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ROLE OF MATERNAL MELATONIN IN THE DEVELOPMENT OF THE MICROBIOME IN CHILDREN

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▪ This review presents literature data on the role of melatonin in regulating the composition of the microbiota and on the variety of functions it performs that are synchronized with the circadian rhythm of vital activity of the body. During pregnancy, the restructuring of the intestinal, vaginal and placental microbiota is provided by a significant increase in the production of epiphyseal melatonin, which contributes to the creation of optimal conditions for the development of microflora in early ontogenesis. In the absence of circadian production of melatonin, a pregnant woman retains dysbiosis, which determines the transmission of altered intestinal microflora to the fetus and subsequent metabolic dysregulation in the child's body.

▪ **Keywords:** microbiota; melatonin; pregnancy; placenta; fetus.

РОЛЬ МАТЕРИНСКОГО МЕЛАТОНИНА В ФОРМИРОВАНИИ МИКРОБИОМА РЕБЕНКА

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▪ В обзоре представлены данные литературы о роли мелатонина в регуляции состава микробиоты и многообразии выполняемых ею функций, синхронизированных с циркадным ритмом жизнедеятельности организма. Во время беременности перестройка состава кишечной, вагинальной и плацентарной микробиоты обеспечивается за счет значительного увеличения продукции эпифизарного мелатонина, что способствует созданию оптимальных условий для формирования микрофлоры в раннем онтогенезе. При отсутствии циркадной продукции мелатонина у беременной сохраняется дисбиоз, что определяет трансмиссию измененной кишечной микрофлоры к плоду и последующую дерегуляцию метаболических процессов в организме ребенка.

▪ **Ключевые слова:** микробиота; мелатонин; беременность; плацента; плод.

In the last decade, significant progress has been achieved in studying the composition of the microbiota and the subtle mechanisms of its influence in the human body (including metabolic, immune, and endocrine processes) and the brain [1–3]. Particular attention is paid to the formation of microflora in early ontogenesis, which is the critical period of morphological and functional development of all vital body systems [4–6]. It has been established that the process of microbial colonization of a child begins *in utero* and continues during birth and the feeding process [7, 8]. The maternal microbiome is significant in the mother–placenta–fetus system in programming the child's health in the subsequent years of life [9].

The gut microbiota of a mother represents a complex community that enables maintenance of a dynamic metabolic balance during pregnancy. In a healthy woman before pregnancy, anaerobic bacteria of mainly two phylotypes, *Bacteroidetes* and *Firmicutes*, dominate in the intestinal

microflora, with *Bacteroidetes* predominating [10–12]. Microbiota is involved in the metabolism of carbohydrates, proteins, and peptides [13, 14] and in the regulation of lipid assimilation from food [15], fermentation of dietary fibers [16], and production of short-chain fatty acids and vitamins, including biotin and vitamin K [17]. Bacteria control the intestinal mucosal barrier state, affecting cell proliferation [18] and intestinal wall vascularization [19], promote immunity maturation, and protect against pathogenic microorganisms [20]. They play a significant role in fetal formation of the relationship between the intestine and brain (the gut–brain axis), as well as the intestine and hypothalamic–pituitary–adrenal system [21, 22].

The variety of functions performed by the microbiota in a healthy body is provided by communication between various bacterial ecosystems, their balanced interaction, and subordination to the central key regulator, melatonin, which synchronizes the work of the clock genes of the microbiota and the host organism under various environmental conditions in the circadian rhythm. The host and microbiome relationship in the gut is confirmed by the existence of circadian fluctuations in the gut microbiota under the influence of exogenous melatonin [23]. Thus, *Enterobacter aerogenes* responds to the pineal and gastrointestinal hormone melatonin by increasing the mass and activity with a circadian rhythm [24]. It is the host's circadian clock that regulates the composition and localization of the intestinal microbiome [25, 26]. As a result, circadian dysregulation of melatonin production in the host negatively affects the state and vital activity of microbes, which also produce melatonin [27]. Rhythmic oscillations of the gut microbiome are associated with similar oscillations in serum metabolite levels, which in turn triggers circadian expression of gene patterns in the liver and affect oxidative phosphorylation and other pathways [23].

Melatonin is produced not only in the pineal gland but also by enterochromaffin intestinal cells, intestinal mucosa, natural killer cells, and endothelial cells. When implemented in a circadian rhythm, intestinal melatonin helps maintain synchronization of clocks, including food intake and myoelectric rhythm [28]. The circadian clock network, triggered and controlled by melatonin, represents the basis for maintaining all physiological processes, and its destruction leads to disease development [29].

During pregnancy, hormonal restructuring occurs in the body, and the composition of the intestinal microbiota changes [30]. In the first trimester, it does not differ from that before pregnancy; however, in the second and third trimesters, the proportion of proinflammatory *Proteobacteria* decreases, including the species *Enterobacteriaceae* and *Streptococcus*, but the mass of the anti-inflammatory bacteria *Faecalibacterium prausnitzii* increases. In addition, the count of *Bifidobacterium* and *Lactobacilli* increases significantly [31, 32]. Therefore, it was concluded that such processes are of great importance for the outcome of physiological pregnancy, since in the absence of excessive accumulation of these bacteria, preterm labor was registered [33, 34]. In addition, such changes in the intestinal microbiota modulate weight gain in a pregnant woman, increase glucose tolerance, reduce insulin resistance, and stimulate the immune system [35, 36]. *Bifidobacterium* interacts with host immune cells and modulates innate and adaptive immune processes [37]. It is recognized that the increase in the mass of *Bifidobacterium*, especially in the third trimester of pregnancy, reflects the evolutionary process of preparation for lactation and childbirth [32], in which they also dominate and, by producing lactic acid, participate in oligosaccharide metabolism and immune system maturation [38–40]. Specific strains of *Bifidobacterium* were found in fetal meconium [41].

During pregnancy, the composition of the intestinal microbiota is not the only change. The amount of *Lactobacillus* spp. increases in the vagina, and the count of anaerobic bacteria decreases [42–44]. Lactobacilli protect the vaginal ecosystem from colonization by other types of bacteria [45–47]. Their metabolites suppress the proinflammatory cytokines interleukin (IL)-6, IL-8, and IL-1RA [48] and stimulate antiviral responses [49]. Women with a normal vaginal microbiome have a 75% lower risk of preterm delivery than those without a *Lactobacilli* count increase [50]. The predominance of lactobacilli in the vaginal microbiome of a pregnant woman is significant in microbial colonization of the upper gastrointestinal tract of the newborn and in its protection during preterm birth [51].

The placental microbiome consists mainly of nonpathogenic *Firmicutes*, *Tenericutes*, *Proteobacteria*, *Bacteroides*, and *Fusobacteria*, and its composition correlates with that in the oral cavity of a woman [51]. Intracellular bacteria are found in the trophoblast, the basal decidual membrane [52–54]. A low prevalence and biomass of microbes regardless of the gestational age are noted [55, 56]. The intrauterine environment is characterized by low diversity and low microbiome mass, which is believed to create tolerance to commensal bacteria in the uterus [57]. By the end of pregnancy, the *Bifidobacterium* and *Lactobacilli* counts in the placenta significantly increase [58].

The regularity of the microbiome composition restructuring during pregnancy is determined by an increase in melatonin production in a healthy woman. It was revealed that circadian fluctuations in its level increase most significantly after week 24, and the hormone level in the blood serum reaches its maximum values before childbirth, which coincides with the dynamics and maximum presentation of *Bifidobacterium* and *Lactobacilli* [59]. Thus, during physiological pregnancy, melatonin levels from the first to third trimesters amount to 29.7 ± 9.9, 39.1 ± 11.2, and 76.5 ± 38.3 pmol/L, respectively [60]. Along with an increase in the epiphyseal melatonin levels in a woman's body, extrapineal melatonin production also changes, especially in the placenta, where already at week 7 of pregnancy, the expression of N-acetyltransferase and hydroxyindole-O-methyltransferase enzymes involved in melatonin synthesis is noted, which reaches its maximum in the third trimester [61]. Placental melatonin, due to paracrine, autocrine, and intracrine mechanisms, also provides the optimal counts of *Bifidobacterium* and *Lactobacilli* in the child environment, which determines the normal course of pregnancy and provides for the birth of a healthy child [61, 62].

It has been revealed that the entodermal canal is formed in early embryogenesis with the intestinal nervous system, with subsequent development of epithelium and mesenchymal cells. The first endocrine cells appear in the rectum and colon of the fetus at weeks 6–9 of intrauterine development. Subsequently, their count increases progressively, and maternal melatonin, as well as its own melatonin produced in enterochromaffin intestinal cells, promotes differentiation and regeneration of epithelial cells and regulates vascularization and permeability of the intestinal wall [63, 64]. Melatonin receptors are found in all parts of the fetal gastrointestinal tract, liver, and pancreas [65]. Maternal melatonin synchronizes peripheral oscillators in these organs and coordinates their function with the rhythms of clock genes of suprachiasmatic nuclei and other body tissues, including the adenohypophysis and adrenal glands [66]. The circadian rhythm of the expression of clock genes of the fetal large intestine is determined by week 33 of intrauterine development. In the antenatal period of ontogenesis, maternal melatonin is a key molecule that directs and coordinates the genetic process of the development of the relationship between clock genes in the child's tissues and the microbiota being formed [67].

According to the data of experimental and clinical studies using contemporary technologies, the microbiome of a child is established even before birth and plays a significant role in the development of the immune system and metabolism [68, 69]. The oral cavity microbiota of the newborn is associated with that in the mother's placenta [70]. Meconium contains a microbial community similar to that in the placenta and amniotic fluid, which is due to its ingestion by the fetus [71]. Using 16S rRNA sequencing of the meconium microbiota profile, the authors confirmed intrauterine colonization [72].

The composition and diversity of the intestinal microbiota have been established to be altered in individuals with an irregular circadian rhythm in the production of epiphyseal melatonin [73, 74]. Thus, in patients with obesity, metabolic syndrome, prediabetes, and gestational diabetes, in contrast to people without these disorders, the count of *Firmicutes* is increased and that of *Bacteroidetes* is reduced, and there is an excess number of *Enterobacteriaceae*, *Escherichia coli*, and *Staphylococcus*, but small number of *Bifidobacterium* [75, 76]. In the absence of circadian fluctuations of epiphyseal melatonin and dysbiosis, the supplementation of exogenous melatonin increased the *Bifidobacterium* and *Lactobacillus* microbiota and decreased pathogenic *Bacteroides* and *Enterobacter*, which confirms its key role in the regulation of the intestinal

microbiota composition, especially during pregnancy [71, 77]. The treatment method of vaginal and intestinal dysbiosis using melatonin in combination with probiotics has been revealed to be highly effective [78]. Since there is an increase in the incidence of obesity and diabetes mellitus in patients of childbearing age, this fact is of particular practical importance. Dysbiosis of the intestinal microbiota determines the transmission of the altered intestinal microflora from the mother to the fetus, which is confirmed by the data on its composition in the meconium of children with different birth methods, in preterm children and newborns with macrosomia, in which *Proteabacterium* dominates [33, 57, 68]. Antibacterial therapy and drugs used during pregnancy, as well as cesarean section, which are often used in this pathology in mothers, have an adverse effect on the microbial colonization of a newborn [79]. The count of *Bacteroides* reduces significantly during the first weeks of life [58], which contributes to programming of metabolic and neurological disorders in the offspring of obese mothers [21].

It should be emphasized that maternal melatonin, even after the delivery of a child, significantly affects the formation of its microflora through breast milk. Melatonin taken in with a mother's milk determines the dominance of *Bifidobacteria*, coordinates the rhythmic activity characteristic of the microbiota itself, and influences the development of the child's brain through the gut–brain axis [25]. This effect is enhanced by the influence of breast milk oligosaccharides, which are synthesized in the mammary gland, and affect the formation of intestinal microflora, which is actively involved in the synthesis and metabolism of melatonin. The highest count of *Bifidobacteria* and lowest counts of *Clostridium difficile* and *E. coli* were recorded in full-term breastfed newborns of healthy mothers, and the genes of *C. difficile*, *Escherichia*, *Shigella*, and *Bacteroides* dominated in those fed with formula milk [80].

Thus, the absence of circadian production of melatonin in a pregnant woman, associated with existing pathology (obesity, diabetes mellitus, metabolic syndrome, endometriosis, polycystic ovaries, pregnancy complications with gestosis, chronic placental insufficiency, etc.), as well as work at night, impedes the genetic process of the microbiome formation in a child, which leads to the development of dysbiosis and deregulation of metabolic processes in a child's body in subsequent months and years of life. The adverse consequences in the offspring of the listed risk groups should be prevented by including melatonin in the complex therapy of dysbiosis both at the family planning stage and during pregnancy.

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