

# In Melatonin: pregnancy and childbirth

## Abstract

In a review summarizes the mechanisms of synthesis of melatonin and its regulatory effect aimed at successful pregnancy and fetal development of functional systems. Shows a synergistic effect of melatonin and oxytocin during pregnancy and childbirth. Underlined the importance of an individual approach to the appointment in childbirth medicines is a physiological antagonist of melatonin.

**Keywords:** melatonin, pregnancy, childbirth, the fetus

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**Ailamazyan Edward Karpovitch, Evsyukova Inna, Kvetnoy Igor Moiseevich**

Department of physiology and pathology, Research Institute of Obstetrics and Gynecology, Russia

**Correspondence:** Ailamazyan Edward Karpovitch, Director, RAMS, z.d.n. Russian Federation, Professor. Research Institute of Obstetrics and Gynecology, Ott, 199034, Russia. St. Petersburg, Mendeleev line, 3, Email [iagmail@ott.ru](mailto:iagmail@ott.ru)

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## Introduction

Melatonin as a regulator of daily and annual cycles of physiological functions of the body and, in particular, the reproductive system of animals and humans in recent years has increasingly attracted the attention of researchers.<sup>1-5</sup> However, not only changes in melatonin production depending on the length of the light and the dark time of day is determined by seasonal and daily rhythms of reproduction system restructuring, but its unique antioxidant, immunomodulating properties as well as participate in the metabolic processes at the cellular and tissue levels provide reproductive health.<sup>6-10</sup> Melatonin is synthesized in the pineal gland,<sup>11</sup> which is the physiological control of the endocrine function to a large extent is light regime. Light information from the retinal ganglion cells through retino-hypothalamic tract enters the suprachiasmatic nuclei (SCN) of the hypothalamus, where the signals are in the upper cervical ganglia and then sympathetic noradrenergic pathways reach epiphysis where melatonin is synthesized.<sup>12-14</sup> Light inhibits the production and secretion of melatonin, so its maximum level in the epiphysis and human blood is observed in the middle of the night, and the minimum - in the daytime.<sup>12,15,16</sup> The presence of circadian rhythm of melatonin production is a marker for normal operation of the circadian regulation of endogenous biological rhythms and their synchronization with the external rhythm of the daily alternation of day and night.<sup>17,18</sup> Melatonin is produced not only in the epiphysis. Ekstrapinealno melatonin was found in all organs: the gastrointestinal tract, liver, kidneys, adrenal glands, heart, thymus, gonads, placenta, uterus, platelets, eosinophils, leukocytes, and other cells of the immune system.<sup>9,19-23</sup> Thus its synthesis in mitochondria of eukaryotic cells indicates unique protection melatonin cellular organelles from oxidative damage and maintaining their physiological functions.<sup>7,24,25</sup> Melatonin is synthesized from the amino acid tryptophan by hydroxylation of which (an enzyme tryptophan hydroxylase) and decarboxylation (the enzyme 5-oksitriptofandekarboksilaza) is converted into serotonin. Using enzymes N-atsetiltransferazy (NAT) and oxindole-O-methyltransferase (HIOMT) formed of serotonin, melatonin. From pinealocytes pineal melatonin is released into the blood and cerebrospinal fluid, as melatonin is secreted by other cells in the body, it enters the blood in small amounts, giving a field of its synthesis paracrine and autocrine effect.<sup>26</sup> With a hydrophilic molecule of melatonin at the same time it is highly lipophilic and therefore easily penetrates the blood-brain and the placental barrier, takes place in the capillaries, where 70% of melatonin binds to albumin.<sup>27</sup> The

half-life of melatonin ranges from 30 to 45 minutes.<sup>8,28</sup> Melatonin is metabolized in the liver and kidneys. The end products of metabolism -6-sulfatoksi-melatonin and acetylsalicylic acid.

Melatonin provides regulating effect through binding to receptors. A person identified two types of membrane receptors (MT1 and MT2) and chromosomal localization (chromosome 4q35 and 11q21-22), and nuclear receptors (ROR $\alpha$ ).<sup>25,29,30</sup> Receptors for melatonin detected in suprachiasmatic nuclei of the hypothalamus, the cerebellum, retina, spleen, liver, genital gland, mammary gland, uterus, thymus, gastrointestinal tract, platelets, lymphocytes.<sup>12,31-36</sup> In the brain revealed numerous specific membrane proteins of melatonin receptors, coupled with guanine nucleotide-binding protein (G-protein) and the maximum shown in the hypothalamus and pituitary gland.<sup>37,38</sup> Receptor even in the absence of melatonin having high permeability exerts a systemic effect of the molecule at the cellular level by modulating the cytoskeleton and mitotic functions through binding to calmodulin and as a free radical scavenger.<sup>39,40</sup> It should be noted that melatonin synthesized in the pineal gland, has a modulating effect on the function neurohypophysis in particular allocation of oxytocin, vasopressin, prolactin.<sup>41,42</sup> Furthermore, melatonin affects the sexual development and reproductive function through local exposure and activation of receptors in the hypothalamus-pituitary-gonadal system.<sup>43-45</sup> It plays an important role in maintaining the proper function of ovarian follicles and ovulation in the implementation of the progesterone production.<sup>10,46-49</sup> With the onset of pregnancy, melatonin and circadian rhythm of secretion determine its success and for the birth of a healthy baby. First, the melatonin and its metabolites function as direct absorbers produced during pregnancy of free radicals stimulate antioxidant enzymes, thereby providing a stable protection against free radical damage at the cellular and tissue levels in a single system mother - placenta - fetus.<sup>50-55</sup> With the ability to inhibit gene expression of inducible NO-synthase and cyclooxygenase melatonin limits the production of proinflammatory molecules (prostanoids, leukotrienes, cytokines, etc.), thereby carrying out an anti-inflammatory protection.<sup>56,57</sup> As an immunomodulator and a regulator of vascular-platelet hemostasis,<sup>35,58</sup> it is involved in the implantation process, placentation, morphological and functional development of the placenta and the preservation of its neuroimmunoendokrinnoy function, aimed at the formation and establishment of vital functional systems of the fetus.<sup>59-61</sup> It is shown that the cytotrophoblast and syncytiotrophoblast cells not only contain membrane receptors MT1 and MT2, but they themselves synthesized

melatonin, providing paracrine, autocrine and intracrine effect in the placenta and is also a powerful antioxidant effect.<sup>62,63</sup> By adjusting the process retains apoptosis melatonin balance cytotrophoblast and syncytiotrophoblast cells, thereby maintaining homeostasis placenta. Produced in the placenta melatonin is secreted into the amniotic fluid where, researchers believe it performs antioxidant and anti-inflammatory effect.<sup>64,65</sup> If melatonin is synthesized in cells of the amniotic membrane is not yet established.<sup>54</sup>

It is found that the melatonin level in the blood of pregnant increases, particularly after 24 weeks and reaches a maximum before birth.<sup>66,67</sup> Some researchers attribute this trend increase during pregnancy activity of enzymes involved in the synthesis of melatonin in the pineal gland.<sup>68</sup> Others, given the fact that melatonin levels during pregnancy raises both at night and in the daytime, as the source of placental considering melatonin, the synthesis of which is much greater than that in the epiphysis.<sup>66,67</sup> The present data confirm the hypothesis of absence of such dynamics melatonin preeclampsia during pregnancy complication in which the products are greatly reduced due to placental melatonin expression changes and suppressing activity involved in its synthesis enzymes and a significant inhibition of expression of MT1 and MT2 receptors.<sup>69</sup> It is believed that pregnancy-related changes ekstrapinealno production of melatonin in the placenta, the fetus, in a woman's body, along with the increasing role of the epiphyseal maternal melatonin define the conditions for optimum adaptation to the pregnancy of all functional systems and preparing for the birth of the child.<sup>49</sup> Penetrates easily to the fetus maternal melatonin plays a key role in the functional development of the central nervous system and its formation of the circadian rhythms of life.<sup>70,71</sup> After delivery of melatonin levels is greatly reduced in the daytime and night-time.<sup>54</sup> Numerous studies in recent years have shown a close one-way interaction of melatonin and oxytocin during pregnancy and childbirth. It is known that production of oxytocin in decidual tissue increases during the third trimester of pregnancy and particularly immediately before birth.<sup>72</sup> uterine sensitivity to oxytocin during pregnancy increases by 10-20 times and reaches its maximum at the time of delivery to a large extent due to the activation of the oxytocin receptor gene.<sup>73</sup> Oxytocin acts on the muscle fibers, reducing the resting potential of the cell membrane, and thereby muscle stimulation threshold, thereby increasing the frequency and intensity of uterine contractions.<sup>74</sup> It increases the production of prostaglandins in fetal membranes and stimulates the synthesis and release of cytokines, involved in the regulation of formation of prostaglandins.<sup>73-76</sup> Circadian rhythm of secretion of oxytocin occurs during pregnancy, does not change with changing light conditions and to a large extent determines the circadian rhythm offensive birth.<sup>77,78</sup> In recent years, gene expression is detected circadian clock directly in the uterus of nonpregnant and pregnant rodents and suggested the hypothesis that it is the melatonin circadian signal which initiates the onset of labor.<sup>79</sup> This is also evidenced by the results of experimental studies have shown that in rats the onset of childbirth did not depend on the time of day when the removal of the pineal gland, but the circadian rhythm was restored after the administration of melatonin.<sup>80</sup> It was found that people in most cases, onset of labor occurs late at night or in the early morning hours when melatonin secretion is increased.<sup>81-86</sup> cervical ripening and disclosure of uterine throat occurs with greater frequency between 24.00 and 05.00 o'clock in the morning.<sup>87,88</sup>

Study of the role of melatonin in the labor and delivery mechanisms has shown that it increases the oxytocin-induced contraction of the myometrium with the participation of protein kinase C and protein

- connexin 43, acting through the MT2 receptors, which means it carries unidirectional oxytocin effects.<sup>89</sup> In addition, he sensitizing cells to oxytocin of the myometrium. Its paracrine effect facilitates simultaneous reduction of smooth muscle cells.<sup>90</sup> It is found that in utero melatonin receptor expression as high as oxytocin and therefore nocturnal melatonin levels rise significantly contributes to development of optimum labor and childbirth.<sup>54,66,67</sup> It is shown that in bright lighting at night time peak melatonin secretion is suppressed, and this hinders the development of regular uterine contractions.<sup>67</sup> The authors stress that in connection with the use of artificial light at night, especially in hospitals, there is a tendency to reduce the frequency of births in the night, and the development of the weakness of labor.<sup>54</sup> Since melatonin enhances synergistically with oxytocin uterine contractions is proposed to use at the weakness of labor and labor induction with oxytocin and promote the synthesis of melatonin by changing generic lighting unit.<sup>91,92</sup> Furthermore, installed anxiolytic and analgesic effects of melatonin and implementation mechanisms through receptors GHB and MT1, MT2,  $\mu$ - opioid receptors and recovering  $\beta$ -endorphin,<sup>93-95</sup> with the anxiolytic effect is much greater than that after administration of the preparations bezdiazepinovo series.<sup>94,95,96</sup> It is therefore proposed to use melatonin for sedation<sup>97</sup> and painful contractions of myometrium.<sup>93,98</sup> Melatonin for pain has been successfully used in neonatal intensive care children<sup>98</sup> and its use in anesthetic practice can significantly reduce the dosage necessary for anesthetic preparations and provide an anxiolytic and anti-inflammatory effects in the postoperative period.<sup>48,74,94,95,99-102</sup> Discussing the possible uses of melatonin in obstetrics authors emphasize the absence of adverse effects on the condition of the mother and child.<sup>71,91,103</sup> In contrast, use of melatonin at complication of pregnancy gestosis contributes to significant improvement in the prevention of fetal life and delay its prenatal development.<sup>104</sup> At the same time, it stresses the importance of an individual approach not only to the appointment of melatonin, but also drugs that suppress its secretion or seizing receptors.<sup>51,91</sup> Thus, it is shown that agonist seduksen benzodiazepine receptors having GABA-ergic mechanisms as the other GABA-positive substances are physiological antagonists of norepinephrine, serotonin, melatonin, oxytocin and prostaglandin F2 $\alpha$  by the action on the uterus.<sup>75,105-108</sup>

Thus, increased in the last decade, the interest of researchers to study the physiological role of melatonin in the reproductive function has given sufficient evidence not only his chronotropic activity, but also a number of other pharmacologically valuable properties that determine the optimal course of pregnancy and childbirth, making a promising development of new approaches to its use in obstetrics. At the same time, existing data indicate the need for special attention to keeping in obstetric hospitals light conditions needed for the endogenous production of melatonin, as well as restrictions on the use of its suppressive drugs.

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## Conflict of interest

Authors declare that there is no conflict of interest.

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