УДК 618.2-06:616-053.3
https://doi.org/10.17816/JOWD69187-94

ROLE OF THE MATERNAL MELATONIN CIRCADIAN RHYTHM ABSENCE IN EARLY CATCH-UP GROWTH IN CHILDREN

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For citation: Evsyukova II, Ailamazyan EK. Role of the maternal melatonin circadian rhythm absence in early catch-up growth in children. *Journal of Obstetrics and Women's Diseases.* 2020;69(1):87-94. https://doi.org/10.17816/JOWD69187-94

Received: December 19, 2019 Revised: January 16, 2020 Accepted: February 10, 2020

▪ The review presents the results of experimental and clinical studies, according to which the absence of circadian melatonin production in pregnant women associated with the pathologies they have (obesity, diabetes mellitus, metabolic syndrome, pregnancy complicated by gestosis and chronic placental insufficiency, etc.) disrupts the genetic process of organizing the rhythmic activity of genes of the suprachiasmatic nuclei of the hypothalamus and melatonin production in the pineal gland of the fetus, leading to dysregulation of metabolic processes in the child's body after birth and programming pathology in following life. The significance of this factor in the pathophysiological mechanisms of catch-up growth during the first months of life determines a new approach to assessing the risk of obesity and necessitates learning the consequences of impaired development of the brain and other functional systems in fetuses that are born earlier than the 26th week of pregnancy and are thereby deprived of maternal melatonin, a key signaling molecule that directs and coordinates the genetic development process, during the most critical period of early ontogenesis.

▪ **Keywords:** melatonin; circadian rhythm; pregnancy; fetus; programming; obesity.

РОЛЬ ОТСУТСТВИЯ ЦИРКАДНОГО РИТМА МАТЕРИНСКОГО МЕЛАТОНИНА В ГЕНЕЗЕ РАННЕГО СКАЧКА РОСТА У ДЕТЕЙ

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Для цитирования: Евсюкова И.И., Айламазян Э.К. Роль отсутствия циркадного ритма материнского мелатонина в генезе раннего скачка роста у детей // Журнал акушерства и женских болезней. – 2020. – Т. 69. – № 1. – С. 87–94. https://doi.org/10.17816/JOWD69187-94

Поступила: 19.12.2019 Одобрена: 16.01.2020 Принята: 10.02.2020

▪ В обзоре представлены результаты экспериментальных и клинических исследований, показавших, что отсутствие циркадианной продукции мелатонина у беременной, связанное с имеющейся у нее патологией (ожирение, сахарный диабет, метаболический синдром, гестоз, хроническая плацентарная недостаточность и т. п.), не только приводит к задержке становления ритмической активности специфических генов плода, но и лежит в основе дерегуляции метаболических процессов в организме ребенка и программирования патологии в последующие годы жизни. Значение этого фактора в патофизиологических механизмах скачка роста уже в первые месяцы жизни определяет новый подход к оценке риска ожирения и обусловливает необходимость изучения последствий нарушения развития мозга и других функциональных систем у плодов, родившихся ранее 26-й недели беременности и вследствие этого лишенных материнского мелатонина — ключевой сигнальной молекулы, направляющей и координирующей генетический процесс развития в самый критический период раннего онтогенеза.

▪ **Ключевые слова:** мелатонин; циркадный ритм; беременность; плод; программирование; ожирение.

Root cause analysis of increasing obesity in children has shown a link with excessive weight gain in the first months of life. This phenomenon is called an "early growth spurt" [1–4]. This excess weight gain was observed in children whose intrauterine development took place in unfavorable conditions, that is, in mothers with obesity, diabetes, metabolic syndrome, chronic diseases of three or more functional systems (cardiovascular system, gastrointestinal tract, immune system, etc.), as well as in the case of pregnancy complications with chronic placental insufficiency, preeclampsia, and gestational diabetes mellitus [5–7]. While body weight at birth was significantly higher than needed for gestational age in some children, body weight in others lagged behind the growth curve, showing an asymmetric pattern in intrauterine development [8–10]. However, all children showed the appearance of visceral obesity in the first months of life [11–13], and in subsequent years, they developed type 2 diabetes mellitus, metabolic syndrome, and pathology of the cardiovascular and nervous systems [14–16].

Based on the study of various mechanisms that determine the programming of this pathology and its adverse consequences [17–20], several hypotheses have been proposed to explain the etiopathogenesis of growth spurt and its impact on subsequent dev Based on the study of various mechanisms that determine the programming of this pathology and its adverse consequences [17–20], several hypotheses have been proposed to explain the etiopathogenesis of growth spurt and its impact on subsequent development. Thus, according to the hypothesis of "economical phenotype," in conditions of insufficient nutrient intake, the adaptive response of the fetus is aimed at optimizing the growth and development of organs such as the heart and brain, to the detriment of visceral organs (liver, pancreas, etc.), which during the child's adaptation to new environmental conditions leads to morphofunctional changes in the latter, contributes to the violation of metabolic processes and excessive accumulation of adipose tissue [21, 22]. Other hypotheses concern the role of diabetes mellitus, excessive nutrition and a high-fat diet of a pregnant woman in the development of hyperglycemia, hyperinsulinemia, hyperleptinemia, and increased cortisol levels in the fetus with subsequent modulation of the metabolic response of hypothalamus neurons [23–26]. It is believed that the growth spurt is associated with excessive protein consumption (early protein hypothesis) in the early postnatal period. A high level of protein in the infant's diet leads to an increase in the concentration of insulinogenic amino acids in the blood plasma, which stimulate the production of insulin-like growth factor and insulin that leads to obesity. A lack of breastfeeding and increased protein levels during artificial feeding are considered as a high risk of developing obesity [8].

Thus, it is in the perinatal period that a violation of the genetic program for the development of hormonal and metabolic regulatory mechanisms in a child's functional systems determines the development of obesity in early childhood. The main mechanisms for the formation of this pathology are oxidative stress, epigenetic regulation, glucocorticoid effect, as well as the participation of neuroactive steroids, somatolactogens, and related peptides, namely, insulin-like growth factor (IGF-1) and oxytocin [27–29]. In this case, each proposed mechanism presents the role of the hormone melatonin, the absence or lack of which contributes to the progression of obesity. Thus, melatonin, being an oxygen free radical scavenger, the most powerful antioxidant, and activator of other antioxidants (catalase, superoxide dismutase, glutathione peroxidase), prevents the development of oxidative stress and mitochondrial dysfunction in the mother-placenta-fetus system [30–32]. It suppresses the activity of neuronal and inducible nitric oxide synthases and the generation of highly toxic peroxynitrite, but it induces the activity of endothelial synthase, thereby contributing to the improvement of utero-placental blood circulation [33]. Due to the presence of G-protein-linked receptors in fetal tissues, melatonin has a direct modulating effect on cortisol production in the adrenal glands and on lipolysis in brown adipose tissue [34]. A pathophysiological link between melatonin and the functioning of the hypothalamic-pituitary-adrenal system has been established [35]. It is known that severe oxidative stress can significantly change the expression of genes involved in controlling the body's energy homeostasis [36].

Studies confirm the influence of homeostasis disorders in the mother and placenta on the

development of epigenetic processes (DNA methylation, histone modification, etc.) in the perinatal period. Thus, the features of expression of genes involved in the control of differentiation and functioning of adipose tissue cells, liver, hypothalamic neuropeptides, and glucocorticoid receptors in the genesis of a growth spurt were established [37–41]. Epigenetic modifications in the structure of histone (H3K4), an insulin-like growth factor in the liver, lead to an increase in the level of IGF-1 in the blood of a growth-retarded fetus, which determines its growth spurt in the first months of life [42, 43]. However, it is melatonin that plays a key role in protecting against epigenetic changes in a gene expression, including clock-controlled genes that are involved in the regulation of circadian rhythms of metabolic processes [44, 45]. Thus, with a low melatonin production in a single mother-placenta-fetus system, it becomes possible to adversely affect one or another factor during critical periods of fetal development, which leads to "programming" of metabolic disorders.

Melatonin is synthesized in the epiphysis, the endocrine function of which depends on the light mode. Light information from the retinal ganglion cells passes through the retinohypothalamic tract to the superchiasmatic nuclei of the hypothalamus, which are circadian rhythm generators or biological clocks. From there, the signals go to the upper cervical ganglia and then along the sympathetic noradrenergic pathways reach the epiphysis where melatonin is synthesized. Light inhibits the production and secretion of melatonin; therefore, maximum levels of melatonin in the human blood are observed at night and minimum levels in the daytime. The daily rhythm of melatonin production serves as a marker of normal circadian regulation of endogenous biorhythms and their synchronization [46]. Extrapineal melatonin is found in all organs and cells [47]. Melatonin is synthesized from the amino acid tryptophan, which is converted to serotonin by hydroxylation (the enzyme tryptophan hydroxylase) and decarboxylation (the enzyme 5-oxy-tryptophanecarboxylase). With the help of the enzymes N-acetyltransferase and oxyindolomethyltransferase, melatonin is formed from serotonin. From pinealocytes of the epiphysis, melatonin is released into the blood and spinal fluid, and the melatonin secreted in other cells of the body enters the blood in small quantities, exerting paracrine and autocrine influence at the sites of its synthesis [48]. Melatonin performs regulatory functions in all tissues and cells through binding to receptors. Two types of membrane receptors (MT1 and MT2) and their chromosomal localization (chromosomes 4q35 and 11q21-22) as well as nuclear receptors (RORα) have been identified in humans [49].

Melatonin is involved in the processes of the morphofunctional development of the placenta and the preservation of its neuroimmunoendocrine function, aimed at the formation of vital functional systems of the fetus. During a physiologically occurring pregnancy, circadian fluctuations of the body mass increase 5–10 times, and the content of the hormone in the blood serum reaches its maximum values before delivery [50, 51]. It has been established that maternal body mass starts the genetic process of morphological and functional development of the fetal epiphysis and circadian functioning of the superchiasmatic nuclei. Due to this, from the 26th week of intrauterine development, it is at night that maternal epiphyseal melatonin includes circadian rhythms of Clock genes involved in the regulation of metabolic processes and the vital activity of fetal functional systems [52]. This ensures postnatal adaptation to new environmental conditions and integration of endogenous biorhythms of the child's functional systems into the circadian system that is regulated by its own superchiasmatic nuclei depending on changes in light [53]. The absence of such influence of the maternal melatonin in children born before the 26th week obviously determines the high incidence and subsequent disability.

It should be emphasized that in all the above diseases and pregnancy complications of women whose children are predisposed to obesity, the level of melatonin in the blood does not increase at night [30, 54–57]. Experimental studies have shown that in this situation, the offspring also has low production of epiphyseal melatonin, its circadian rhythm is absent not only at birth, but also in later life, which determines the early implementation of metabolic programming [58–60]. The formation of the circadian rhythm of epiphyseal melatonin production normally continues at an accelerated pace in the first days and weeks of life, and maternal influence on this

process is carried out through breastfeeding. It is known that breast milk contains more than 60 biologically active factors, and the concentration of somatotropic hormone, prolactin, IGF-1, insulin, leptin, relaxin, and epidermal growth factor in breast milk is higher than in the mother's peripheral blood [61–64]. Healthy mothers have high levels of tryptophan and melatonin in breast milk, especially in colostrum, which are sensitive to circadian changes [65, 66]. That is why a clear daily rhythm of melatonin production is formed against the background of breastfeeding by the end of the second month of life that is facilitated by the observance of the feeding regime [50].

Melatonin, being a key regulator of carbohydrate and fat metabolism, controls adipocyte differentiation, lipogenesis, lipolysis, capture of fatty acids and glucose, as well as the influence of insulin and energy reserves, simultaneously performs circadian organization of metabolism in muscles, adipose tissue, liver, and pancreas [67]. By binding to specific nuclear receptors (RORα/RZR), melatonin controls cell growth and cell differentiation [68], which opens up wide opportunities for its participation in epigenetic modification of DNA and histones, which is directly related to the development of various pathologies.

The inhibition in the genetic process of formation of the circadian rhythm of melatonin production leads to desynchronization of metabolic processes, violation of energy metabolism and excessive weight gain [63, 69, 70]. In addition, mothers with low melatonin production tend to have reduced lactation, and most of them are forced to finish feeding the milk formula, in which the protein level exceeds its content in the mother's milk, which contributes to an even greater growth spurt. Taking into account the pathophysiological mechanism of programming and development of obesity, the children of these mothers should use mixtures with a protein level close to that in women's milk, enriched with alpha-lactalbumin with a high content of tryptophan and, in addition, including oligosaccharides. The latter significantly optimize the formation of intestinal microflora, which is actively involved in the synthesis and metabolism of melatonin [71, 72]. Over the last years, the attention of researchers has been drawn to the experimental study of the effect of melatonin use during pregnancy and postnatal ontogenesis in order to reprogram the development of pathologies [73–75], which will allow determining objective risk criteria and developing methods for preventing pathological processes.

Conclusion

The absence of circadian melatonin production of a pregnant woman, associated with her existing pathology (obesity, diabetes mellitus, metabolic syndrome, gestosis, chronic placental insufficiency, etc.), not only leads to inhibition in the formation of rhythmic activity of specific fetal genes, but also underlies the deregulation of metabolic processes in the child's body and programming of pathology in the subsequent years of life. The significance of this factor in the pathophysiological mechanisms of growth spurt in the first months of life determines a new approach to assessing the risk of obesity and causes the need to study the consequences of impaired brain development and other functional systems in fetuses born earlier than the 26th week of pregnancy and thus deprived of maternal melatonin-a key signaling molecule that directs and coordinates the genetic development process during the most critical period of early ontogenesis.

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