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Probiotics - should pediatricians and neonatologists use them? A literature review

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Abstract

Aim of the study

Our aim was to review current knowledge regarding the application of probiotics in the neonatal patient population, summarize existing guidelines, and analyze treatment outcomes.

Materials and methods

The following review of the literature available in the PubMed and Google Scholar databases was performed, using the keywords: “Probiotics”, “Newborns”, “Intestinal dysbiosis”, “necrotizing enterocolitis”, “sepsis”, “caesarian section”, “allergy”.

In recent years, interest in probiotics in publications has been steadily increasing. This is associated with the discovery of the relationship between disruptions in the gut microbiome and dysfunction of the immune system, and consequently, the development of various diseases and allergies.

The composition of the natural gut microbiota in newborns can undergo changes, and as a result, we can influence it both prenatally and postnatally. According to available research, factors influencing it include the timing and

method of delivery, maternal antibiotic use during pregnancy and breastfeeding, as well as antibiotic use in newborns after birth, and the method of feeding the child.
It is suspected that disturbances in the composition of gut microbiota from the earliest stages of life contribute to the development of disorders such as functional gastrointestinal disorders (diarrhea, constipation, irritable bowel syndrome), inflammatory bowel diseases, allergies, atopic dermatitis, neurodevelopmental disorders (autism spectrum disorders), and increased risk of obesity in later years of the child's life.
When significant dysbiosis occurs, stimulating the growth of protective and nutritive autochthonous bacteria on the intestinal epithelium is difficult to achieve in any other way than using appropriately selected probiotic strains. However, it is important to remember to choose probiotics with a well-researched quantitative and qualitative composition, and to select them depending on the underlying disease, as well as the age and other conditions of the patient.

Key words: “allergy”; “cesarean section”; “intestinal microbiota”; “dysbiosis”; “newborns”; “necrotizing enterocolitis”; “sepsis”; “probiotics”

1. Introduction

According to the latest definition by the Food and Agricultural Organization (FAO) and the World Health Organization (WHO), probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [1]. This definition has also been recognized and endorsed by the International Scientific Association for Probiotics and Prebiotics (ISAPP) [2].
Particularly emphasized are the benefits derived from their antagonistic action against other microorganisms, including pathogens, during the development of a healthy gut microbiome in the first 1000 days of human life, including the prenatal period [3].
The human microbiome comprises a collection of saprophytic and commensal microorganisms that inhabit the human body [4].
Thanks to evolution and the refinement of diagnostic methods, we know that its development is influenced by both prenatal, perinatal, and postnatal factors. Among these factors, we include the transmission of the maternal microbiome through the placenta to the fetus, as indicated by studies demonstrating the presence of microbial genetic material and their metabolic products in the maternal and amniotic fluid, thus showing the indirect influence of products and medications consumed by pregnant women as well as their lifestyle choices.
Subsequently, the newborn's microbiome is influenced by the gestational age at birth and the method of delivery, while among the postnatal risk factors, we can include, among others, the method of infant feeding and the treatment administered to them, with particular emphasis on antibiotic therapy [5].

It is suspected that abnormalities in the composition of the gastrointestinal microbiota carry many negative health consequences in the future through the development of intestinal dysbiosis, which is a quantitative or qualitative disturbance of the microbiome resulting in the development of serious complications such as sepsis or necrotizing enterocolitis in the neonatal period, as well as the development of diseases in the future such as inflammatory bowel disease, obesity, or allergies. Hence, it seems justified to conduct research and create recommendations for probiotic preparations containing specific strains, which constitute a part of the prevention of microbiota disorders and support the treatment of selected medical conditions.

Considering the above, the aim of this paper is to present current information regarding the use of probiotic strains with proven efficacy and safety profiles.

2. Probiotics in newborns delivered by cesarean section.

In Poland, the percentage of pregnancies ending in cesarean section is close to 47% (data from the National Health Fund for the year 2022, as of March 11, 2024), making our country one of the leaders in Europe. This type of delivery is associated with impaired colonization of the gastrointestinal tract of newborns by commensal microorganisms [6]. An additional factor disrupting this process is the use of perioperative antibiotic therapy [7].

Newborns delivered vaginally possess gut microbiota similar to that of their mother's vaginal microbiota. It includes bacteria from the Lactobacillus spp. group, which protect against the growth of pathogenic bacteria such as Escherichia coli or Enterococcus spp., stimulate the immune system, and stabilize the gut microbiome. Cesarean section delivery deprives the newborn of these benefits, resulting in colonization by environmental and hospital personnel flora, thereby impairing colonization by bifidobacteria [8]. Consequently, the developing dysbiosis becomes a component of the pathogenesis of many diseases later in life.

As indicated by the results of meta-analyses in children born by cesarean section, compared to those born vaginally, there is an increased risk of developing conditions such as overweight and obesity (even by over 50%), asthma and respiratory infections (by approximately 20-30%), as well as psychological disorders such as autism (by up to 33%) or ADHD (Attention Deficit Hyperactivity Disorder) [6][9][10][11].

In shaping the proper gut flora in newborns, especially those born by cesarean section, breastfeeding plays an unquestionable role [6]. Breast milk contains both probiotic bacteria from the Bifidobacterium and Lactobacillus groups, as well as oligosaccharides (HMOs - human milk oligosaccharides), which serve as nourishment for the beneficial bacteria residing in the intestines.

As indicated by a study conducted by Cheng Guo et al., providing newborns born by cesarean section with an exclusively breastfed diet for the first six months of life allows for the development of a microbiome similar to that of vaginally born and breastfed infants [12]. The result of this was a reduction in complications such as respiratory infections and diarrhea in these children.

There are several factors that modify the composition of breast milk. It has been shown that significant influences include the BMI of breastfeeding mothers, their diet during pregnancy and lactation, medications they take, and any co-existing diseases. Additionally, the duration of pregnancy and lactation, the method of delivery, and perioperative antibiotic therapy also play non-negligible roles [13][14][15].

In studies analyzing the number of different bacterial strains depending on BMI, it has been demonstrated that the higher a woman's body mass, the lower the amount of bifidobacteria in their breast milk. Additionally, in the group of women with significant weight gain during pregnancy, a decrease in the percentage of beneficial bacteria was observed, with an increase in bacteria from the Streptococcus and Staphylococcus group.

As indicated by numerous studies analyzed in a 2022 review, in newborns from cesarean section deliveries, particularly those formula fed, it is appropriate to use fortified formula milk with probiotics and prebiotics, or to add probiotics separately to the child's diet. This helps shape the proper microbiota of the gastrointestinal tract in young patients [6][16].

Currently, there are no specific recommendations regarding the use of probiotics in newborns delivered by cesarean section. In the opinion presented by Polish experts, we can read that:

- the use of preparations or mixtures containing probiotics is safe for newborns and infants.
- enriching formula milk with probiotics, prebiotics, or symbiotics has a beneficial effect on the gut microbiome of newborns, making it similar to that of breastfed infants.
- all products containing probiotics and other biotics should be subject to control, and their health-promoting effects should be supported by research.

3. Microbiome disorders and the risk of overweight and obesity

As indicated by some studies, the diet of a pregnant woman, and later, the breastfeeding mother, may influence the composition of the human milk microbiota. Some of the bacteria present in breast milk originate from the mother's own gut microbiota. Consequently, the healthier and more diverse a woman's gut flora is, the richer her milk microbiome will be [13][14][15].

In published studies regarding pregnant and lactating women consuming a high-fat diet, a greater increase in bacteria from the Bacteroides group in their gastrointestinal tract has been observed, followed by the transmission of these bacteria to the child through breast milk. Moreover, it has been shown that obese pregnant women have a higher risk of having overweight children, with an increased risk of developing diabetes [17].

According to another study, which involved monitoring newborns and then tracking their development in subsequent years, the composition of the microbiome in obese children is significantly less diverse than in children with normal weight. Furthermore, there are disturbances in the qualitative composition of their microbiota. This appears to be a potential target for preventing overweight in children and its complications in the future, while also serving as an area for the development and research of additional probiotic strains and preparations [17][18].

4. Newborns treated with antibiotics.

The use of antibiotics by pregnant and breastfeeding women, as well as their administration to newborns, can lead to the development of gut dysbiosis, which may manifest in the child as antibiotic-associated diarrhea, while also potentially leading to the development of many diseases in the future. As demonstrated in a systematic review of over 150 studies, exposure to antibiotics may lead to the development of the following diseases in the future [19]:

- Atopic dermatitis: OR 1.40, 95% CI 1.30-1.52
- Food allergy: OR 1.35, 95% CI 1.20-1.52
- Allergic rhinitis and conjunctivitis: OR 1.66, 95% CI 1.51-1.83
- Wheezing: OR 1.81, 95% CI 1.65-1.97
- Asthma: OR 1.96, 95% CI 1.76-2.17
- Obesity: OR 1.21, 95% CI 1.05-1.40
- Juvenile idiopathic arthritis: OR 1.74, 95% CI 1.21-2.52
- Psoriasis: OR 1.75, 95% CI 1.44-2.11
- Autism spectrum disorders: OR 1.19, 95% CI 1.04-1.36

Among the most important actions in preventing dysbiosis after antibiotic therapy are reducing antibiotic overuse and incorporating probiotics into the therapy.

Probiotics allow to maintain or restore the proper microflora of the gastrointestinal tract during or after antibiotic therapy through receptor and nutrient competition, inhibition of microorganism adhesion to the intestinal epithelium, lowering the pH of the lower gastrointestinal tract to favor the growth of commensal bacteria, stimulating immunity, and producing substances against pathogens [20].

In 2022, a group of experts from ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition) presented the latest guidelines regarding the use of probiotics with proven efficacy in preventing antibiotic-associated diarrhea in children (without specifying neonatal patients) [21]. According to these guidelines, among the best-studied probiotic strains with proven efficacy are S. boulardii or L. rhamnosus GG in a high dose (≥5 × 10^9 CFU/24 h) [22n]. The results of randomized trials indicate that incorporating probiotics in children treated with antibiotics reduces the risk of antibiotic-associated diarrhea by half.

It's worth emphasizing a few additional principles in the use of probiotics:

- probiotics should be initiated as soon as possible after starting antibiotic treatment.
- they should be used throughout the entire duration of antibiotic therapy (the duration can even be extended up to 14 days after discontinuation of antibiotics, although there is a lack of solid data on this).
- the method of administering the antibiotic (oral/intravenous) does not influence the decision to add a probiotic; what matters is the type of antibiotic and individual risk factors such as the duration of antibiotic therapy, patient's age, need for hospitalization, comorbidities, and previous episodes of antibiotic-associated diarrhea.

Currently, there are no guidelines regarding the use of probiotics in preventing antibiotic-associated diarrhea in neonatal patients. However, due to concerns about the efficacy of the Saccharomyces boulardii strain, which in this patient group may increase the risk of developing fungemia, it seems reasonable to avoid this probiotic in newborns [23n].

5. Probiotics and premature babies

For a newborn's body to function properly after birth, it should have a well-developed immune system and intestinal barrier. Premature babies are particularly vulnerable to various postnatal complications. In this group, even in developed countries, there is still a high mortality rate caused by sepsis or serious gastrointestinal infections, including necrotizing enterocolitis (NEC) [23n].

In premature infants, the predominant bacteria in the gastrointestinal tract are from the Enterobacteriaceae and Clostridium genera, while in full-term newborns, bacteria from the Bifidobacterium and Lactobacillus genera prevail. This is significant because the second group of bacteria are components of probiotic preparations commonly used and have a positive impact on the development of the gastrointestinal epithelium and shaping the immune system [24n][25].

The etiology of complications associated with prematurity, such as NEC or sepsis, remains not entirely clear. However, it is undoubtedly influenced by the immature immune system and the incompletely developed intestinal barrier, as well as the associated gut dysbiosis.

Numerous recent studies indicate that probiotic preparations containing one or several strains of bacteria have a beneficial effect on reducing the risk of sepsis, NEC, and overall mortality in premature infants [26][27].

However, it should be noted that in meta-analyses regarding the use of probiotics in premature infants, they were discussed as a group of preparations rather than individual probiotic strains. It was also not determined whether single- or multi-strain preparations are superior, nor was the duration of therapy specified.

The issue of probiotic therapy in premature infants has been addressed by ESPGHAN (European Society for Paediatric Gastroenterology, Hepatology and Nutrition). In their published recommendations, they emphasized the effectiveness of the following strains in reducing the risk of NEC grades 2 and 3:

- Lactobacillus rhamnosus GG ATCC53103 (daily dose 1x10^9-6x10^9 CFU)
- a combination of strains Bifidoacterium infantis Bb-02, Bifidobacterium lactis Bb-12, Streptococcus thermophilus TH-4 at a dose of 3x10^8-3.5x10^8 each [23n].

Probiotic strains approved for premature infant treatment	**Safety/risk**
Strains not producing D-lactate	Safety regarding D-lactate in premature infants has not been adequately studied
Strains not containing plasmids with antibiotic resistance genes	Risk of transferring antibiotic resistance genes to gut bacteria
Preparations manufactured in accordance with Good Manufacturing Practice (GMP)	Clearly defined and tested composition with minimal risk of preparation contamination

However, it has not been demonstrated that the recommended probiotic strains in premature infants reduce the risk of sepsis development or overall mortality. The ESPGHAN Society has also issued negative recommendations for the use of such strains in premature infants, such as [23n]:

- Lactobacillus reuteri DSM 17938- due to the lack of proven effectiveness in reducing the risk of NEC, sepsis, and mortality, as well as the production of D-lactate (the safety and role of which in the development of lactic acidosis in this group of newborns is not well studied).
- Lactobacillus acidophilus NCDO 1748- as above.
- Saccharomyces boulardii CNCM I-745- due to the lack of proven effectiveness in reducing the risk of NEC, sepsis, and mortality, as well as the risk of developing fungemia, especially in patients with compromised immunity and central line insertion.

6. Probiotics in newborns and allergy prevention

Currently, the allergy issue affects nearly one-third of the global population and constitutes an important aspect in the practice of physicians across all specialties in developed countries. As research indicates, the problem will continue to grow in the coming years [28].

There are many theories regarding the causes of allergies. One of them suggests the influence of disrupted gut microbiota resulting from factors such as excessive hygiene, overuse of antibiotic therapy, an increasing rate of cesarean sections, consumption of ready-made, highly processed foods, and spending less time outdoors [3].

According to research, disturbances in the gastrointestinal microbiota in newborns predispose them to the development of allergic diseases in the future. As scientists have noted, the imbalance between beneficial bacteria

such as Bifidobacterium and Lactobacillus, and harmful bacteria like Enterobacteriaceae and Clostridium, is significant [24][29].

Hence, the role of probiotics in preventing the development of allergies appears to be crucial. In a position statement published by the World Allergy Organization (WAO) in 2015, approval was expressed for the use of probiotics to reduce the risk of developing atopic dermatitis in children from families with a history of allergies during both prenatal and postnatal periods. However, this position did not address the impact of probiotic therapy on other forms of allergies, nor did it specify which probiotic strains should be used or in what doses.

In 2020, a group of Polish specialists in the field of allergic diseases, after analyzing numerous studies, issued their own opinion regarding the justification for the use of probiotics in the prevention of these diseases [30]. They stated that probiotics can and should be used in the prevention and treatment of atopic dermatitis (AD), allergic rhinitis, and asthma. Attention was also drawn to the fact that only thoroughly researched preparations should be used.

Summary

Expanding knowledge about gut microbiota in the aspect of preventing diseases and the influence of probiotics on its modification are of crucial importance for the health protection of the youngest patients. A particularly vulnerable group of patients exposed to complications of gut dysbiosis are newborns.

The current state of knowledge confirms the validity of using probiotics in pediatric and neonatal patient groups. However, there is still a lack of an adequate number of high-quality studies and meta-analyses evaluating which specific strains, in what doses, and in which conditions to use. Additionally, the questionable quality of many probiotics and the lack of regulation regarding the testing of their composition do not positively influence the perception of these preparations in the medical community.

Nevertheless, currently, there are probiotic preparations available on the market with tested compositions and safety profiles. Therefore, it would be appropriate to recommend them for newborns both in prevention and treatment.

Author's contribution

Conceptualization, Justyna Marcicka, Wojciech Mądry and Aleksandra Mazurkiewicz; methodology, Joanna Męczyńska; software, Nazarii Saiuk; check, Joanna Męczyńska, Tomasz Seredyński and Michał Andrzej Kozicz; formal analysis, Magdalena Kołodziej and Adriana Wojciechowska; investigation, Adriana Wojciechowska and Weronika Salasa; resources, Magdalena Kołodziej; data curation, Wojciech Mądry; writing - rough preparation, Justyna Marcicka; writing - review and editing, Aleksandra Mazurkiewicz and Nazarii Saiuk; visualization, Michał Andrzej Kozicz; supervision, Tomasz Seredyński; project administration, Joanna Męczyńska; receiving funding, Weronika Salasa

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