PROBIOTICS IN THE FIRST 1000 DAYS

FERTILITY - PREGNANCY - INFANCY
First 1000 days of life: women, infants and their microbes

This article will introduce the impact of the microbiome from preconception through pregnancy to early childhood. The potential of probiotic usage during this period to increase the chance of conception, and to enhance the development and maturation of the child during pregnancy, infancy and early childhood will be discussed. Research in this field is paving the way to a deeper understanding of the importance of the microbiome in human development and life.

Nutritional science recognize the importance of appropriate nutrition during pregnancy and the first 2 years of life – the first 1000 days - to achieve proper development and maturation of the fetus and newborn. Increasing knowledge of the pivotal impact of the microbes associated with humans, termed the human microbiome, is also supporting the hypothesis of the importance of the first 1000 days1, and recent scientific exploration suggest that the preconception period is equally critical2.

Fertility – Microorganisms impact conception

The vaginal microbiome is important for women’s intimate health and maintaining a healthy vaginal microbiome may enhance fertility and conception. Research has also discovered that an endometrial microbiome, different from the vaginal microbiome, exists and that they both play a role in conception. Specifically, lactobacilli-dominated endometrial and vaginal microbiomes are greatly associated with positive reproductive outcome3–5. Preliminary case reports suggest that the application of probiotics to enhance pregnancy outcomes in women undergoing in vitro fertilization could be beneficial6.

Pregnancy – A balanced microbiome provides advantages

During the first 1000 days of life, adequate intake of carbohydrates, proteins and lipids are recommended, as well as the consumption of particular essential micronutrients important for pregnancy including zinc, folate and vitamin D13. The maternal physiological changes occurring in pregnancy can cause adverse conditions, of which some have been correlated e.g. periodontitis and gestational diabetes mellitus14. With physiological changes comes changes to the maternal microbiome in different body sites, including the uterus and placenta, previously considered to be sterile. These microbial changes have also been associated with adverse physiological conditions in the mother15. An imbalanced vaginal microbiome lacking lactobacilli may affect outcomes of pregnancy for mother and newborn alike. The adverse pregnancy complications include preterm birth, sepsis, miscarriage and preterm premature rupture of membranes (PPROM)16–19.

Fact box:

Lactobacilli in the male urogenital microbiome is associated with health.

Preclinical investigation has indicated that PB01 may lead to improved sperm motility and increased antioxidative capacity, which could protect the male

Men seeking to impregnate women are recommended to make various lifestyle changes, such as exercise, cessation of smoking and dietary habits and even consumption of specific dietary supplements1,4 is sometimes recommended. Microbes associated with the male urogenital area have been more or less neglected, but more focus is now being dedicated to understanding the male urogenital microbiome. In general, the microbiome in the male urogenital system is more diverse than the healthy vaginal microbiome, but does also feature lactobacilli7. Lactobacilli has been identified in higher amounts in seminal fluid from healthy men compared to patients with prostatitis, suggesting that lactobacilli also are associated with health in men10. Although less investigated, the use of probiotics has recently presented itself as an intriguing mean to improve male fertility potential11,12.

Fact box:

Microbes play a role in fertilization, conception and pregnancy

A well-balanced vaginal microbiome is important for optimal birth
The maternal microbiome is a factor in the proper development of the fetus, both when it comes to preparing the fetal immune system for delivery into the world, but also for establishing a well-balanced intestinal microbiome. Probiotics have been suggested to provide a potential for supporting an appropriate development of the fetal and infant gut microorganisms, in addition to priming the fetal and infant immune system\textsuperscript{20,21}. Furthermore, probiotics have shown promising effects on maternal adverse conditions, such as gestational diabetes, preterm birth, preeclampsia and PPROM\textsuperscript{22–24}.

Infancy – A healthy development depends on microorganisms

The gut microbiome of the infant, dominated by bifidobacteria, is characterized by less microbial diversity compared to the adult gut microbiome. Besides the maternal microbiome, two other factors heavily affect the composition and development of the infant gut microbiome: mode of delivery and type of feeding. Several studies have shown that the gut microbiota of infants born by C-section is less diverse and contains fewer bifidobacterial than those born vaginally. Furthermore, delivery by C-section has been associated with a higher risk of developing inflammatory bowel disease (IBD) and obesity\textsuperscript{11,25}.

In relation to feeding of the newborn, breastfeeding is preferred over formula-feeding. Breastfeeding has a profound effect on the development of the newborn and the infant gut microbiome as breast milk, in addition to nutrients and protective compounds for the newborn, also provides nutrients for the developing gut microbiome. These nutrients, termed human milk oligosaccharides (HMOs), are specifically metabolized by bacteria in the newborn gut, strongly favoring the proliferation of bifidobacteria, which is essential for the proper development of the infant gut microbiome\textsuperscript{11,15,26–28}.

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Within the first 3 years of life, the gut microbiome matures and develops into an adult-like gut microbiome with a multitude of different microbial species, primarily bacteria. The transition is mainly driven by the weaning of the infant and gradual introduction of solid foods. The primary changes observed are a decrease in bifidobacteria and an increase in bacteroioidetes and firmicutes\textsuperscript{25,30}. The proper development of the gut microbiome has been proposed to be of utmost importance, as an inappropriate development of the microbiome can lead to various adverse conditions in the long-term, including asthma\textsuperscript{31}.

In relation to the infant and child microbiome, probiotics may shape the microbiome toward a healthy, balanced state. Especially bifidobacteria, frequently in combination with lactobacilli, have proven beneficial in children, where a dysbiotic microbiome is implied, e.g. antibiotic-associated diarrhea, various infections and even IBD conditions (ulcerative colitis)\textsuperscript{32}. The combination of bifidobacteria and lactobacilli has also been shown to reduce the risk of atopic dermatitis, when the probiotics have been consumed by infants/children\textsuperscript{33}. Furthermore, probiotics seem to affect the overall health of preterm infants with a marked reduction in the risk of developing necrotizing enterocolitis (NEC)\textsuperscript{34}. Finally, it has recently been suggested that probiotic consumption during pregnancy could even affect the composition of HMOs in breast-milk\textsuperscript{35}.

Figure 2: The illustration highlights the major bacterial groups in the gut microbiome at various stages of life, and the factors affecting the composition of microorganisms at different life stages. One OTU is considered to reflect one bacterial species. The figure is from reference 30 (Dicks et al., 2018).
Fact box:

Mode of delivery and type of feeding crucial for infant gut microbiome development.

The gut microbiome settles within first 3 years of life.

Increasing amounts of research have provided evidence that the microbiota is pivotal in the development of the infant, in addition to nutrition. These findings have fostered the concept of "the first 1000 days", which covers pregnancy and the first 2 years of life. This has been extended to "the first 1500 days" concept, which takes into account the accumulating research showing the importance of the microbiome during pre-conception. In all of the stages covering the first 1500 days – from preconception to pregnancy and birth, through infancy and until the second year of life – probiotics is suggested to be a very important tool to ensure an optimal conception state, pregnancy progression, infant development and child maturation.

References


19. Lamont RF, Sobel JD, Akins RA, et al. The vaginal


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