Role of sleep disorders during gestation on fetal programming for the development of obesity and chronic-degenerative diseases

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Abstract

Sleep disturbances are common in the third trimester of pregnancy and produce changes in the secretion of melatonin in pregnant women who sleep less than eight hours or undergo sleep disturbances, which promote various physiological changes in the mother that contribute to present fetus low birth weight (LBW) in the fetus. LBW is associated with a phenomenon known as “metabolic programming,” in which the fetus is subjected to a stressful situation that results in irreversible metabolic alterations that predispose the development of obesity in adulthood.

KEY WORDS: Sleep disturbances. Melatonin. Metabolic programming. Obesity. Metabolic diseases.

Introduction

Sleep as a physiological process and its alterations is a topic that has gained importance in recent years, due to their impact on nutritional status¹⁻³ and on the development of chronic degenerative diseases,^{4,5} which increase the risk of cardiovascular disease.¹

Sleep is not merely absence of wakefulness, it is a state during which the brain performs a series of highly specialized physiological activities. It is a process whereby the metabolism, tissue restoration, memory consolidation and general homeostatic balance remain active.⁶ Therefore, any alteration of this process that entails a decrease in total sleep time (TST) can impact on the maintenance of physiological activities, and seriously affect physical and mental health status and social interaction of the individual.⁷ The negative impact of TST reduction has been studied in adult individuals, young people and pediatric population; however, the physiological conditions of pregnancy and lactation have been less addressed, even when nutritional and

metabolic state anomalies at early stages of development have been observed to favor a phenomenon known as “metabolic programming” also known as “early origin of metabolic diseases”, which are processes whereby the organism is protected from the stressful environment it is exposed to, but these have long-term repercussions for being irreversible and closely associated with an increase in the prevalence of obesity and metabolic diseases once an adult.⁸

In pregnancy, maternal hormones secretion is affected by the light-darkness cycle, including melatonin, thyroid stimulating hormone, growth hormone and cortisol, and thus it has been suggested that the metabolic processes regulated by these hormones can be seriously affected,⁹ altering fetal physiology.

Investigation regarding the importance of TST reduction on metabolic programming is currently under inquiry, this way, it has been proposed that melatonin treatment may generate a “metabolic reprogramming” phenomenon that can modify or attenuate the harm generated by early programming.¹⁰

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Basic concepts of sleep

Sleep is an active regulated process, essential to preserve health and well-being.⁹ It can be divided in two stages: slow-wave (SWS) sleep and rapid eye movement (REM) sleep. The first one is called like this because, during this stage, the electroencephalographic record reports slow waves of large amplitude and low frequency; body movements are sporadic, and breathing and heart rate are decreased. On the other hand, REM sleep is divided into phases N1, N2 and N3, which include deep sleep. Throughout the night, the different sleep stages alternate generating sleep cycles, often four to six cycles per night with a duration of 90 to 120 minutes each.^{9,11}

Different studies have reported that TST demands vary depending on the age, for instance: according to the National Sleep Foundation, a newborn (0 to 3 months) requires between 14 and 17 hours of sleep daily, while an adult sleeps between seven and nine hours and an older adult between seven and eight hours per day.¹² However, there are no reports suggesting a significant adjustment in TST in a particular physiological state, such as pregnancy, even though this implies an intense anabolic state.

Melatonin and its relationship with sleep

Melatonin is an indolamine (N-acetyl-5-methoxytryptamine), mainly produced by the pineal gland.^{13,14} In addition, it is also synthesized by the retina, the thymus, bone marrow, the respiratory epithelium, the skin, the intestine, the salivary glands, lymphocytes and platelets.¹⁵ In addition, it is produced in the ovary and in the placenta of the pregnant mother, with a secretion rate that considerably impacts on the progress of pregnancy.¹⁶

Central melatonin secretion occurs as a result of a circadian control mechanism (24-hour secretion pattern); its levels remain low during the day and increase from 20:00 hours on, reaching a maximum secretion peak at around 3:00 hours, which is maintained until shortly before 7:00, after which, it abruptly decreases.¹⁷ This secretion peak may be totally or partially decreased if the subject is exposed to light at night, because secretion is controlled by the suprachiasmatic nucleus, whose functions are synchronized by the light-darkness cycle and therefore it works like an endogenous clock regulator of various processes.¹⁸ Melatonin synthesis is stimulated through the retino-hypothalamic-pineal

multi-synaptic pathway integrated by the retina (luminous state recognition point), the paraventricular nucleus, the intermediate lateral nucleus and the superior cervical ganglion, which finally communicates with the pineal gland.¹⁷ During the day, the photoreceptors (cones and rods) of the retina are hyperpolarized and at rest, while with darkness they are activated and stimulate the retino-hypothalamic-pineal pathway, releasing norepinephrine into the sympathetic terminals that innervate the pineal gland and stimulating melatonin synthesis in the pinealocytes.¹⁹

Sleep in the pregnant woman

The normal physiological periods the woman is subjected to throughout life, such as puberty, menstruation, pregnancy and menopause, are associated with the risk of suffering from some type of sleep disorder.²⁰ The physiological changes that occur during pregnancy are also associated with changes in the architecture of sleep. TST increases slightly during the first trimester of pregnancy in comparison with the non-pregnant state²¹ and progressively decreases during the third trimester. Sleep disturbances are present in all three trimesters of gestation, but during the third one, a greater impact on the quality and quantity of sleep is observed;²² in this period, TST increases by approximately half an hour and is followed by a reduction in sleep quality due to restless legs syndrome and nocturnal awakening, which are more commonly reported.²⁰

Sleep disturbances have been associated with some hormonal changes, including:

- Increased levels of progesterone, which causes fatigue and daytime sleepiness.
- Increase in estrogen levels, which selectively decreases REM sleep activation in the ventrolateral preoptic area.
- Alterations in cortisol secretion, which decreases REM sleep and increases slow-wave sleep.
- Alterations in prolactin levels, whose secretion exacerbates slow-wave sleep.
- Alterations in growth hormone levels, which are associated with the onset and maintenance of slow-wave sleep, in addition to playing an important role in fetal growth and development.^{21,23}

Although these changes are due to a normal physiological process in pregnant women, they can generate complications, especially in the presence of obesity, since sleep apnea prevalence is higher. In

addition, several studies have described that women with preeclampsia, a condition associated with maternal obesity, experience respiratory disturbances, nocturnal hypoxia, obstructive sleep apnea²⁴ and snoring events more frequently.^{24,25}

Importance of melatonin in pregnancy

Melatonin serum levels in women are known to have a daytime rhythmicity with important increments towards the end of pregnancy. Melatonin concentrations in pregnant women during the sleep phase (02:00 hours) show a slight increase since the 24th week of gestation, and reach a peak around week 32 to 36, in comparison with non-pregnant women. These levels return to normality two days after delivery.²⁶

Maternal melatonin concentrations have a significant and close correlation with the levels found in the umbilical vein ($r = 0.924$, $p < 0.001$). In addition, melatonin levels in umbilical cord blood have been observed to be higher in neonates born at night in comparison with those who were born during the day. These events suggest that melatonin is transferred from the maternal blood to fetal circulation with high efficiency, despite the fact that the fetus can produce its own melatonin with a circadian rhythmicity.²⁷

The photoperiodic information perceived by the mother from the external environment, which promotes melatonin secretion, plays an important role in synchronizing the initiation of circadian processes in the fetus.¹⁶ Thus, during intrauterine life, the fetal organism “learns” or programs its physiological mechanisms to determine light-darkness cycles through the expression of various clock-genes such as Bmal-1, Per1-3 and Cry1-2, in an effect that is dependent on maternal melatonin secretion rhythms.²⁸

In addition to the effects on circadian patterns in the fetus, melatonin has been proposed to modulate other physiological processes,²⁸ such as inflammatory and antioxidant states, the pancreatic function, intestinal motility, body weight, reproduction and the anti-jet lag effect.¹⁹

Melatonin also appears to be essential for carrying a good pregnancy to term. According to Sandyk et al. report (1992), this hypothesis is based on different observations:

- Melatonin plasma levels increase between 200 and 300 % during first 20 weeks of pregnancy.
- Melatonin decreases uterine contraction.
- Melatonin stimulates progesterone secretion, which decreases uterine contraction and prevents immune rejection of the trophoblast, which has

the function of providing nutrients from the mother to the fetus through the uterine artery.²⁹ Alteration of these trophoblasts causes intrauterine growth restriction and preeclampsia.²²

- Melatonin inhibits the synthesis of prostaglandins during pregnancy, which are important inducers of uterine contraction and labor.
- Pinealectomy increases the number of spontaneous abortions in pregnant rats.

Melatonin and its relationship with low weight and metabolism of the newborn

Low birth weight is a consequence of different stressors (nutritional, hormonal and oxygen supply-related) the fetus is subjected to during pregnancy, and against which it presents biochemical, structural or functional adaptation strategies that protect it from such stress at the expense of weight gain and organs and systems proper maturation, thus promoting the development of metabolic disease in adulthood. This phenomenon has been described by Barker as the “fetal origin of metabolic disease” hypothesis³⁰ or by Luke as “metabolic programming”.³¹

The study of the impact of low birth weight has been relevant because it explains the increase in neonatal and infant morbidity and mortality, as well as the increase in obesity and metabolic disease; the analysis has been broadened to the intrauterine programming of different tissues, such as the thyroid gland, due to the relevance thyroid hormones in the regulation of body weight and food ingestion.³²

Placental dysfunction, which is suggested to be a consequence of melatonin levels decreasing or alterations in its secretion rhythm, suggests the possibility that light-darkness cycles disruption during pregnancy has long-term metabolic consequences, including an increase in adiposity, hyperleptinemia, hyperinsulinemia and lower glucose tolerance.^{33,34} Although the mechanisms whereby these alterations are generated have not been fully understood, it has been suggested that melatonin may play an important role in the establishment of metabolic alterations in adulthood.³³

Maternal melatonin functions could be divided into those that can affect placental functions and those that directly impact the fetal organism.¹⁶ Regarding the first described, melatonin has been defined for counteracting the generation of free radicals, thus avoiding the oxidative stress that characterizes placental alterations initial stages. In this sense, women with preeclampsia who show low levels of melatonin have a

deficiency in the passage of nutrients and oxygen supply to the fetus, which promotes pregnancy complications, preterm delivery and low birth weight.^{16,35}

On the other hand, depending on its secretion rhythm, the melatonin produced by the maternal body is easily transported through the placenta and reaches fetal circulation. It is essential for regulating some functions during development:³⁵ nervous system maturation, neonatal temperature regulation,³⁶ determination of circadian rhythms of other tissues such as the liver,¹⁶ synchronization of fetal circadian cycles,^{16,28,35} mediation in the expression of the leptin gene in adipocytes through its interaction with MT1-type receptors (melatonin receptors),³⁷ which promotes food ingestion control and favors body weight regulation;^{38,39} as well as pancreatic function and glucose metabolism adequation.⁴⁰

All this highlights the significance of studies respecting sleep problems during pregnancy, in order to promote a homeostatic state for the mother that favors satisfactory fetal growth and development, ensures the health status of the newborn and prevents early development of obesity and metabolic diseases.

Conclusions

The reduction in the amount of sleep or sleep disturbances promote changes in maternal melatonin circadian secretion, which may impact on the contribution of this hormone to the fetus-placental unit. The negative impact of low melatonin production has been described in relation to placental structure and function, which affects the supply of oxygen and nutrients to the fetus; disruption of fetal suprachiasmatic nucleus maturation that leads to an alteration of circadian cycles; finally, insulin resistance and leptin secretion dysfunction alter the control of food intake and body weight gain. All these mechanisms can somehow contribute to low birth weight, which generates a metabolic programming phenomenon due to sleep disturbance that impacts on the development of obesity and metabolic disease in adulthood; therefore, it is necessary to promote sleep hygiene strategies during this period that favor maternal and newborns' health in order to early prevent the development of obesity and metabolic disease.

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