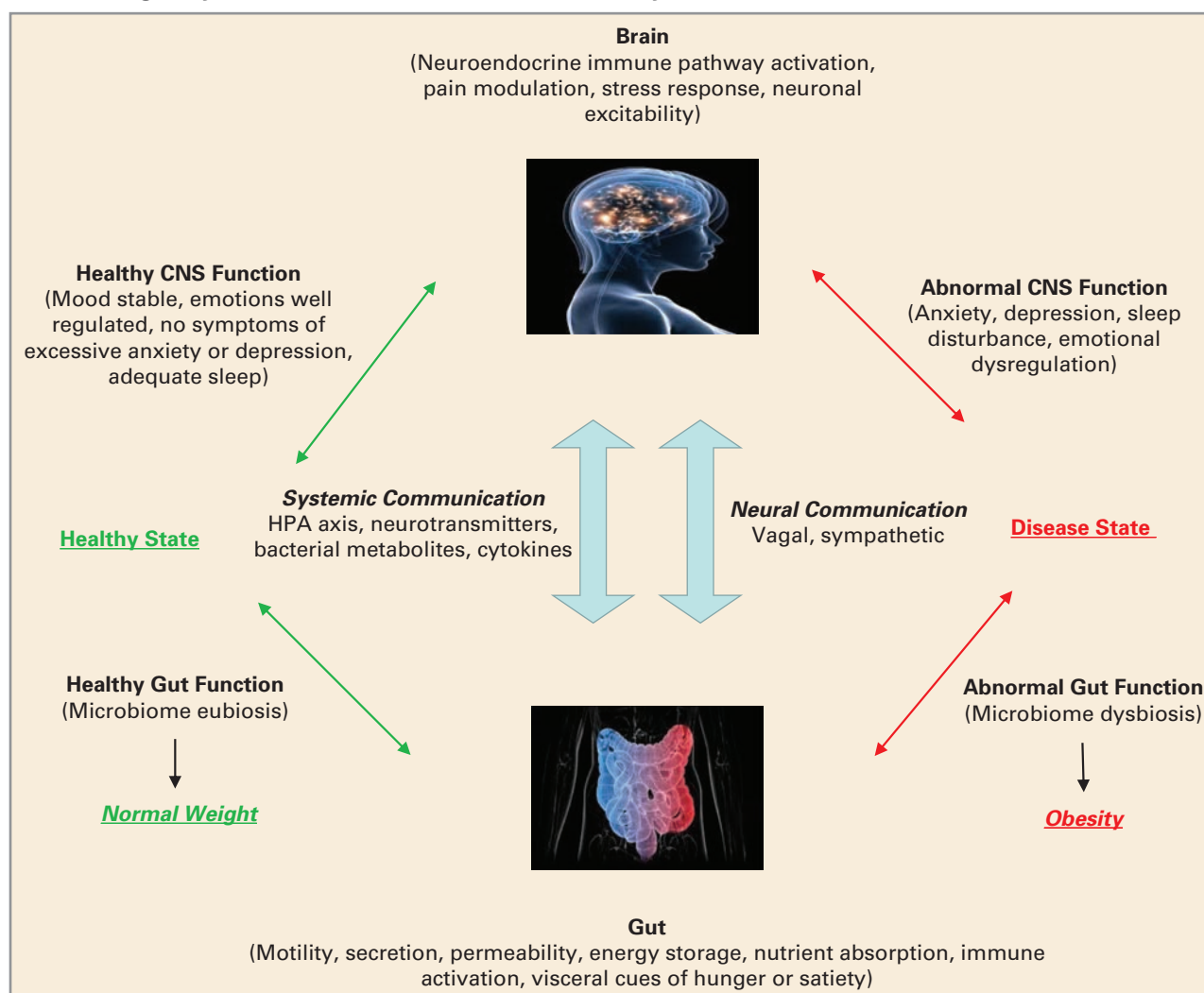
tyrate, are byproducts of fiber fermentation called prebiotics and serve as an energy source to intestinal epithelial cells and enhance the connections between these cells (David et al., 2014). Short-chain fatty acid production by the gut microbiota is negatively correlated with body mass index (Gomez-Arango et al., 2016a). Increased maternal serum SCFA levels can positively influence metabolic changes seen in pregnancy: maternal weight gain, glucose metabolism, and levels of various metabolic hormones (Koren et al., 2012; Priyadarshini et al., 2014). A recent study to evaluate the relationships among maternal weight, gut microbiome, blood pressure, and plasminogen activator inhibitor-1 (PAI-1) levels in overweight and obese pregnant women found the abundance of butyrate-producing bacteria to be significantly negatively associated with systolic and diastolic blood pressure and PAI-1 levels (Gomez-Arango et al., 2016a). These findings suggest increasing butyrate-producing bacteria may contribute to lower blood pressure in overweight and obese pregnant women. Studies of omega-3 long-chain polyunsaturated fatty acids also suggest protection of the intestinal wall through strengthening of cellular connections (Li et al., 2008). A recent clinical trial examined the effect of 2,000 mg omega-3 supplementation versus placebo in overweight and obese pregnant women (Haghiac et al., 2015). Although the gut microbiome was not evaluated, the primary finding was a significant reduction in the plasma inflammatory marker C-reactive protein (CRP) among the supplemented group (Haghiac et al.). This could prove to be a strategy to reduce the low-grade inflammation and higher obstetric risks suffered by overweight and obese women or those with gestational diabetes.

The Brain-Gut Axis

Animal and human studies support the existence of a significant bidirectional relationship between the gut and the brain, involving multiple neurologic and endocrine signaling systems (Mayer, Knight, Mazmanian, Cryan, & Tillisch, 2014). Normal central nervous system function relies on a healthy gut microbiome or “eubiosis” (Aitken & Gewirtz, 2013). The discovery of two-way signaling between the gut and brain has led to this system being coined, the “Brain-Gut Axis” (Foster & McVey Neufeld, 2013; Gareau, 2014). In a healthy individual, the autonomic nervous system, the enteric nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and the immune system work in synchrony bidirectionally between brain and gut (Cepeda, Katz, & Blacketer, 2017; Foster & McVey Neufeld). When there is a disruption of any of the components of this system, disease may manifest (Foster & McVey Neufeld; Gareau). The bidirectional nature of the brain-gut axis, magnified by gut inflammation, can impact the central nervous system, body weight, immune status, and behavior (Cepeda et al.) (Figure 1).

The impact of stress on the neuroendocrine system, especially when chronic, can result in immunologic dysregulation and heightened risk and virulence of infection (Cepeda et al. 2017). Disproportionate rates of infections have been found in chronically stressed minority populations and are thought to be a source of higher rates of

Figure 1. The bidirectional communication of the brain-gut axis occurs via systemic and neural mechanisms. It contributes to a healthy state with gut eubiosis and normal weight or a disease state with gut dysbiosis and increased risk of obesity



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preterm birth in these populations through dysbiotic gut microbe translocation mechanisms previously described (Culhane, Rauh, & Goldenberg, 2006; Mendez, Hogan, & Culhane, 2014).

Hormonal Changes in Pregnancy and the Gut Microbiome

The prenatal period is marked by dramatic hormonal shifts with resultant unique inflammatory and immune changes that alter gut function and bacterial composition (Brantsaeter et al., 2011; Koren et al., 2012). Estrogen and progesterone impact the composition of the gut microbiome through their effect on bacterial metabolism and growth and virulence of pathogenic bacteria (Mulak, Taché, & Larauche, 2014). An example of this is the susceptibility to *Listeria monocytogenes* infections in pregnancy partly due

to elevated estrogen and progesterone levels leading to adverse outcomes, including preterm birth or stillbirth (García-Gómez, González-Pedrajo, & Camacho-Arroyo, 2013). Dramatic changes in ovarian hormones during the prenatal and postpartum periods also affect gut contractility and transit (Mayer, Savidge, et al., 2014). It is plausible that the hormone levels involved in increasing gut transit time are an adaptive response to allow greater nutrient and energy harvest, thus promoting weight gain in pregnancy.

Metabolic Changes in Pregnancy and the Gut Microbiome

The consequences of gut dysbiosis that lead to obesity and, likely, to excessive gestational weight gain have only recently been explored in human pregnancy (Angelakis, Merhej, & Raoult, 2013). Of particular interest is the

recognition that the immune and metabolic changes that occur normally in pregnancy are comparable to metabolic syndrome outside of pregnancy (Chassaing & Gewirtz, 2014). With no differences in diet, including total energy intake, pregnant women have been found to gain greater adiposity with significantly higher leptin, insulin and insulin resistance measures, cholesterol, and glycated hemoglobin with each trimester of pregnancy compared with their nonpregnant counterparts (Collado, Isolauri, Laitinen, & Salminen, 2008). The microbial diversity in the gut at the start of pregnancy appears to be similar to that of nonpregnant women (Santacruz et al., 2010). Yet, as the pregnancy advances, the abundance of gut bacteria associated with inflammatory states increases in nearly 70% of women (Santacruz et al.). The greatest change in the gut microbiota occurs in the ratio of certain key bacteria (*Firmicutes: Bacteroidetes*), mimicking the higher levels of *Firmicutes* seen in obesity (Santacruz et al.). Levels of proinflammatory cytokines (including IFN- γ , IL-2, IL-6 and TNF- α) also rise in serum; adipose and placental tissue later in pregnancy and the mucosal surfaces throughout the gastrointestinal tract reflect a low-grade inflammatory state (Cani et al., 2012). Thus, although these same metabolic and immunologic changes in a man or nonpregnant woman would be considered abnormal and a sign of a disease state, in the context of a normal pregnancy, they appear to be required, improving energy storage in fat and providing for fetal growth and lactation (Cani et al.; Chassaing & Gewirtz).

Clinical Implications of the Gut Microbiome in Pregnancy

The gut microbiome and the brain-gut axis are key players in the critical prenatal period when the maternal



Nursing strategies such as the judicious use of antibiotics and personalized education about a healthy lifestyle can promote a pregnant woman's eubiotic gut.

Clinical Implications

Nurses can promote gut health in pregnant women by:

- Conducting a detailed dietary assessment, individualized education, and counseling to follow a diet with 70–90 g low fat, organic protein daily, unsaturated fatty acids, whole grains, high fiber, low-processed sugars that include daily probiotic dairy or other cultured food products (especially containing *L. acidophilus*, *B. lactis*, and *L. rhamnosus*).
- Encouraging omega-3 polyunsaturated fatty acid dietary intake, such as through ground flax seeds, wild-caught salmon and tuna (up to twice weekly), or 2,000 mg pharmaceutical grade omega-3 supplementation that can increase intestinal wall integrity, reduce inflammatory markers in serum and tissues, and improve glucose metabolism.
- Assessing clinical prenatal labs that reflect gut health including normal glucose tolerance test and complete blood cell count.
- Identifying clinical conditions that reflect gut dysbiosis including preexisting eating disorders such as obesity, insufficient or excessive weight gain; gastrointestinal disorders including hyperemesis gravidarum, cholelithiasis, gastroesophageal reflux disease; infectious conditions such as listeriosis or toxoplasmosis; and obstetric complications such as preterm labor, gestational diabetes, or preeclampsia.
- Evaluating sources and perceived level of stress, mood, pain, sleep, and support systems used to help women in identifying ways to improve the gut-brain axis (consider psychiatric or social work referral, prenatal exercise, non-pharmacologic sleep hygiene aids, or chiropractic care).
- Monitoring gestational weight that follows the IOM (2009) guidelines to minimize the risk of metabolic and hypertensive disorders and central nervous system dysregulation, especially in high-risk groups. Counseling to increase dietary fiber and probiotic foods or supplements can confer additional protection to overweight and obese women.

and fetal microbiome are particularly sensitive and changes can impact fetal brain development (Borre et al., 2014; Mayer, Knight, et al., 2014). Negative interference with the brain-gut axis (depicted on right side of Figure 1) during these times is associated with a higher maternal and child risk for chronic intestinal disorders, conditions that affect weight and growth, and even neuropsychiatric disorders (Mayer, Knight, et al., 2014). Healthcare recommendations that promote the Institute of Medicine (IOM, 2009) guidelines for maternal weight gain by prepregnant body mass index (BMI) category, high-quality diet, and gut eubiosis should be considered in the delivery of prenatal care and in education for pregnant women. Stress, infection, and antibiotic use, especially during pregnancy, can lead to dysbiosis and may increase risk of maternal and infant neurodevelopmental disorders (Bilder et al., 2013; Vela et al., 2015).

Appropriate type, duration, and indication of prebiotic, probiotic, and antibiotic use in the prevention and treatment of illness will become an important topic for discussion with pregnant women in the future, as all act on the gut microbiome and may have an impact on overall health and gestational weight gain (Griffin, 2015). There are no current clinical guidelines to facilitate these discussions pending further research.

Dietary and lifestyle patterns that impact the brain-gut axis also need to be assessed. When a mother gains excessive gestational weight or enters pregnancy obese, metabolic changes in pregnancy are magnified, and thus the risk of gestational diabetes, fetal macrosomia, or preeclampsia is elevated (Josefson, Hoffmann, & Metzger, 2013). Identification of food sensitivities (gluten, dairy, nuts are common) and elimination of those foods from the diet reduces systemic inflammation and improves gut health. Pre- and probiotic use and increasing dietary fiber and fermented foods rich in probiotics and enzymes (such as yogurt, kefir, and miso) promote eubiosis of the gut, possibly reducing risk of elevated blood pressure and improving metabolic parameters in vulnerable overweight and obese pregnant women. Further, fiber can improve constipation and other gastrointestinal conditions commonly seen in pregnant women (Griffin, 2015; Shin 2015). Primary care and preconception evaluations should also include dietary and lifestyle assessment and counseling to reach a healthy prepregnant BMI and optimize overall health (Egan et al., 2014).

Supplementation with specific strains of probiotics, such as *Lactobacillus rhamnosus* GG and *Lactobacillus acidophilus*, combined with dietary counseling has proven effective in improving glucose metabolism in healthy pregnant and lactating women (Brantsaeter et al., 2011). Daily intake of milk-based dietary probiotics has been reported to reduce blood pressure in pregnancy as well as the incidence of preeclampsia among primiparous women (Brantsaeter et al.; Gomez-Arango et al., 2016b, Laitinen et al. 2009; Luoto et al., 2010). Lactose intolerance can often be managed by ingestion of lactase enzymes with the dairy or limiting intake to lactose-free dairy products. Daily yogurt consumption containing *L. rhamnosus* was found to have a significant protective effect against heavy metal toxicity (mercury and arsenic) in pregnant women with high-risk diets (Bisanz et al., 2014). Probiotic milk and other food products may, therefore, be worth consideration for women at greater risk for gestational diabetes, preeclampsia, and some environmental toxins.

Conclusion

Diet and lifestyle practices are modifiable factors that can affect the brain-gut axis, and ultimately, the long-term health of women and infants. The degree to which the gut microbiome contributes to the neurodevelopmental, immunological, and intestinal health of the pregnant woman and her fetus is only now beginning to be measured. Health practices and novel therapies to promote eubiosis and treat dysbiosis of the maternal gut are still to be discovered but will likely prove fundamental in the care of women in pregnancy. ✚

The gut microbiota progressively changes with each trimester of pregnancy; the composition is most commonly dominated by *Firmicutes* as in obese populations.

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