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Microbiome Aspects of Perinatal and Neonatal Health

Katherine E. Gregory, PhD, RN

Abstract

Our human cells are outnumbered ten to one by bacterial cells. For this reason, the role of microorganisms, specifically bacteria, in health and disease has brought forth intense research via the Human Microbiome Project (HMP). The HMP is a National Institutes of Health sponsored effort to build upon the Human Genome Project in understanding human genetic and physiologic diversity. Perinatal and neonatal health represents areas of high importance for knowledge generated by the HMP as the microbiome is largely influenced during pregnancy, birth, and the neonatal period by nutrition, lifestyle, environmental factors of care, and the administration of medications, specifically antibiotics. As nurses have a depth of expertise in these areas, they will make a significant contribution towards better understanding the role of the microbiome in disease, and how to manipulate the microbiome to advantage patients towards health. This paper describes the human microbiome and why it is important to overall health and disease. Three major unsolved problems in perinatal and neonatal health including (i) preterm birth; (ii) the neonatal consequences of vaginal versus cesarean birth; and (iii) neonatal gastrointestinal disease, specifically, necrotizing enterocolitis, are discussed in the context of current and future research on the human microbiome.

Keywords

microbiome; perinatal; neonatal

Microorganism: from the Greek: μικρός, *mikrós*, "small" and ὀργανισμός, *organismós*, "organism"; or **microbe**: An organism that is unicellular or lives in a colony of cellular organisms.

Bacteria: from the Greek: βακτήριον, *baktērion*, "small staff"; a large group of single-celled, prokaryote microorganisms.

Microorganisms are small unicellular organisms that colonize and form complex communities, often called microbiota, at various sites within the human body. Humans first discovered microorganisms in 1675, when Anton van Leeuwenhoek designed a microscope capable of observing these small organisms. Since their discovery, scientists have sought to quantify the number and diversity of microorganisms, the vast majority of which are bacterial cells. Bacteria are a large group of single-celled, prokaryote microorganisms. It is now known that the human microbiota is composed of approximately 10^{14} bacterial cells and that these bacterial cells outnumber the total number of human cells by approximately

Corresponding Author: Katherine E. Gregory, PhD, RN, Assistant Professor, W.F. Connell School of Nursing, Boston College, 140 Commonwealth Avenue, Chestnut Hill, MA 02467, Haley Nurse Scientist, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

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10 times[1,2]. Thus, from a cellular point of view, humans are more bacteria than they are human.

The work of Pasteur, Lister, and Koch demonstrated that microbes play a significant role in the cause and prevention of human disease. Building on this work, the aim of contemporary scientists has been to develop a more precise understanding of the mechanisms of action between microbes and human cells. As a result, new knowledge about specific factors that play a role in the complex relationships between human cells and bacterial cells has been developed. It is now known that bacteria are both helpful and harmful to their human hosts. Furthermore, evidence suggests that human health may be most influenced by the diversity of bacteria found within the human microbiota; the bacteria that are absent may be as important as the bacteria that are present[1]. Perinatal and neonatal health represents areas of high importance for this new knowledge and an intense area of research because the human microbiome is significantly influenced during pregnancy, birth, and the neonatal period. This paper will describe the human microbiome and why it is important to overall health and disease. Discussion pertaining to research on the microbiome will focus on three major unsolved problems in perinatal and neonatal health: (i) preterm birth; (ii) the neonatal consequences of vaginal versus cesarean birth; and (iii) neonatal gastrointestinal disease, specifically, necrotizing enterocolitis.

The Human Microbiome

A microbiome is defined as the totality of microbes, their DNA, and their unique interactions in a defined environment[3]. A microbiome naturally exists and can be identified in soil, in water, and in humans[3]. The *human microbiome*, broadly defined, is the full collection of microbes (bacteria, fungi, viruses, etc.) and their DNA that naturally exist in a given habitat of the human body[1,3]. The definition of a habitat is defined over a range of scales, from the entire body to a specific surface area, such as the gut or a specific region within the gut. Several habitat areas with diverse microbiomes have been identified in the human. These include the skin, the nasal and oral cavities, and the gastrointestinal and urogenital systems[4]. The habitat with the largest and most complex arrangement of microorganisms is the gastrointestinal system, which includes approximately one trillion (10^{12}) bacterial cells per one gram of feces in the average human individual[2]. This habitat is the most important to human health, not only because of the vast number and diversity of microorganisms present, but because of the attributes of the gastrointestinal system as an organ of digestion, absorption, and immunity.

Bacterial cells are typically considered harmful due to their ability to cause infection. However, it is important to emphasize that bacterial cells are often helpful to the human host. For example, the functional contributions of bacteria present within the gut include synthesis of vitamins, harvest of otherwise inaccessible nutrients, regulation of drug metabolism, renewal of gut epithelial cells, and development and activity of the immune system[1]. It is the variability between harmful and helpful bacteria that dictates health or disease. The variation in a specific microbiome may result from a combination of factors such as host genotype, host physiology, host immune system (including the properties of the innate and adaptive immune systems), host lifestyle (including diet), host pathobiology (disease status), host environment, and the presence of transient populations of microorganisms[1]. Identifying which microbes exist within specific habitats, their variation within a microbiome, how they interact with the human host, and ultimately, how much they matter to health and disease are the primary aims of the researchers involved in the Human Microbiome Project (HMP).

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The Human Microbiome Project

The Human Microbiome Project (HMP) is a component of the National Institutes of Health (NIH) Roadmap for Medical Research Program. Launched in 2007, the HMP is a 5-year, $115 million trans-NIH effort to build upon the Human Genome Project in understanding the range of human genetic and physiologic diversity, and, in turn, accelerate the discovery and translation of scientific knowledge into public health benefits[1]. The goal of the HMP is to extensively characterize the human microbiome and create a data-rich resource that will enable in-depth study of its variation in relation to any number of relevant variables (i.e. genotype, disease, age, nutrition, medication, and other environmental factors)[1]. Specific focus areas of the HMP include understanding the impacts of the microbiome on health, advancing tools and technology that will facilitate the analytical approach to the microbiome, and grappling with the ethical, legal, and social implications of the human microbiome.

The most common clinical condition currently studied in the context of the microbiome has been obesity[5–7]. Obese patients have been shown to have a different intestinal microbiota than their lean counterparts[5–7]. In addition, major alterations of the microbiota within the gut and its microbiome have been associated with obesity and with body weight loss[6]. These observations are explained by the notion that bacteria living in the gut have an impact on host metabolism via signaling pathways, with effects on inflammation, insulin resistance, and deposition of energy in fat stores[6]. Thus, it is hypothesized that the microbiota present in obese individuals creates greater quantities of energy which are absorbed across the intestine and in turn, contribute to the excessive weight in these individuals. Returning the gut microbiota to a healthy state, possibly via pre or probiotics, may be a promising path towards mitigating the conditions associated with obesity and helping to maintain a healthy weight[8]. The work conducted to date on the microbiome and obesity underscores the importance of better understanding the mechanisms of action between bacteria, especially the intestinal bacteria, and the function of human cells.

The Microbiome in Perinatal and Neonatal Health

The microbiome is significant to perinatal and neonatal health in that it has been shown to play a key role in pregnancy and preterm birth[9,10]. And, for all infants, the development of the human microbiome is greatly influenced during birth and the neonatal period[11,12]. Thus, it is important for perinatal and neonatal nurses to understand the role of the microbiome during pregnancy and the neonatal period, and to consider how future research on the microbiome may contribute towards the unsolved problems in perinatal and neonatal health.

Pregnancy and preterm birth

Preterm birth is the most significant unsolved problem in perinatal health and the leading cause of neonatal mortality and morbidity worldwide[13]. While the cause of preterm birth is multifactorial, evidence suggests that microorganisms leading to intra-uterine infection play a major role in preterm labor and delivery[10]. There are several potential sites of bacterial infection within the gravid uterus. These include the choriodecidual space (between the maternal tissues and fetal membranes), within the fetal membranes (the amnion and the chorion), and within the placenta, the amniotic fluid, or the umbilical cord of the fetus[10]. While it is most common for infection to occur following rupture of membranes, microbiologic evidence has shown that intrauterine infection also develops under conditions of intact membranes[10]. These intra-uterine infections are often sub-clinical, with few signs or symptoms. Thus, disruptive changes in the microbiome may be undetected prior to the onset of preterm labor. In addition, these infections are typically caused by cultivation-resistant microbes (i.e. mycoplasmas), which require specialized techniques for

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identification. This is problematic because culture-independent techniques (i.e. molecular methods such as polymerase chain reaction) capable of identifying these microbes are not typically available in the clinical setting.

Through the use of culture-independent methods, researchers have identified microbes that play a role in preterm labor, which were previously undetected in the amniotic fluid[9]. These methods have been used to amplify, identify, and quantify ribosomal DNA (rDNA) specific to bacteria from the amniotic fluid of patients with spontaneous preterm labor and birth. Study findings, which identified 17 unique bacterial species, have shown significant associations between the presence and quantity of microbes in amniotic fluid and preterm delivery[9]. While research has not proved causation between any one microbe in the amniotic fluid and preterm labor and birth, findings suggest that among patients with spontaneous preterm labor and intact membranes, the amniotic cavity harbors a greater diversity of microbes than previously expected[9]. Future research that further quantifies the diversity of microbes within the amniotic fluid and their interaction with the human cells of the pregnant woman will be an important step towards preventing preterm labor and birth.

Vaginal versus cesarean birth

In the United States, more than 30% of all babies were born via Cesarean Section (C-section) in 2007[14]. Several factors have contributed to the current rate of C-section, and multiple studies have explored the neonatal consequences of surgical birth[15,16]. One of the major consequences of birth type is initial exposure to microorganisms. For this reason, investigators aiming to better understand the human microbiome have begun to explore the influence of vaginal and cesarean birth on early neonatal bacterial colonization.

It is thought that the human fetus develops in a sterile uterine environment and that the first exposure to microorganisms occurs at birth. When the fetus is born via the vaginal canal, the bacterial exposure is representative of the microbes present in the mother's vagina. When the fetus is born via cesarean section, the bacterial exposure is representative of the mother's skin[11]. The result of this difference is that infants born vaginally acquire bacterial species including *Lactobacillus, Prevotella*, and *Sneathia*, and infants born by C-section obtain *Staphylococcus, Corynebacterium,* and *Propionibacterium*. The differences in these exposures are significant. Not only are the functionalities of the bacterial species specific to the vagina and skin unique, but of greater importance, birth represents an important moment in bacterial colonization and the only opportunity for human passage through the vaginal canal and exposure to the vaginal microbiome.

Infants born vaginally have been shown to acquire bacteria much like that found in their own mother's vaginal canal. In vaginally born infants, the infant's intestinal microbiota is more similar to the mother's vaginal bacteria than the intestinal microbiota of other vaginally born infants[17]. In contrast, the intestinal microbiome of infants born via c-section lack any bacteria representative of the vaginal canal. The bacteria present on the skin of c-section mothers are no more similar to their own infant's microbiome that to other infants born via c-section[17]. This suggests that incidental exposures to skin bacteria in the hospital environment may contribute as much or possibly more to the developing intestinal microbiota of c-section born infants.

The direct transmission of the vaginal microbiota to an infant during birth is likely to be an important defense mechanism. Evidence suggests that approximately 64 to 82% of all reported cases of staphylococcus aureus (MRSA) infections observed in infants follow c-section birth[17]. This may be explained by the fact that infants born via c-section lack exposure to the protective bacteria present in the vaginal canal and are predominately colonized by *Staphylococcus* and other microorganisms from the mother's skin. Future

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research must seek to further explain the mode of transmission of bacteria between mother and infant during birth, and the resulting colonization of infants born via vaginal and c-section birth. When the diversity of bacteria present based on the type of delivery is more fully understood, and the ideal composition of the neonatal intestinal microbiome is established, interventions aimed at enhancing the microbiome will be developed. Nursing research will make a significant contribution in developing and implementing these interventions, which will improve perinatal and neonatal health outcomes.

Neonatal gastrointestinal disease: Necrotizing enterocolitis in the preterm infant

The gut is the primary organ of digestion and absorption. In addition to its digestive and absorptive capabilities, it is the largest organ of immunity. During early colonization, which takes place throughout the neonatal period, microbes become established within the gut and begin interacting with the human host[18]. This requires the intestinal barrier to differentiate between protective and destructive microorganisms[19]. Both short and long-term health outcomes have been shown to be influenced by this process of differentiation and resulting intestinal colonization. In addition to obesity, studies conducted on inflammatory bowel disease[20], allergic response[21], cancer[22], and late-onset autism[23] suggest that the composition of colonizing microbiota of the intestine, first established during infancy, may be an important factor in the development of these conditions.

Premature infants have an abnormal colonization, tend to colonize with fewer bacteria, are routinely administered antibiotics, are often born via c-section, and are exposed to highly pathogenic institutional organisms[24–27]. Thus, examining the intestinal bacteria present in premature infants may be an important determinant in the pathogenesis of disease, specifically inflammatory gastrointestinal disease such as necrotizing enterocolitis (NEC)[28].

It has long been suggested that microbes play a role in the pathogenesis of NEC; however, the mechanism of microbial action leading to this disease has not been fully explained. Technology has evolved such that instead of simply culturing stool samples from patients to determine the content of bacteria in the gastrointestinal tract, molecular approaches now exist by which this can be done more accurately. The ability to accurately determine the composition of the intestinal microbiota via stool samples is important because stool samples provide the necessary cells for these targeted analyses and have the advantage of a noninvasive approach that does not deplete the infant of a highly limited blood volume.

Using advanced technologies and stool samples, studies have shown that infants who develop NEC have greater exposure to antibiotics and significantly less bacterial diversity in their intestinal microbiome[29]. The limited diversity identified in these infants is an important finding; it adds evidence to the evolving notion that NEC, like many diseases, is not caused by a single bacterial organism but the presence of certain pathogenic bacteria and the lack of protective bacteria[30]. Evidence pertaining to the use of probiotics for the prevention of NEC supports these findings in that adding protective bacteria to the intestinal microbiome is beneficial to disease prevention and health promotion[31]. Further research is needed to more fully identify which bacteria are present under conditions of disease and health in preterm infants. Once these bacteria are identified, interventions such as the administration of pre and probiotics may be further developed and implemented.

Conclusion

The human microbiome in perinatal and neonatal health represents an important item on the agenda for future research. Several of the unsolved problems that occur during pregnancy and the neonatal period are likely to be influenced by bacterial colonization and the evolving microbiome. The microbiome is largely influenced by nutrition, lifestyle, environmental

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factors of care, and the administration of medications, specifically antibiotics. As nurses have a depth of expertise in these areas, they will make a significant contribution towards better understanding the role of the microbiome in health and disease. More importantly, future perinatal and neonatal nursing initiated research will contribute towards developing new knowledge on how to manipulate the microbiome to prevent disease and advantage patients towards health.

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