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PROBIOTIČKA SUPLEMENTACIJA ZA RESTAURACIJU CREVNE MIKROBIOTE KOD NOVOROĐENČADI ROĐENIH CARSKIM REZOM

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SAŽETAK

Rano uspostavljanje crevne mikrobiote novorođenčadi značajno je poremećeno kod dece rođene carskim rezom, uz karakteristično odsustvo korisnih anaerobnih bakterija i veći udeo oportunističkih mikroorganizama. Ova početna disbioza povezana je sa povećanim rizikom od alergija, infekcija i drugih imunoloških disbalansa. Probiotička suplementacija predstavlja strategiju za ispravljanje ovih poremećaja. Upotreba specifičnih sojeva, posebno iz rodova *Lactobacillus* i *Bifidobacterium*, može ubrzati kolonizaciju crevnom mikrobiotom koja je slična onoj kod dece rođene vaginalnim putem. Ovi probiotici moduliraju imunološki odgovor, smanjujući Th2 profil i podstičući antiinflamatorne signale, dok istovremeno jačaju intestinalnu barijeru i poboljšavaju produkciju kratkolančanih masnih kiselina. Klinički podaci ukazuju na pozitivne efekte, uključujući smanjenje gastrointestinalnih tegoba i incidencije nekrotizirajućeg enterokolitisa kod prevremeno rođene dece, kao i poboljšanje imunoloških markera. Mehanizmi delovanja obuhvataju konkurenciju za resurse, produkciju bakteriocina i interakciju sa imunim ćelijama. Iako postojeći dokazi podržavaju potencijal probiotika u obnovi mikrobiote, varijabilnost među studijama ističe potrebu za dugoročnim praćenjem i standardizovanim protokolima kako bi se potpuno procenili zdravstveni ishodi kod ove populacije.

Ključne reči: microbiota, novorodjenčad, probiotici

Uvod

Novorođenčad rođena carskim rezom često imaju drugačiju strukturu crevne mikrobiote u poređenju sa onima rođenim vaginalnim putem, što se može manifestovati smanjenom raznovrsnošću bakterijskih populacija i odsustvom određenih korisnih bakterija koje se prenose tokom prirodnog porođaja (1). Proces kolonizacije creva kod ovih beba započinje kasnije i uz prisustvo veće proporcije oportunističkih mikroorganizama, što može imati dugoročne posledice po njihov imunološki i metabolički razvoj. Kod dece rođene vaginalnim putem u prvim mesecima života dominiraju bakterije iz porodice *Bifidobacteriaceae*, dok su kod dece rođene carskim rezom češće prisutne različite gram-pozitivne i gram-negativne bakterije koje inače nisu karakteristične za zdrave odojenčad u ranom periodu razvoja (2). Ove promene u mikrobioti su povezane sa povećanim rizikom od alergija na hranu, respiratornih infekcija i drugih imunoloških disbalansa. Pretpostavlja se da je jedan od mehanizama pomeranje imunološkog odgovora ka Th2 profilu, koji pogoduje razvoju atopijskih reakcija pri izlaganju antigenima (3). Disbioza kod novorođenčadi može uticati na proizvodnju citokina poput IL-4 i IL-10, kao i na sintezu kratkolančanih masnih kiselina koje igraju ključnu ulogu u održavanju intestinalnog integriteta.

Probiotička suplementacija predstavlja strategiju koja ima za cilj da ispravi ove poremećaje kroz unos specifičnih sojeva bakterija. Sojevi iz rodova *Lactobacillus* i *Bifidobacterium* su najčešće korišćeni zbog svoje sposobnosti da moduliraju imunološki odgovor, redukuju inflamaciju i poboljšaju funkcionalnost crevnog epitela. Osim toga, probiotici mogu poboljšati toleranciju na oralne antigene i smanjiti učestalost gastrointestinalnih tegoba poput kolika, distenzije abdomena ili produženog plača kod odojčadi (4). Kod novorođenčadi rođene carskim rezom, dodavanje probiotika, posebno u prvim mesecima života, ima potencijal da ubrza maturaciju crevne mikrobiote tako da ona bude sličnija mikrobioti dece rođene vaginalno (1). Neka istraživanja ističu da dojenje može delimično da ublaži razlike između ovih grupa beba, ali efekat je izraženiji kada se dojenju doda ciljano probiotičko delovanje. Na primer, kod novorođenčadi kojima su davani probiotički

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PROBIOTIC SUPPLEMENTATION FOR THE RESTORATION OF INTESTINAL MICROBIOTA IN NEWBORNS BORN BY CESAREAN SECTION

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SUMMARY
The early establishment of intestinal microbiota in newborns is significantly disrupted in children born by cesarean section, characterized by the absence of beneficial anaerobic bacteria and an increased proportion of opportunistic microorganisms. This initial dysbiosis is associated with an increased risk of allergies, infections, and other immune imbalances. Probiotic supplementation represents a strategy to correct these disorders. The use of specific strains, particularly from the genera Lactobacillus and Bifidobacterium, can accelerate the colonization of the intestinal microbiota to resemble that of vaginally born children. These probiotics modulate the immune response, reducing the Th2 profile and promoting anti-inflammatory signals, while simultaneously strengthening the intestinal barrier and enhancing the production of short-chain fatty acids. Clinical data indicate positive effects, including a reduction in gastrointestinal complaints and the incidence of necrotizing enterocolitis in preterm infants, as well as improved immune markers. The mechanisms of action include competition for resources, production of bacteriocins, and interaction with immune cells. Although existing evidence supports the potential of probiotics in restoring the microbiota, variability in studies highlights the need for long-term monitoring and standardized protocols to fully assess health outcomes in this population.

Keywords: microbiota, newborns, probiotics

Introduction

Infants born by caesarean section often have a different structure of intestinal microbiota compared to vaginally born infants, which can be manifested by reduced diversity of intestinal microbiota and absence of certain beneficial bacteria that are transferred during vaginal delivery (1). The process of intestinal colonization in these babies begins later and with the presence of greater proportion of opportunistic microorganisms, which can have a long-term impact on their immunological and metabolic development. In vaginally born neonates, *Bifidobacteriaceae* are among the dominant bacteria in the first months of life, while children born by caesarean section are more often found to have different gram-positive and gram-negative bacteria that are not characteristic of healthy infants in the early period of development (2). These changes in the microbiota are associated with an increased risk of food allergies, respiratory infections and other immune imbalances. One of the assumed mechanisms is the shift of the immune response towards the Th2 profile, which favors the development of atopic reactions when exposed to antigens (3). Neonatal intestinal dysbiosis can affect the production of cytokines such as IL-4 and IL-10, as well as the synthesis of short-chain fatty acids that have a key role in maintaining intestinal integrity.

Probiotic supplementation is a strategy that tries to correct these disorders through the intake of specific strains of bacteria. Strains from the *Lactobacillus* and *Bifidobacterium* genera are most commonly used due to their ability to modulate the immune response, reduce inflammation and improve the functionality of the intestinal epithelium. In addition, probiotics, can improve the tolerance to oral antigens and reduce the incidence of gastrointestinal complaints such as colic symptoms, abdominal distension or prolonged crying in infants (4). In infants born by caesarean section, the supplementation of probiotics, especially in the first months of life, has the potential to accelerate the maturation of intestinal microbita, so that it is more similar to the microbiota of vaginally born children (1). Some studies point to the fact that breastfeeding can partially repair the differences between these groups of babies, sojevi poput *Lactobacillus rhamnosus* GG beleži se smanjenje Th2 odgovora i bolja imunološka ravnoteža u odnosu na kontrolne grupe bez probiotika (3). Treba napomenuti da prenatalni i postnatalni faktori dodatno utiču na razvoj mikrobiote. Antibiotska terapija majke ili deteta, način ishrane (dojenje ili formula), kao i gestacijska starost pri rođenju mogu menjati dinamiku kolonizacije creva (5). Pored direktnih efekata na digestivni sistem, probiotici mogu doprineti opštem zdravlju preko tzv. osovine „crevo–mozak" koja povezuje gastrointestinalnu aktivnost sa neurološkim funkcijama (6). Zapaženo je da balansirana mikrobiota može uticati na sintezu neurotransmitera, modulaciju nervnog sistema, pa čak i raspoloženje novorođenčadi. Time probiotička intervencija dobija širi značaj, jer ne pomaže samo lokalno unutar creva, već doprinosi i stabilnijem neuroimunološkom razvoju.

Kada govorimo o kliničkom dokazivanju efikasnosti probiotika kod novorođenčadi rođene carskim rezom, treba biti svestan ograničenja postojećih studija. Neke meta-analize ukazuju na pozitivan trend poboljšanja mikrobiote kod ove populacije, ali varijabilnost protokola (razlike u vrstama probiotika, doziranju, dužini primene) otežava donošenje čvrstih zaključaka (4). Potrebna su dugotrajnija praćenja kako bi se procenio stvarni uticaj ovih intervencija na zdravlje nekoliko godina nakon primene. Sa naučne strane postoji interesovanje za kombinovane intervencije koje spajaju probiotike sa prebioticima ili drugim bioaktivnim supstancama koje hrane korisne bakterijske populacije.

Cilj ovog preglednog rada bio je da analizira uticaj probiotičke suplementacije na restauraciju crevne mikrobiote kod novorođenčadi rođene carskim rezom.

Metode

Pregled literature za ovaj pregledni rad sproveden je korišćenjem nekoliko elektronskih baza podataka: PubMed, NCBI, SCIndex i Google Scholar. U cilju pretraživanja literature korišćene su ključne reči: „microbiota", „novorodjenčad" i „probiotici". Uključeni su u analizu samo oni radovi koji su bili na engleskom jeziku i koji su objavljeni u periodu od 2015. do 2025. godine.

Osnove crevne mikrobiote kod novorođenčadi

Crevna mikrobiota kod novorođenčadi predstavlja složen ekosistem sastavljen od hiljada različitih mikroorganizama, među kojima dominiraju bakterije, ali su prisutni i arheje, gljive, virusi i protozoe (6). Genetski potencijal ovih mikroorganizama prevazilazi ljudski genom, sa procenama koje sugerišu da ukupan broj gena mikrobiote može biti i do stotinu puta veći od broja gena u ljudskim ćelijama. Takva raznolikost omogućava istovremeno obavljanje velikog broja biohemijskih funkcija – od fermentacije nerazgradivih dijetalnih vlakana do sinteze vitamina poput B12 ili K. Kolonizacija creva započinje neposredno nakon rođenja. Kod beba rođenih vaginalnim putem prvi važni kontakti sa mikroorganizmima se ostvaruju tokom prolaska kroz porođajni kanal, kada se na površine tela prenose bakterije iz majčine vaginalne i intestinalne mikrobiote (7). Kod carskog reza ovaj proces izostaje, pa inicijalnu kolonizaciju dominantno čine mikrobi iz bolničkog okruženja ili sa kože majke i/ili medicinskog osoblja (8). Posledica toga je promenjena struktura ranog mikrobioma, odnosno smanjenje udela *Bifidobacterium* i *Lactobacillus*, kao i povećanje učestalosti oportunističkih vrsta koje mogu posedovati rezistenciju na antibiotike.

Struktura mikrobiote zavisi od niza faktora – tipa porođaja, načina ishrane (majčino mleko i/ili formula), prenatalne izloženosti antibioticima, genetske predispozicije i čak geografske specifičnosti sredine u kojoj novorođenče raste. Majčino mleko pospešuje rast korisnih bakterija zahvaljujući prisustvu oligosaharida koji služe kao prebiotici, dok formula često dovodi do drugačijih profila kolonizacije (9). Dosadašnja istraživanja pokazuju da kod novorođenčadi koja konzumiraju majčino mleko tokom ranog perioda postoji veća stabilnost i raznovrsnost bakterijske zajednice i tokom prve godine života. Mikrobiota u neonatalnom periodu je dinamična, te u prvih nekoliko meseci dolazi do brzih promena u sastavu usled prilagođavanja nove populacije mikroorganizama crevnim uslovima domaćina. Rani mikrobni profili kod zdrave odojčadi uključuju visoku zastupljenost anaerobnih bakterija koje proizvode kratkolančane masne kiseline (eng. *Short-Chain Fatty Acids / SCFA*), poput acetata i butirata, što igra važnu ulogu u očuvanju integriteta intestinalnog epitela i modulaciji imunološkog odgovora (10).

Kod dece sa disbiozom mogu se identifikovati promene poput povećanog prisutva gram-negativnih koliformnih bakterija koje često proizvode lipopolisaharide (LPS), snažne induktore inflamacije (11). Smanjena raznovrsnost mikrobiote se povezuje sa nestabilnijim imunološkim adaptacijama, but the effect is more pronounced when breastfeeding is supplemented with targeted probiotic action. For example, the administration of strains such as *Lactobacillus rhamnosus GG* in newborns shows the suppression of Th2 response and better immune balance compared to control groups without probiotics (3). It should be noted that prenatal and postnatal factors additionally influence the development of microbiota. The antibiotic treatment of mothers or infants, the feeding method (breastfeeding or formula feeding), as well as the gestational age at birth can alter the dynamics of intestinal colonization (5). In addition to direct effects on the digestive system, probiotics can contribute to general health through the so-called "gut-brain" axis that connects gastrointestinal activity with neurological functions (6). It has been noted that balanced microbiota can influence the synthesis of neurotransmitters, the modulation of nervous system and even the mood of infants. Thus, probiotic intervention gains wider significance, because it not only helps locally inside the intestines, but can contribute to a more stable neuro-immunological development.

As far as clinical evidence of the effectiveness of probiotics in newborns born by caesarean section is concerned, one should be aware of the limitations of existing studies. Some meta-analyses indicate a positive trend of improving the microbiota in this population, but the variability of the protocol (differences in the types of probiotics, dosage, duration of administration) makes it difficult to draw strong conclusions (4). Longer follow-up studies are needed to assess the actual health impact of these interventions several years after administration. From the scientific perspective, there is interest in interventions that combine probiotics with prebiotics or other bioactive substances that feed beneficial bacterial populations.

The aim of this review article was to analyze the impact of probiotic supplementation on the restoration of intestinal microbiota in infants born by caesarean section.

Methods

The literature search for this review article was conducted using several electronic databases: PubMed, NCBI, SCIndex, and Google Scholar. The following key words were used for the literature search: "microbiota", "newborns" and "probiotics". Only studies in English that were published between 2015 and 2025 were included in the analysis.

Basics of intestinal microbiota in neonates

The intestinal microbiota in neonates is a complex ecosystem composed of thousands of different microorganisms, among which bacteria are dominant, but archaea, fungi, viruses and protozoa are also present (6). The genetic potential of these microorganisms exceeds the human genome, while estimates suggest that the total number of genes in the microbiota may be up to a hundred times greater than the number of genes in human cells. Such diversity enables the simultaneous performance of a large number of biochemical functions – from the fermentation of non-degradable dietary fibers to the synthesis of vitamins such as B12 or K. Intestinal colonization begins immediately after birth. In vaginally born infants, the first important contacts with microorganisms occur when the baby passes through the birth canal, where bacteria from the mother's vaginal and intestinal microbiota are transferred to the body surface (7). In case of caesarean section, this process is absent, so the initial colonization is dominated by microbes from the hospital environment or from the skin of mother and/or medical staff (8). Consequentially, the structure of the early microbiome is changed, that is, the proportion of *Bifidobacterium* and *Lactobacillus* is reduced, while the frequency of opportunistic species that may be resistant to antibiotics is increased.

The structure of microbiota depends on a number of factors – type of delivery, feeding method (breastfeeding and/or formula feeding), prenatal exposure to antiobiotics, genetic predisposition and even the geographical specificity of the environment in which the infant grows. Breast milk promotes the growth of beneficial bacteria due to the presence of oligosaccharides that serve as prebiotics, while formula feeding often leads to different colonization profiles (9). Previous research shows that in infants who consume breast milk in the early period, there is a greater stability of bacterial community and a greater diversity in the first year of life. The microbiota in the neonatal period is dynamic, and in the first few months there are rapid changes in its composition due to the adaptation of the new population of microorganisms to the intestinal conditions of the host. Early microbial profiles in healthy infants include a high abundance of anaerobic bacteria that produce short-chain fatty acids (SCFA) such as acetate and butyrate, which play an important role in preserving the integrity of the intestinal epithelium and modulating the immune response (10).

što može povećati rizik za razvoj alergijskih reakcija ili gastrointestinalnih poremećaja u kasnijem životnom dobu. Mehanizam uključuje ne samo proinflamatorne signale, već i slabiju stimulaciju regulacionih T ćelija, koje inače sprečavaju prekomerne imunološke reakcije. Kod zdrave odojčadi odnosi između dominantnih rodova kao što su *Bifidobacterium, Lactobacillus*, kao i *Streptococcus thermophilus* održavaju homeostazu crevnog okruženja (12). Već mala odstupanja od ovog obrasca mogu dovesti do promene funkcionalnih puteva koji uključuju metabolizam žučnih kiselina ili sintezu bioaktivnih polipeptida.

Važan aspekt sastava crevne mikrobiote jeste njena sposobnost interakcije sa imunološkim sistemom domaćina. Kod novorođenčadi rođene carskim rezom primećen je manjak određenih tzv. nedostajućih mikroba – vrsta koje bi bile prisutne kod vaginalnog porođaja – što može rezultirati nezrelim imunološkim profilima tokom kritičnog perioda razvoja (8). Ovo stanje može pratiti povećana kolonizacija oportunističkih patogena sa potencijalnom rezistencijom na lekove, što predstavlja dodatni klinički izazov. Na nivou metaboličkog kapaciteta mikrobiota utiče na probavu složenih ugljenih hidrata, metabolizam proteina i lipida kao i apsorpciju elemenata poput gvožđa ili cinka (13). Njena pravilna struktura doprinosi uravnoteženoj produkciji metabolita koji dalje učestvuju u signalnim putevima osovine crevo–mozak–imuni sistem. Zbog toga, odstupanja od normalnog sastava ne pogađaju samo lokalno crevo već mogu imati sistemske posledice po opšte zdravlje deteta.

Uticaj carskog reza na razvoj mikrobiote

Kod porođaja carskim rezom dolazi do prekida prirodnog prenosa mikroorganizama sa majke na novorođenče, što rezultira potpuno drugačijim obrascem rane kolonizacije creva u odnosu na prirodni vaginalni porođaj. Umesto kontakta sa majčinom vaginalnom i intestinalnom florom, inicijalni mikrobi prilikom carskog reza potiču pre svega iz spoljašnje sredine – bolničkog okruženja, medicinske opreme i kože osoblja ili same majke (14). Ovakav izvor inokuluma dovodi do toga da dominaciju u ranim danima života često preuzimaju fakultativno anaerobne bakterije poput određenih sojeva *Staphylococcus, Corynebacterium* i enterobakterija, umesto obligatnih anaeroba koji inače čine jezgro zdrave neonatalne mikrobiote. Na taj način se odlaže naseljavanje korisnih vrsta poput *Bifidobacterium* i *Lactobacillus*, što prolongira prelazak ka stabilnoj anaerobnoj zajednici. Već nekoliko sati nakon rođenja, u crevima odojčadi rođenih ovim putem mogu se registrovati veće koncentracije oportunističkih mikroorganizama poreklom iz bolničke sredine, uključujući i one sa višestrukom rezistencijom na antibiotike (15). To uvećava rizik od potencijalnih infekcija i neželjenih imunoloških reakcija dok je epitelna barijera još u fazi sazrevanja. Istovremeno, izostanak ranog stimulusa od strane korisnih anaeroba može poremetiti razvoj regulacionih T-ćelija, doprinoseći Th2 polarizaciji imunološkog odgovora i povećanom riziku od atopijskih bolesti (16). Osim tipa bakterijskih sojeva, promenjena je i hronologija kolonizacije. Dok vaginalno rođena deca relativno brzo (tokom 10 dana) postižu visok udeo bifidobakterija i laktobacila, kod dece rođene carskim rezom takav profil može kasniti nedeljama ili mesecima (7).

Pored samog načina porođaja, dodatni faktori kao što su skraćeno trajanje dojenja, produžen boravak u bolnici ili antibiotska profilaksa tokom hospitalizacije dodatno utiču na dinamiku kolonizacije (17). Neka istraživanja pokazuju da ovakvi obrasci mogu trajati i tokom prve godine života ako ne postoji intervencija koja bi podržala povratak korisnih bakterija. Specifične studije ispitivale su uticaj vitamina D u prenatalnom periodu na mikrobiotu novorođenčadi rođene carskim rezom, pronalazeći povezanost između nivoa 25(OH)D i abundancije nekih taksona poput *Acinetobacter* i *Corynebacterium* (18). Ovi rezultati sugerišu da nutritivni status majke može modifikovati inicijalni obrazac kolonizacije čak i kada nema kontakta sa vaginalnom florom. Međutim, prisustvo vrsta kao što je *Ruminococcus gnavus*, koje su negativno povezane sa nekim imunološkim parametrima kod beba rođenih ovim putem, ukazuje na potencijalne dugoročne posledice koje nadilaze samu ranu kolonizaciju. U poređenju sa prirodnim porođajem primećuju se trajne razlike u nivoima glavnih bakterijskih filuma. Na primer odnos *Firmicutes/Bacteroidetes* često je pomeren ka većem udelu *Firmicutes* kod beba iz carskog reza, a ponekad se beleži i povećan odnos *Enterobacteriaceae* prema *Bacteroidaceae* (19). Takva struktura može pojačati inflamatorni tonus crevnog okruženja i uticati na metabolizam lipida, te energetsku homeostazu domaćina. Pošto se ovi parametri formiraju tokom "kritičnog prozora" prvih meseci života, odstupanja izazvana načinom porođaja mogu imati reperkusije na razvoj gojaznosti ili metaboličkih poremećaja u kasnijem životnom dobu. Razlika

In infants with dysbiosis, changes such as the increased presence of gram-negative coliform bacteria that often produce lipopolysacharides (LPS), powerful inducers of inflammation can be changed (11). The reduced diversity of microbiota is associated with more unstable immune adaptations, which may increase the risk of developing allergic reactions or gastrointestinal disorders later in life. The mechanism includes not only pro-inflammatory signals but also a weaker stimulation of regulatory T cells that normally prevent excessive immune responses. In healthy infants, relationships between dominant genera such as *Bifidobacterium, Lactobacillus,* and *Streptococcus thermophilus* maintain homeostasis of intestinal environment (12). Even small deviations from this pattern can lead to changes in functional pathways which include the metabolism of bile acids or the synthesis of bioactive polypeptides.

An important aspect of the composition of intestinal microbiota is its ability to interact with the host's immune system. In neonates born by caesarean section, the lack of certain, so-called missing microbes – strains that would be present in vaginal delivery – which can result in immature immune profiles during a critical period of development (8). This condition can be accompanied by increased colonization of opportunistic pathogens with potential resistance to drugs, which represents an additional clinical challenge. At the level of the metabolic capacity of the microbiota, it affects the digestion of complex carbohydrates, the metabolism of proteins and lipids, as well as the absorption of elements such as iron and zinc (13). Its regular structure contributes to the balanced production of metabolites that further take part in the signaling pathways of the axis gut-brain-immune system. Therefore, deviations from the normal composition do not only affect the local intestine, but can have systemic consequences for the infant's general health.

The influence of caesarean section on the development of microbiota

During caesarean delivery, the natural transmission of microorganisms from mother to newborn is interrupted, which results in a completely different pattern of early intestinal colonization compared to natural vaginal delivery. Instead of contact with the mother's vaginal and intestinal flora, the initial microbes during caesarean section originate primarily from the external environment – hospital environment, medical equipment and the skin of the staff or the mother herself (14). This source of inoculum leads to the domination of facultative anaerobic bacteria in the early days of life including certain strains such as *Staphylococcus, Corynebacterium* and enterobacteriaceae, instead of obligate anaerobes that normally form the core of a healthy neonatal microbiota. In this way, the colonization of beneficial strains such as *Bifidobacterium* and *Lactobacillus* is postponed, which prolongs the transition to a stable anaerobic community. Several hours after birth, higher concentrations of opportunistic microorganisms originating from the hospital environment, including those with multiple resistance to antibiotics, can be registered in the intestines of infants born this way (15). This increases the risk of potential infections and unwanted immune reactions while the epithelial barrier is still in the maturation phase. At the same time, the lack of an early stimulus from beneficial anaerobes can disrupt the development of regulatory T-cells, which increases the possibility for the biased orientation of the immune system towards the Th2 profile which is associated with atopic diseases (16). Apart from the kind of bacterial strains, the chronology of colonization is also changed. While vaginally born children reach a high proportion of bifidobacteria and lactobacilli relatively quickly (within 10 days), in children born by caesarean section such a profile can be delayed by weeks or months (7).

In addition to the type of delivery, additional factors such as reduced duration of breastfeeding, prolonged hospital stay or antibiotic prophylaxis during hospitalization additionally affect the dynamics of colonization (17). Some research shows that such patterns can persist during the first year of life if there is no intervention to support the return of beneficial bacteria. Specific studies have examined the influence of vitamin D in the prenatal period on the microbiota of neonates born by caesarean section, and found the connection between the level of 25(OH)D and the abundance of some taxa such as *Acinetobacter* and *Corynebacterium* (18). These results suggest that maternal nutritional status can modify the initial colonization pattern even when there is no contact with vaginal flora. However, the presence of strains such as *Ruminococcus gnavus*, which are negatively associated with some immunological parameters in infants born this way, indicates potential long-term consequences that surpass the early colonization itself. Compared to natural delivery, persistent differences in the levels of the main nije samo kvantitativna nego i funkcionalna: odsustvo dobrih anaeroba dovodi do niže proizvodnje SCFA, posebno butirata, koji je ključan za ishranu kolonocita i ima antiinflamatorna svojstva (3). Niža koncentracija SCFA može kompromitovati integritet mukozne barijere i povećati propustljivost creva za antigene iz hrane ili patogene mikroorganizme. Na imunološkom nivou to znači češću aktivaciju proinflamatornih puteva preko LPS-a gram-negativnih bakterija koje preovlađuju pri disbiozi. Iako vremenom dolazi do delimične konvergencije mikrobioma između beba rođenih različitim metodama, pojedine razlike ostaju detektabilne čak do kraja prve godine života.

Za neke funkcionalne grupe bakterija oporavak bez ciljane intervencije je spor ili nepotpun. Tu se otvara prostor za probiotike kao strategiju intervencije; selekcija sojeva sličnih onima kojima bi beba bila izložena pri vaginalnom porođaju potencijalno može ubrzati formiranje zaštitnog anaerobnog ekosistema. Treba istaći da nisu svi slučajevi carskog reza jednaki – elektivni porođaj bez pucanja vodenjaka potpuno eliminiše kontakt sa materinim genitalnim traktom, dok kod hitnog carskog reza nakon delimično započetog prirodnog porođaja može doći do ograničenog prenosa majčinskih bakterija. Ove razlike mogu donekle modifikovati obrazac inicijalne kolonizacije, pa ih treba uzeti u obzir prilikom procene rizika i planiranja intervencija.

Definicija i osnovne karakteristike probiotika

Probiotici se definišu kao "živi mikroorganizmi koji, kada se primenjuju u adekvatnim količinama, donose zdravstvenu korist domaćinu" (14). Najčešći probiotici pripadaju rodovima *Lactobacillus* i *Bifidobacterium*, iako se koriste i drugi poput *Streptococcus thermophilus, Saccharomyces boulardii* i određeni sojevi enterokoka. Svaki od njih poseduje specifične mehanizme delovanja – neki kolonizuju mukozne površine i konkurišu patogenima za vezivanje na receptorske strukture, drugi proizvode kratkolančane masne kiseline koje regulišu pH crevnog lumena, a treći podstiču sintezu antimikrobnih peptida ili bakteriocina koji direktno inhibiraju rast patogenih bakterija. Liu et al. (20) navode da delovanje probiotika uključuje konkurenciju za kolonizaciona mesta i nutritivne resurse, inhibiciju rasta štetnih bakterija putem produkcije SCFA i bakteriocina, modulaciju imunološkog odgovora stimulacijom citokina i imunoglobulina, te poboljšanje integriteta crevne barijere stimulacijom produkcije mucinskih glikoproteina. Probiotici kod novorođenčadi mogu doprineti ubrzanom uspostavljanju stabilne bakterijske zajednice putem povećanja ekspresije proteina u epitelu, čime se smanjuje propustljivost intestinalne barijere za antigene ili toksine. Neki sojevi iz roda *Bifidobacterium* povezani su sa indukcijom antiinflamatornih citokina IL-10 i TGF-β, kao i sa funkcionalnom diferencijacijom regulatornih T-ćelija (Tregs) (21), čime se doprinosi održavanju ravnoteže između proinflamatornih i antiinflamatornih signala u crevima.

Osnovna karakteristika probiotičkih mikroorganizama je njihova otpornost na uslove u gornjem delu digestivnog sistema. Oni moraju preživeti nisku pH vrednost u želucu i dejstvo žučnih soli u tankom crevu. Ovo je omogućeno specifičnim adaptivnim mehanizmima na ćelijskoj membrani, koji obezbeđuju očuvanje funkcionalnosti enzima neophodnih za metaboličku aktivnost nakon dospevanja u kolon. Probiotici deluju i putem interakcija sa ćelijama urođenog imuniteta – dendritske ćelije prepoznaju mikrobne obrasce probiotičkih sojeva preko receptora kao što su TLR2 (eng. *Toll- like receptor 2*) ili TLR4 (eng. *Tumor nekrosis faktor / TNF*), što može dovesti do sinteze citokina koji oblikuju adaptivni imunski odgovor. Neke bifidobakterije indukuju produkciju IFN-γ i TNF-α od strane imunih ćelija, dok laktobacili mogu smanjiti nivoe IL-4, IL-5 i IL-13, čime doprinose smanjenju alergijskog potencijala (22). Ove imunomodulatorne osobine čine ih pogodnim kandidatima za prevenciju atopijskih bolesti kod populacija sa većim rizikom usled disbioze u ranom životnom periodu.

Vrste probiotika relevantnih za novorođenčad

Kod novorođenčadi, posebno onih rođenih carskim rezom, izbor odgovarajućih probiotičkih sojeva mora uzeti u obzir specifične potrebe njihove još nezrele crevne mikrobiote i imunološkog sistema. Najčešće proučavani probiotici za ovu populaciju pripadaju rodovima *Lactobacillus* i *Bifidobacterium*, budući da ovi mikroorganizmi prirodno dominiraju u mikrobioti zdravih terminski rođenih beba koje su dojene majčinim mlekom. Kod beba sa odloženom anaerobnom kolonizacijom, poput one rođene carskim rezom, cilj je ubrzati uspostavljanje kolonizacije vrstama koje proizvode kratkolančane masne kiseline i doprinose modulaciji imunološkog odgovora. Među laktobacilima, *Lactobacillus rhamnosus* GG bacterial phyla are observed. For example, the ratio *Firmicutes/Bacteroidetes* is often shifted to a higher proportion of *Firmicutes* in infants born by caesarean section, and sometimes an increased ratio of *Enterobacteriaceae* to *Bacteroidaceae* is also observed (19). Such a structure can increase the inflammatory tone of intestinal environment and influence of lipid metabolism and energy homeostasis of the host. Since these parameters are formed during the "critical window" of the first months of life, deviations caused by the type of delivery can have consequences on the development of obesity or metabolic disorders later on. The difference is not only quantitative but also functional: the lack of good anaerobes leads to a lower production of SCFA, especially butyrate, which is crucial for colonocyte nutrition and has anti-inflammatory properties (3). A lower SCFA concentration can compromise the integrity of the mucosal barrier and increase intestinal permeability to food antigens or pathogenic microorganisms. At the immunological level, this means more frequent activation of pro-inflammatory pathways via LPS of gram-negative bacteria that prevail in dysbiosis. Although, a partial convergence of the microbiome between infants born in different ways occurs over time, certain differences remain detectable even by the end of the first year of life.

For some functional groups of bacteria, recovery without targeted intervention is slow or incomplete. This opens up space for probiotics as an intervention strategy; the selection of strains similar to those to which the infant would be exposed during vaginal delivery can potentially accelerate the formation of a protective anaerobic ecosystem. It should be noted that not all cases of caesarean section are equal – elective delivery without the rupture of the amniotic sac completely eliminates contact with the maternal genital tract, while in case of emergency caesarean section after a partially initiated natural delivery, there may be a limited transfer of maternal bacteria. These differences can somewhat modify the pattern of initial colonization, so they should be taken into account when assessing the risk and planning interventions.

Definition and basic characteristics of probiotics

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, bring health benefits to the host" (14). The most common probiotics belong to the genera *Lactobacillus* and *Bifidobacterium*, although others such as *Streptococcus thermopillus, Saccharomyces Boulardii* and certain strains of enterococcus are also used. Each of them has specific mechanisms of action – some colonize mucosal surfaces and compete with pathogens for binding to receptor structures, some produce short-chain fatty acids that regulate the pH of the intestinal lumen, and others stimulate the synthesis of antimicrobial peptides or bacteriocins that directly inhibit the growth of pathogenic bacteria. Liu et al. (20) state that the action of probiotics includes the competition for colonization sites and nutritional resources, the inhibition of growth of harmful bacteria through the production of SCFA and bacteriocins, the modulation of immune response by stimulation of cytokines and immunoglobulins, and the improvement of integrity of intestinal barrier by stimulation of mucin glycoprotein production. Probiotics in infants have the potential to accelerate the establishment of a stable bacterial community through mechanisms such as increased protein expression in the epithelium, which reduces the permeability of the intestinal barrier for antigens or toxins. Some strains of the genus *Bifidobacterium* are associated with the induction of anti-inflammatory cytokines IL-10 and TGF-ß, and functional differentiation of regulatory T-cells (Tregs) (21). Thus, balance between pro-inflammatory and anti-inflammatory signals within the gut is achieved.

The main characteristic of probiotic microorganisms is their resistance to conditions in the upper gastrointestinal tract. They have to survive the low pH value in the stomach and the action of bile salts in the small intestine. This is possible thanks to special adaptive mechanisms on the cell membrane that preserve the functionality of enzymes necessary for metabolism after reaching the colon. Probiotics also act through interactions with cells of innate immunity – dendritic cells recognize the microbial patterns of probiotic strains through receptors such as TLR2 (*Toll-like receptor 2*) or TLR4 (*Tumor necrosis factor – TNF*) which may result in the synthesis of cytokines that shape the adaptive response. Some bifidobacteria induce the production of IFN-γ and TNF-α by immune cells, while lactobacilli can reduce the levels of IL-5, IL-5 and IL-13, thus reducing the allergic potential (22). These immunomodulatory properties make them attractive candidates for the prevention of atopic diseases in populations at higher risk due to early life dysbiosis.

predstavlja jedan od najpoznatijih i najčešće korišćenih sojeva. Njegova sposobnost da se vezuje za intestinalni epitel, produkuje antimikrobne supstance i smanjuje Th2 tip imunog odgovora čini ga pogodnim za prevenciju alergijskih bolesti kod odojčadi (10). Pored toga, studije pokazuju njegovo delovanje na skraćenje trajanja epizoda dijareje i smanjenje rizika od infekcija povezanih sa primenom antibiotika kod dece. Još jedan važan soj je *Lactobacillus acidophilus*, koji produkuje mlečnu kiselinu, čime snižava pH lumena creva i inhibira rast gram-negativnih patogena. Kod novorođenčadi je dokumentovana njegova sinergija sa bifidobakterijama pri formiranju stabilne zajednice koja potiskuje oportunističke vrste. U grupi bifidobakterija izdvajaju se *Bifidobacterium bifidum* i *Bifidobacterium infantis*, naročito značajne zbog svoje sposobnosti razgradnje humanih mlečnih oligosaharida (HMO) iz majčinog mleka (23). Time direktno ostvaruju nutritivnu prednost u odnosu na druge bakterijske vrste u neonatalnom crevu. Njihova metabolička aktivnost dovodi do produkcije acetata koji jača integritet epitelne barijere i stimuliše rast drugih korisnih anaerobnih bakterija. Kod beba rođenih carskim rezom ova grupa probiotika može imitirati kolonizaciju karakterističnu za vaginalni porođaj, čime se ubrzava razvoj imunološke tolerancije. Pored bakterijskih probiotika*, Saccharomyces boulardii*, probiotička kvasnica, ima primenu kod odojčadi u kontekstu prevencije antibioticima izazvanog poremećaja mikrobiote i dijareje. Njegovi mehanizmi delovanja uključuju neutralizaciju toksina patogenih bakterija i stimulaciju lokalnog imunog odgovora putem povećanja sekretornog IgA (10). Iako nije tipičan stanovnik ljudske mikrobiote, *S. boulardii* prolazno kolonizuje crevo, pružajući zaštitu tokom trajanja terapije.

Važno je napomenuti da je kod proizvoda namenjenih novorođenčadi prisutna izražena potreba za standardizacijom, od identifikacije soja do kontrolisanog broja živih ćelija po jedinici proizvoda. Varijabilnost između preparata može otežati poređenje studija [10]. Takođe se uzimaju u obzir faktori kao što su otpornost na gastrointestinalni tranzit i stabilnost pri skladištenju. Kod novorođenčadi rođene carskim rezom dodatno je važno pratiti brzinu pojave ključnih anaerobnih bakterija u mikrobioti nakon suplementacije probioticima. Praćenjem odnosa *Firmicutes/Bacteroidetes* i kvantifikovanjem SCFA moguće je objektivno proceniti efikasnost intervencije. Postoje dokazi da određeni sojevi, poput *L. rhamnosus* GG, u kombinaciji sa *B. bifidum* ostvaruju bolje rezultate u smislu brže normalizacije ovih parametara u poređenju sa monoterapijom pojedinačnim sojem (24). Takve interakcije mogu biti ključne za uspeh kolonizacije ako se ciljanoj probiotičkoj kombinaciji omogući odgovarajuća nutritivna podrška.

Efikasnost probiotika u obnovi mikrobiote kod novorođenčadi rođene carskim rezom

Analiza dostupnih kliničkih studija koje su ispitivale primenu probiotika kod novorođenčadi rođene carskim rezom ukazuje na izraženu heterogenost u pogledu dizajna, korišćenih probiotičkih sojeva, trajanja intervencije i definisanja ishoda. U brojnim randomizovanim kontrolisanim ispitivanjima cilj je bio procena sposobnost probiotičkih preparata da ubrzaju kolonizaciju ključnim obligatnim anaerobima, poput *Bifidobacterium* i *Bacteroides*, čiji se razvoj prirodno odlaže kod ove populacije. Neka istraživanja fokusirala su se na praćenje promene odnosa *Firmicutes/Bacteroidetes* kao indikatora adaptacije mikrobiote ka obrascu svojstvenom vaginalno rođenim bebama (25). Rezultati sugerišu da suplementacija specifičnim sojevima laktobacila i bifidobakterija može dovesti do bržeg smanjenja učešća oportunističkih proteobakterija povezanih sa inflamatornim procesima. Poseban segment studija analizirao je imunološke ishode uz istovremeno praćenje mikrobioloških parametara. Kod dece koja su dobijala probiotike kao što su *Lactobacillus rhamnosus* GG ili *Bifidobacterium bifidum*, zabeleženo je povećanje produkcije sekretornog IgA i antiinflamatornog citokina IL-10, što ukazuje na aktivaciju tolerogenog imunološkog profila (10). Ova modulacija imunog odgovora povezivana je sa nižom učestalošću alergijskih reakcija tokom prvih godina života, iako rezultati različitih studija nisu bili potpuno konzistentni. Neke intervencije uključivale su kombinacije više sojeva u jednom preparatu, pri čemu su takvi pristupi nastojali su da obuhvate širi spektar mehanizama – od kompetitivnog potiskivanja patogena do regulacije inflamacije putem SCFA metabolita. Sukeníková et al. analizirali su ranije probiotičke protokole kod novorođenčadi visokog rizika od alergija, pri čemu se za soj *Escherichia coli* O83:K24:H31 beležila indukcija IL-10 i ekspresije CD83 u dendritskim ćelijama, bez značajnijih promena u globalnoj strukturi mikrobiote nakon deset godina (16). Ovakvi rezultati otvaraju pitanje da li pozitivni imunološki efekti zahtevaju direktnu rekonstrukciju mikrobiote ili se mogu postići modulacijom ćelijskih funkcija nezavisno od promene sastava zajednice.

Types of probiotics relevant to newborns

In newborns, especially those born by caesarean section, the specific needs of their immature intestinal microbiota should be taken into account when selecting the appropriate probiotic strains. The most commonly studied probiotics for this population belong to the genera *Lactobacillus* and *Bifidobacterium*, because these microorganisms naturally dominate the microbiota of healthy full-term breastfed infants. In infants with delayed anaerobic colonization, such as these delivered by caesarean section, the goal is to accelerate the colonization of strains that produce short-chain fatty acids and modulate immune responses. Among lactobacilli, *Lactobacillus rhamnosus GG* is one of the best known and most commonly used strains. Its ability to bind to the intestinal epithelium, to produce antimicrobial substances and reduce the Th2 type of immune response makes it suitable for the prevention of allergic diseases in infants (10). In addition, studies show its impact on reducing the duration of diarrhea and reducing the risk of antibiotic-related infections in infants. Another important strain is *Lactobacillus acidophilus* which produces lactic acid by lowering the pH of intestinal lumen, which inhibits the growth of gram-negative pathogens. In newborns, its synergy with bifidobacteria has been observed during the formation of a stable community which suppresses opportunistic species. In the group of bifidobacteria, *Bifidobacterium bifidum* and *Bifidobacterium infantis* stand out as particularly relevant due to their ability to metabolize human milk oligosaccharides (HMO) from breast milk (23). Thus, they are given a direct nutritional advantage over other strains in the neonatal intestines. Their activity results in the production of acetate, which strengthens the integrity of the epithelial barrier and stimulates the growth of other beneficial anaerobes. In infants born by caesarean section, this group of probiotics can imitate the colonization characteristic of vaginal delivery, thus accelerating the development of immune tolerance. In addition to bacterial probiotics, *Saccharomyces boulardii*, a probiotic yeast is applied in infants in the context of prevention of antibiotic-induced microbiota disruption and diarrhea. Its mechanisms include the neutralization of toxins of bacterial pathogens and stimulation of the local immune response by increasing secretory IgA (10). Although it is not a typical inhabitant of human microbiota, *S.boulardii* transiently colonizes the gut providing protection during the therapy.

It is important to note that with preparations intended for infants, there is a pronounced need for standardization, from the identification of strains to the controlled number of live cells per unit of product. The variability between preparations can make it difficult to compare studies (10). Factors such as resistance to gastrointestinal transit and storage stability are also taken into account. In infants born by caesarean section, the velocity of the appearance of key anaerobes in the microbiota should additionally be monitored after probiotic supplementation. By monitoring the ratio of *Firmicutes/Bacteroidetes* and quantifying SCFA, it is possible to objectively assess the effectiveness of therapy. There is evidence that certain strains such as *L. rhamnosus GG* when combined with *B.bifidum* give better results in terms of faster normalization of those parameters in comparison to monotherapy with one strain (24). Such interactions may be critical for the colonization success if the appropriate nutritional support is added to the targeted probiotic combination.

The effectiveness of probiotics in recovering the microbiota in infants born by caesarean section

The analysis of available clinical studies that examine the application of probiotics in infants born by caesarean section shows pronounced heterogeneity in terms of design, strains used, duration of intervention, and definition of final outcomes. In a number of randomized controlled studies, the aim was to assess the ability of probiotic preparations to accelerate the colonization by key obligate anaerobes, such as *Bifidobacterium* and *Bacteroidetes*, whose development is naturally postponed in this population. Some studies focused on monitoring changes in the *Firmicutes/Bacteroidetes* ratio as an indicator of microbiota adaptation to a pattern characteristic of vaginally born babies (25). The results suggest that supplementation with specific strains of lactobacilli and bifidobacteria can lead to a faster reduction in the participation of opportunistic proteobacteria associated with inflammatory processes. A separate section of studies analyzed immune outcomes while simultaneously monitoring microbiological parameters. In children who received probiotics such as *Lactobacillus rhamnosus GG* or *Bifidobacterium bifidum,* an increase in the production of secretory IgA and the anti-inflammatory cytokine IL-10 was registered, indicating the activation of a tolerogenic immune profile (10). This modulation of immune response was associated with a lower frequency of allergic re-

U pojedinim studijama korišćeni su presečni dizajni sa kraćim periodima intervencije, što otežava procenu dugoročnih efekata. Na primer, ispitivanja koja su trajala četiri do šest nedelja pokazala su nagli rast populacija bifidobakterija kod tretirane grupe, ali praćenje nakon prekida suplementacije otkrilo je povratak profila ka početnom stanju kod dela ispitanika. Ovi nalazi ukazuju na potrebu za dužom primenom probiotika ili kombinovanjem probiotika sa nutritivnim faktorima, poput humanih mlečnih oligosaharida, koji u majčinom mleku podstiču rast ovih bakterija (26). Fokus na prevremeno rođenu decu sa većim rizikom od nekrotizirajućeg enterokolitisa (NEC) otkriva dodatne koristi probiotika. Naime, zabeleženo je smanjenje incidencije NEC-a i mortaliteta, što se dovodi u vezu sa jačanjem epitelne barijere i potiskivanjem patogenih proteobakterija. Kombinacije laktobacila i bifidobakterija pokazale su bolje rezultate od monoterapije jednim sojem, posebno kada je praćen nivo butirata u stolici kao indirektni pokazatelj aktivnosti korisnih anaerobnih bakterija (3).

Jedna meta-analiza koja je uključivala različite populacije neonatalnih pacijenata pokazala je da elektivni carski rez nosi povećan rizik od disbioze, dok probiotička intervencija može smanjiti razlike u mikrobnoj raznovrsnosti između ove grupe i vaginalno rođene dece tokom prvih šest meseci (25). Međutim, heterogenost studija, uključujući različite protokole suplementacije i vreme započinjanja terapije (od prvih dana života do druge nedelje), ukazuje na to da nije moguće izdvojiti jedinstven optimalni pristup. Analize efikasnosti probiotika primenom molekularnih metoda sekvenciranja (16S rRNA ili metagenomski pristupi) pružile su jasniju sliku o promenama na nivou taksona nakon intervencije. Kod novorođenčadi tretirane višesojevnim probiotičkim preparatima primećena je veća stabilnost zajednice tokom vremena i manja varijabilnost između uzoraka različitih ispitanika. Takva ujednačenost ide u prilog hipotezi da rani unos probiotika može usmeriti razvoj mikrobiote ka stabilnom adultnom (odraslom) profilu ranije nego što bi to inače bilo slučaj. Neke studije usmerene na funkcionalne ishode koristile su metaboličke markere poput koncentracija SCFA ili aktivnosti enzima povezanih sa metabolizmom žučnih kiselina (27). U grupama koje su primale probiotike beležena je veća produkcija acetata i butirata, kao i povoljniji profil žučnih kiselina, koji doprinosi održavanju otimalnog koloničkog pH i inhibiciji rasta patogenih vrsta.

Važno je napomenuti da sigurnosni profil probiotika kod novorođenčadi rođene carskim rezom prema većini studija ostaje povoljan. Takođe, nisu prijavljeni ozbiljni neželjeni događaji, osim retkih slučajeva tranzitorne nadutosti ili promene konzistencije stolice. U kontekstu vulnerabilnih populacija, poput ekstremno nezrele dece ili one sa teškom imunosupresijom, razmatra se potencijalni rizik od bakteremije ili fungemije pri upotrebi određenih sojeva (10), iako su ove pojave izuzetno retke. Ograničenja pregledanih radova odnose se na kratko trajanje praćenja, mali broj ispitanika, kao i nedostatak standardizacije preparata i metoda evaluacije mikrobiote. Ipak, većine autora se slaže da ciljano odabrani probiotički sojevi imaju potencijal da modifikuju disbiozu izazvanu carskim rezom i unaprede imunološke mehanizme domaćina tokom ranog života. Dodatni dokaz dolazi iz istraživanja kod teladi pre odbijanja od mleka, gde višesojevni probiotički dodatak povećava relativni udeo korisnih firmikuta uz istovremeno smanjenje zastupljenosti *Bacteroides*, pri čemu se beleži porast serumskih IgA i IgG vrednosti, što je u skladu sa sličnim efektima opisanim kod humane novorođenačke populacije (28). Sličan obrazac privremene kolonizacije probiotika, koji nestaje po prestanku suplementacije, zabeležen je i kod odraslih pacijenata nakon eradikacione terapije za *Helicobacter pylori*, gde se tokom prve četiri nedelje uočava porast korisnih taksona poput *Lactobacillales*, uz istovremeno smanjenje potencijalno štetnih rodova, dok nakon prekida terapije dolazi do povratka strukture zajednice ka početnom mikrobiološkom profilu (29).

Zaključak

Istraživanja prikazana u ovoj analizi ukazuju na to da rana disbioza kod novorođenčadi rođene carskim rezom predstavlja klinički relevantan faktor sa potencijalnim dugoročnim implikacijama na imunološki i metabolički razvoj. Ova promenjena inicijalna kolonizacija, koju karakteristiše odsustvo ključnih obligatnih anaeroba i povećana zastupljenost oportunističkih vrsta, povezuje se sa povećanom osetljivošću na atopijske bolesti, respiratorne infekcije i gastrointestinalne poremećaje. U cilju korekcije ovih poremećaja, suplementacija probioticima, naročito sojevima iz rodova *Lactobacillus* i *Bifidobacterium*, pokazuje obećavajući potencijal. Dostupni dokazi sugerišu da takve intervencije mogu ubrzati uspostavljanje stabilne i raznovrsne bakterijske zajednice, podstaći proizvodnju kratkolančanih masnih actions during the first years of life, although there was no complete homogeneity of results between different studies. Some interventions included combinations of multiple strains in one product, and such approaches tried to encompass a wider range of mechanisms – from competitive suppression of pathogens to regulation of inflammation through SCFA metabolites. Sukenikova et al. analyzed previous probiotic protocols in infants with a high risk of allergies, where the induction of IL-10 and CD83 expression in dendritic cells was registered for Escherichia coli strain O83:K24:H31 without significant changes in the global microbiota structure after ten years (16). Such results raise the questions about whether positive immunological effects demand a direct reconstruction of microbiota or can be achieved by modulation of cellular functions independent of changes in community composition.

Cross-sectional designs with shorter intervention periods were used in some studies, which made it difficult to assess long-term effects. For example, studies that lasted four to six weeks showed a sudden increase in bifidobacteria populations in the treated group, but the follow-up after discontinuation of supplementation revealed returning of the profile to the initial state in some subjects. This indicates the need for longer administration or combination of probiotics with nutritional factors such as human milk oligosaccharides that naturally feed these bacteria in breast milk (26). A focus on pre-term infants at a higher risk of necrotizing enterocolitis (NEC) reveals the additional benefits of probiotics. Namely, the reduction in the incidence of NEC and mortality was achieved through strengthening the epithelial barrier and suppressing pathogenic proteobacteria. Combinations of lactobacilli and bifidobacteria showed better results than monotherpay with one strain, especially when the parameter of butyrate concentration was monitored in the stool as a proxy for the activity of beneficial anaerobes (3).

One meta-analysis that included different populations of neonatal patients showed that elective caesarean section had an increased risk of dysbiosis, and that probiotic intervention could reduce differences in microbial diversity between this group of infants and vaginally born infants during the first six months (25). However, the heterogeneity of studies – different protocols of supplementation, time of initiation of therapy (from the first days of life to the second week) – means that there is no single, optimal approach. The analysis of effectiveness of probiotics using molecular sequencing methods (16S rRNA or metagenomic approaches) provided a clearer picture of changes at the level of taxa after the intervention. In infants treated with multi-strain probiotic preparations, greater stability of the community was observed over time, as well as smaller variability between samples of different subjects. Such uniformity supports the hypothesis that the early administration of probiotics can “steer” the development of microbiota towards the stable adult-oriented profile earlier than it would naturally occur. Some studies that focused on functional outcomes used metabolic markers such as SCFA concentrations or the activity of enzymes related to bile acid metabolism (27). In groups that received probiotics, a higher production of acetate and butyrate was observed, as well as a more favorable profile of bile acids, which contributes to the maintenance of a healthy colonic pH and the inhibition of pathogenic species.

It is important to note that the safety profile of probiotics in infants born by C-section remains favorable according to the majority of studies. Also, no serious adverse events were reported except for rare cases of transient flatulence or change in stool consistency. In the context of vulnerable populations such as extremely immature children or those with severe immunosuppression, discussions appear about the potential risk of bacteremia or fungemia when using certain strains (10), but these phenomena remain extremely rare. The limitations of reviewed papers are the short duration of follow-up, small number of subjects and the lack of standardization of products and methods of microbiota evaluation. Nevertheless, the consensus of most authors is that targeted probiotic strains have the potential to modify dysbiosis induced by caesarean section and improve the host’s immune mechanisms during early life. An additional argument comes from a study in pre-weaning calves where multi-strain probiotic supplementation increased the relative proportion of beneficial *Firmicutes* with the simultaneous reduction in *Bacteroides*, while increase in serum IgA and IgG levels was observed – which reminds of similar effects described in the human neonatal population (28). A similar pattern of temporary colonization of probiotics that disappears after the cessation of supplementation was also recorded in adult patients after eradication therapy for *Helicobacter pylori*, where an increase in beneficial taxa such as *Lactobacillales* was observed in the first four weeks with a simultaneous decrease in potentially kiselina i modulirati imunološki odgovor u pravcu veće tolerancije.

Efekti primene probiotika, međutim, ne ogledaju se isključivo u mikrobiološkim parametrima. Klinički ishodi, uključujući smanjenu učestalost kolika, dijareje i nekrotizirajućeg enterokolitisa kod prevremeno rođene dece, kao i poboljšane imunološke markere, ukazuju na širi zdravstveni značaj ovih intervencija. Iako postojeće studije pokazuju heterogenost u dizajnu i rezultatima, opšti pravac nalaza upućuje na korist od ciljane primene. Optimalni ishod verovatno zahteva kombinaciju više faktora, uključujući sinergiju između probiotika i ishrane, posebno dojenja koje obezbeđuje prirodne prebiotike. Potrebna su dalja istraživanja sa dužim periodom praćenja i standardizovanim protokolima kako bi se preciznije odredila dugoročna uloga ovih intervencija u oblikovanju zdravlja kod ove populacije. Takav sveobuhvatan pristup može doprineti razvoju personalizovanih strategija za podršku normalnom razvoju crevne mikrobiote i imunološke funkcije kod novorođenčadi rođene carskim rezom.

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harmful genera, while after the cessation of administration the community structure returned to the initial state (29).

Conclusion

Studies presented in this analysis indicate that early dysbiosis in infants born by caesarean section is a clinically relevant factor that may have long-term implications for immunological and metabolic development. This altered initial colonization, characterized by the absence of key obligate anaerobes and increased presence of opportunistic species, is associated with increased susceptibility to atopic diseases, respiratory infections, and gastrointestinal disorders. In order to correct these disorders, supplementation with probiotics, especially strains from the genera *Lactobacillus* and *Bifidobacterium,* shows a promising potential. Evidence suggests that such interventions can accelerate the establishment of a stable and diverse bacterial community, stimulate the production of short-chain fatty acids, and modulate the immune response towards greater tolerance.

However, the effects of the administration of probiotics, are not exclusively reflected in microbiological parameters. Clinical outcomes, including reduced incidence of colic, diarrhea and necrotizing enterocolitis in preterm infants, as well as improved immune markers, highlight the broader health contribution. Although the existing studies show heterogeneity in design and results, general conclusions point to benefits from targeted administration. The optimal outcome probably requires a combination of factors, including synergy between probiotics and diet, especially breastfeeding, which provides natural prebiotics. Further studies with longer follow-up periods and standardized protocols are needed to determine more precisely the long-term role of these interventions related to health in this population. Such a comprehensive approach can contribute to the development of personalized strategies to support the normal development of intestinal microbiota and immune function in infants born by caesarean section.

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