Short Communication

Obstetricians & Pediatricians: Cornerstone to Infant Gut microbiome Development

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Abstract

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Background: It is inevitable that all physicians regardless of their specialty will soon be approaching their patients’ health care with consideration of the gut microbiota as standard practice. Fundamentally, the incorporation of gut microbiome principles into clinical practice can be broadly categorized into two working areas; that of gut microbiome health and that of disease diagnostics which includes the prevention and treatment management of various disorders and diseases.

Significance: Obstetricians and pediatricians currently play critical roles in the development of the infant gut microbiome as each specialty assist mothers-to-be in making decisions regarding mothers’ health, methods of delivery and feeding, and ultimately childhood diet. It is inevitable that all physicians regardless of specialty will soon be approaching patient care with consideration of the gut microbiota.

Aim: Our aim here is to provide obstetricians and pediatricians as well as other physician specialties with clinically relevant information regarding the development of fetal and infant gut microbiomes, fundamentals of gut microbiome dysbiosis which serves as the basis of many disease causations. In summary we provide key points that physicians can immediately incorporate into clinical practice which have a positive impact upon the overall health of the gut microbiome.

Conclusion: Here, we have illustrated the immediate need for physicians and health care providers to understand the role of gut microbiota in human health and disease prevention. We concluded that twenty-first century medicine now includes the incorporation of gut microbiome analysis within clinical practice as part of overall patient health management.

ABBREVIATIONS

OB-GYN: Obstetrician and Pediatric; LPS: Lipopolysaccharide; SCFAs: Short Chain Fatty Acids

INTRODUCTION

The residential microbial populations of the distal large intestines have carried out numerous life functions for human hosts since the dawn of existence [1, 2]. Among an array of biological processes, the fundamental role of the gut microbiota (the specific types of bacteria species) is that of an energy harvester of otherwise indigestible dietary polysaccharides and plant fibers. As an energy harvester the population greatly influences the storage and utilization of energy molecules, the production of vitamins, regulation of host metabolism, and modification of intestinal permeability and the induction of inflammatory cascades [3,4]. Due to the highly individualized and resilient nature of the gut microbiome (specific species, their genes and byproducts), there is now substantial evidence supporting the reality of more cost effective, prevention centered health care which is based upon various metagenomic biomarker profiles and or compositional dynamics (taxonomic profiles) of the gut microbiota [5-8]. However, given the deeply interwoven relationship between the human host and their residential gut microbiota in conjunction with the influence of numerous biological and environmental confounding factors, mainstream utilization of these targeted disease profiles as viable diagnostic tools has been reserved for only a few disorders such as Clostridium difficile infection [9-11].
Albeit, it is inevitable that regardless of their specialty all physicians will soon be approaching patient health care with consideration of the gut microbiota as standard practice [12,13]. The incorporation of gut microbiome principles into clinical practice can be broadly categorized into two working areas; that of gut microbiome health and that of disease diagnostics which includes the prevention and treatment management of various disease states. It is our aim here to provide obstetricians and pediatricians (OB-GYNs) in particular with clinically relevant information regarding the health and development of the infant gut microbiome, the fundamentals of gut microbiome dysbiosis which serves as the basis of many disease causations. In summary we provide key points that physicians can immediately incorporate into clinical practice which have a positive impact upon the overall health of the gut microbiota.

Obstetrician and Pediatric Role in Infant Gut Microbiome Development

Historically medical teachings have characterized the in utero environment and neonate meconium (first stool) as being sterile and free of microbial populations [14]. However, research has shown both to contain various cultivatable and non-cultivable microbes [15-17]. While their true point of origin remains unclear, theories suggest microbial populations within the placenta and amniotic fluid were once vaginal flora that ascended and translocated the choriodedimal membranes and then colonized within these locations [18-20]. Despite the uncertainty of the point of origin, studies have found that early gut microbiome colonization occurs rapidly during gestation as the fetus swallows amniotic fluid. A theory supported as there is a high degree of similarity found between the microbial populations within the amniotic fluid and those present in the meconium [21]. It is well documented that certain bacterial infections of the placenta and amniotic fluid result in a fetal inflammatory response and such infections are associated with prematurity, multiple organ dysfunctions and possibly fetal death [22]. Now, there is also association with postnatal morbidities such as brain white matter disease, chronic lung disease and necrotizing enterocolitis and disturbances within the colonizing fetal gut microbiome occurring throughout gestation, delivery and feeding [23].

The method of delivery and antibiotic usage during infancy and childhood are among the most profound factors beside diet affecting the developing infant gut microbiome. During pregnancy structural changes within the vaginal flora is characterized by a lower population diversity dominated by Lactobacilli, Clostridiales, Bacteroidales, and Actinomycetales. The Lactobacilli primarily assist the neonate and infant in the digestion of breast milk [24]. Breastfeeding then introduces new microbial communities and stimulates the maturation of the neonatal gut microbiome. The use of commercially available formula compared to breast milk has been found to impair the proper development of the neonatal immune system as well as alter gut microbiota [25, 26]. Researchers report that Caesarean delivery and antibiotics during pregnancy, infancy and childhood also increase the risk of many disease states including: obesity, diabetes, asthma, autism, mood disorders and celiac disease in both child and throughout adulthood [27-32] specifically, Caesarean deliveries have been associated with a 46% higher risk of childhood obesity and exposure to antibiotics during the second and third trimesters of pregnancy has been associated with an 84% higher risk of obesity development compared to unexposed children [33]. Antibiotic usage during early age further increases the risk of developing metabolic syndromes and is associated with drastic reduction in species of gut microbiota. Additionally, there is only partial recovery of the gut microbiota to its original pre-antibiotic treatment state with each antibiotic treatment [34]. Understanding obesity is the second leading cause of preventable death in the United States, early prevention during childhood is vital to future reductions in adult overweight and obesity prevalence [35]. Shortly after birth, the neonatal gut microbiota begins to resemble that of the mother’s vaginal flora or in cases of Cesarean section and breast-feeding, those of maternal skin. Facultative bacteria are among the first to colonize within the large intestine followed by environmental transfers of anaerobic bacteria. Neonates are also reported to obtain initial microbial inoculations through contact with the skin of caretakers and or others with close contact [36].

Infants born by Caesarean and or have mothers who received antibiotic treatment during pregnancy, labor and delivery, who have immunologic or metabolic complications may benefit from an inoculum of vaginal bacteria [37]. As researchers and OB-GYNs seek to improve the health of the early infant gut microbiota as well as to decrease the risk of adulthood disease development, fetus born under these conditions are now being swabbed with microbial flora obtained from sterile gauze vaginally implanted within the mother during delivery [38, 39]. Ultimately, OB-GYNs play critical roles the in the initial development of gestational, fetal, neonate and infant gut microbiomes as they assist mothers-to-be in making critical decisions regarding their own health as well as methods of delivery, infant feeding and eventually childhood diet. These decisions are now of even greater importance as each directly affect the future health of the gut microbiota into adulthood.

Characterizing a Healthy Gut Microbiome

Due to the highly individualized nature of the gut microbiome, researchers have yet to agree upon a core taxa shared across all adult populations. Therefore, the characteristics of a “healthy” are loosely defined but are rapidly being elucidated. Fundamentally gut microbiome health is defined in terms of its’ stability, or the ability of the community to withstand imposed stresses over lifetime, its’ resilience, the ability of the community to return to point of structural equilibrium post stressor, the overall diversity or variation within gut microbiota populations and by its richness referring collectively to the genetic and byproduct expressions of the gut microbiome [40-44]. During infancy and early childhood the diversity of the microbiota is very low. Because of this ‘lag time’ in development, the infant gut microbiome is highly unstable compared an adult and is extremely susceptible to perturbation by biological and environmental influences [45-47]. Development is not random and occurs systemically much like other organs within the infant body but poses far greater influence and impact upon overall health [48-50]. The young gut microbiome continues to develop and eventually stabilizes at ~3 years of age when it resembles that of an adult.
At maturity the adult gut microbiota are largely inclusive of two bacterial phenotypes, the **Bacteroidetes** and **Firmicutes**. In lower abundances are **Proteobacteria**, **Actinobacteria**, **Fusobacteria** and **Verrucomicrobia** phyla. Once established the composition of the adult gut microbiota is stable but remains highly susceptible to perturbation through pathogenic infection, environmental exposures lifestyle influences, intestinal surgeries and most significantly antibiotic treatments and dietary changes [51, 52].

Intestinal epithelia cells bound by adherens and tight junctions serve as foundation for the intestinal barrier created by the rigid lipid bilayer of enterocyte brush borders. The barrier consists of two interrelated structures including the enterocyte brush border and the mucoid barrier ≈800 µm thick. The mucoid barrier serves to compartmentalize both the resident gut microbiota as well as ingested pathogenic microbes within the intestinal lumen as the antimicrobial sub layer of the mucoid barrier inhibits their access to epithelial cells [53, 54]. As depicted in (Figure 1), the gut microbiota reside as a tightly bound community encased in a polysaccharide film adjacent to the protective intestinal barrier [55]. The mucosal layer is a key contributor to the structural and functional stability of gut microbiota as well as assists in the formation of gut microbiome ‘biofilm’ which allows the population to be tolerated by the human host immune system [56-58]. The byproducts generated and or released by the microbiota population can diffuse across the mucoid barrier and be carried via the circulatory system to brain or targeted body sites [59, 60]. Biological alterations, host stress, diet and or other biological disturbances between the microbiota biofilm and the mucosal barrier, leaves the human host vulnerable to pathogenic infections and development of other metabolically related diseases [61, 62].

**Gut Microbiome Dysbiosis**

In a state of gut microbiome dysbiosis there is a fundamental shift in the phyla of the gut microbiota resulting in increased proportion of **Bacteroides** compared to the **Firmicutes**. Dysbiosis causation is primarily associated with antibiotic usage and or poor diet in infants, children and adults. However, among other causes age related dysbiosis can also occur in individuals >60 years old [63]. Dietary induced gut microbiome dysbiosis is most common and profound, and is directly associated with the causation of many conditions including intestinal disorders, obesity, diabetes, neurological disorders, autism, coeliac disease, allergy, asthma, cardiovascular disease, behavioral disorders and mood and neurological disorders [64-68]. As shown in (Figure 2), during ‘early phase’ dysbiosis an unhealthy gut microbiome is identifiable by DNA sequencing of patients’ stool sample that is marked by alteration in the overall diversity and richness of the gut microbiota and a decrease in the Bacteroidetes-Firmicutes ratio. ‘Late phase dysbiosis’ is characterized by the effects of early phase that have physically manifest within the human host such as systemic inflammation or adiposity (commonly known as obesity) [see Fig 1 for healthy gut microbiome reference]. While researchers elucidate metagenomic profiles and the taxonomic ratios of microbial populations across different diseases and diet types, there is concurrence that as the prevalence of gram
negative bacteria increases and there is marked thinning of the intestinal mucosal lining during dysbiosis [69, 70]. The term metabolic (microbial) endotoxemia characterizes the thinning of intestinal mucosal lining allowing for increased gut permeability and increased circulation of gram negative bacteria endotoxin, lipopolysaccharide (LPS) [71, 72]. The human immune response to (LPS) includes an inflammatory response capable of suppressing the immune system, increasing systemic inflammation, macrophage infiltration, inflammation within adipose tissue, increases in circulating pro-inflammatory cytokines and activation of colonic NF-κB. Ultimately, researchers have concluded that gut microbiota have propensity set the threshold for development of metabolic endotoxemia and that human diet is one the most, if not the most important factor contributing to gut microbiome dysbiosis [73-75].

Importance of Infant and Childhood Diet

The importance of diet in the development and long-term health of the gut microbiome cannot be over emphasized as it is directly related to gut microbiome dysbiosis which in turn is highly associated with the causation of childhood overweight and obesity [76]. Many foods consumed during infancy and childhood, contain abundant quantities of refined sugar and fat providing excess fuel for gut microbiota [77]. The excess energy is storage within adipocytes induces white adipose tissue to then synthesize and release fatty acids accompanied by pro-inflammatory adipokines (cytokines, chemokines) cascades. This biological cycle of microbial metabolic endotoxemia or adiposity, manifest physically as obesity and is exacerbated through continued consumption of a energy dense, nutrient poor diet commonly referred to as a Westernized diet type [78-82]. Comparing the gut microbiomes of European children consuming a Westernized diet high in fat, sugar and animal protein, to those of children from rural Africa consuming a low animal protein, high-carbohydrate diet, researchers found the African populations had an increase in overall gut microbiome diversity and gene richness. Among other variables possibly affecting the gut microbiota including sex, race or geographic location, the diet contributed more so to the differences between the study populations [83-86].

Researchers have also reported the first year diet is critical as affects gut microbiome development, appetite regulation and adipose stem cell biology [87]. Beginning at birth, the gut microbiota depends upon the host to provide their energy source of natural plant fibers and polysaccharides. These nutrients are then fermented and used to produce short-chain fatty acids (SCFAs); acetate, propionate and butyrate. Important products providing ≈10% of the total dietary energy supply in humans with required concentrations of SCFAs including 40mM acetate, 20mM propionate and 20mM butyrate [88-95]. Ultimately, it is important for physicians to consider the health of the infant and childhood gut microbiome in terms of future disease prevention, especially for detrimental disease such as obesity [96, 97]. There is power in patients knowing the reasons for natural diets and benefits in nourishing their gut microbiota [98]. A summary of clinically relevant points regarding the gut microbiome that can be incorporated by all physician specialties is shown in (Figure 3).
CONCLUSION

While humans share the majority of their genomic composition with others, their gut microbiota are highly unique and individualized. A characteristic potentially making the gut microbiota a cost effective and easily obtainable therapeutic target compared to genetic approaches in disease diagnostics and or treatment, as well as a safer approach in prevention of many metabolic disorders [99]. Through this discussion we have illustrated the immediate need for physicians and health care providers, regardless of the specialty to understand the role of gut microbiota in human health and disease prevention and that incorporation of gut microbiome health into clinical practice is an inevitable occurrence [100]. OB-GYNs serve critical roles in gut microbiome development as many biological and environmental factors directly affect the evolving community. Going forward, twenty-first century medicine will include the incorporation of gut microbiome analysis within clinical practice as part of overall patient health management. It is not unrealistic that OB-GYNs will also serve a significant role in obtaining valuable baseline gut microbiome screenings of infants and children. Ultimately, health wise information providing insight into early stage gut microbiome dysbiosis as well as changes within the adult gut microbiome over time that could be used by primary care physicians in the prevention and treatment of many disorders and disease states [101-106].

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