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THE ROLE OF MELATONIN IN COMPLICATED PREGNANCY

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Summary

Introduction. *In recent years, there have been significant changes in the understanding of the hormone melatonin (MT). It has been confirmed that the processes of conception, pregnancy, and childbirth directly depend on the rhythm and level of MT secretion, but there is no general concept that could describe in detail the mechanisms of influence on ontogenesis.*

The aim of the study. *To assess MT in the blood of pregnant with retrochorial hematoma (RCH) up to 12 weeks of pregnancy.*

Material and methods. *Two groups were formed: 1st comprized 40 pregnant women with RCH, 2nd, control consisted of 44 healthy pregnant. Obstetric research, enzyme immunoassay to determine MT, and ultrasound were performed.*

The approval of the scientific work was obtained from the Bioethical Commission of the Bukovinian State Medical University (Ukraine).

Statistical analysis was performed according to generally accepted methods of variational statistics.

The work is a fragment of the research work "Prevention, diagnosis and treatment of disorders of the perinatal period and the reproductive system of women and adolescent girls" (No. 201110H, state registration number 0111U006499).

Results. *A significant decrease of MT in the 1st group and the dependence of its level on the size of the RCH was revealed: in the case of hematomas up to 1 cm MT (59.31±10.32 pg/ml) ($p < 0.001$), which is not observed in hematomas more than 1 cm, which are dangerous for pregnancy (93.98±14.52 pg/ml), which may indicate a compensatory increase in MT; and the term of pregnancy (in 10-12 weeks 79.03±9.61 pg/ml ($p < 0.05$), in 5-6 weeks 93.78±17.44 pg/ml).*

Conclusions. *In cases of RCH up to 1 cm the content of MT decreases with the development of pregnancy, which can be used as a prognostic marker for the diagnosis of pregnancy complications. The increase in the level of MT with RCH more than 1 cm can be considered as a compensatory increase for the preservation of pregnancy and a regulatory influence on the further course of pregnancy.*

Key words: *Melatonin; Retrochorial Hematoma; Threat of Abortion.*

Introduction

In recent years, there have been significant changes in the understanding of the hormone melatonin (MT) - its physiology, regulatory role and potential benefits in various areas of clinical medicine, as MT properties include anti-inflammatory, antioxidant, neuroprotective, sleep promoting and immune enhancing [1]. It has been shown to be a regulator of physiological processes associated with human reproduction, embryo and fetal development [2].

MT is a lipophilic hormone synthesized and secreted mainly in the pineal gland, which acts as a neuroendocrine transducer of photoperiodic information during the night [3]. MT biosynthesis starts with its precursor tryptophan and consists of several enzymatic steps. In addition, MT can be metabolized by non-enzymatic pathways. It is important that MT metabolites serve to prolong the duration of MT action, as MT is rapidly metabolized in peripheral tissues [4, 5].

MT has amphiphilic properties that allow it to easily penetrate all membranes, transmit photoperiodic information to the fetus, and influence tissue differentiation and hormonal metabolism [6, 7]. The placental tissue is characterized by a very strong association between its two components: the mononuclear cytotrophoblast of the villi and the multinucleated syncytiotrophoblast. MT has an effect on the induction and blocking of apoptosis of the villous cytotrophoblast, promotes the development of syncytiotrophoblast through paracrine, autocrine and/or intracrine action of MT1 and MT2 receptors in the placenta [8], which are used by the placenta to maintain the balance between villous cytotrophoblast and syncytiotrophoblast, thus contributing to the normal development of the placenta [9]. The fusion of villous cytotrophoblasts forms a syncytiotrophoblast through an MT-regulated process [10].

In addition, placental MT interacts with MT1 and MT2 receptors and reactive oxygen species to reduce oxidative damage to the placenta. Because MT protects the placenta from antioxidant effects, it has been recognized as a regulator of placental homeostasis [11]. In the first trimester of pregnancy, the MT1 receptor is more important in promoting synchronization of the villous cytotrophoblast by protecting trophoblastic cells from oxidative damage and promoting apoptosis in altered cells [12, 13].

In animal and human studies, a correlation between the circadian clock and the immune system has been established, as MT has a positive effect on reducing various diseases of inflammatory origin, including preterm birth, gestational diabetes, and pre-eclampsia, by modulating T-cell responses. It has been emphasized that MT is potent in terms of circadian regulation of lymphocyte proliferation, enhancing phagocytosis and stimulating cytokine production [14-17].

MT is required during ovulation, fertilization, embryo implantation, and ultimately as a regulator of pregnancy [18]. Several in vitro and in vivo studies have confirmed that the antioxidant effect of

MT to scavenge free radicals from the oocyte and embryo, together with the immunomodulatory effect, is important to support trophoblast implantation and invasion. This is confirmed by the MT1 and MT2 receptors, which are expressed in the placental tissue during embryo implantation to improve the success and quality of embryo development.

It has been confirmed that the processes of conception, pregnancy and childbirth directly depend on the rhythm and level of MT secretion in the body, but there is no general concept that could describe in detail the mechanisms of influence on ontogenesis.

Some studies indicate that excessive activation of the body's antioxidant system, follicles and oocytes can negatively affect fertilization efficiency and embryo development. Some studies emphasize that the content of MT in the follicular fluid exceeds its level in the blood, i.e., the follicle itself synthesizes it or absorbs it from the blood in larger quantities and plays an important physiological role in the maturation of follicles and oocytes, the process of ovulation and fertilization [19, 20]. Other researchers have shown that MT levels were significantly higher in the serum of women with infertility compared to the control group, and half as high in the follicular fluid [21].

In adults, MT levels remain low throughout the day. Levels begin to rise in the evening, peak between 02:00 and 03:00, and then decline to low diurnal concentrations in the morning. MT production is higher in pregnant women than in non-pregnant women, increases significantly during pregnancy (up to 611.4 pg/mL in the first trimester), peaks in the third trimester, and decreases sharply to 158 pg/mL after delivery. A significant increase in serum MT levels occurs at 24 weeks after implantation to 1246 pg/mL, and increases again to 1372 pg/mL at 32 weeks. These results indicate that the placenta is the major source of MT during pregnancy and support the physiological role of MT during pregnancy. Because the placenta plays a key role in many pregnancy pathologies, placental MT production has been studied in the context of high-risk pregnancies [22, 23].

Several studies have demonstrated the role of systemic and placental oxidative stress in the pathophysiology of miscarriage and recurrent abortion. Insufficient antioxidant protection leads to habitual abortion. MT, as well as chorionic gonadotropin (CG), stimulates the secretion of progesterone, which reduces the degree of uterine tone and prevents immunological rejection of trophoblast, inhibits the synthesis of prostaglandins, which can potentially induce uterine contractions [24, 25].

Thus, in the last decade, the increased interest of researchers in studying the physiological role of MT in reproductive function has provided sufficient evidence not only of its chronotropic activity, but also of a number of other pharmacologically valuable properties that determine the optimal course of pregnancy and childbirth, making it promising to develop new approaches to its use in obstetrics.

Because it is bioavailable and has little or no toxicity, it is considered safe and effective for treating many diseases and maintaining human health. However, there are few data on the effects of MT supplementation during pregnancy and possible outcomes. Therefore, the issue of the effects of MT in obstetrics and its use is not adequately addressed [26, 27], which makes the problem relevant.

Another potential application of MT may be its use in the treatment of insomnia during pregnancy, but there are no studies with primary results demonstrating the safety or efficacy of MT for insomnia or other sleep disorders during pregnancy. The evidence base for the efficacy of MT is just emerging, but an analysis of the frequency of positive pregnancy outcomes in patients showed that it was higher [28, 29].

The aim of this study was to evaluate MT level in the blood of pregnant women up to the 12th week of pregnancy with a threat of abortion manifested by bloody discharge or formation of retrochorionic hematoma (RCH).

Materials and methods of the study

The work is a fragment of research work of the Department of Obstetrics and Gynecology, UDC 618.1-053.34 + 618.1-0536 /.8] -07-084-08 “Prevention, diagnosis and treatment of disorders of the perinatal period and reproductive system of women and adolescent girls” (№201110H, state registration number 0111U006499. The term of implementation is 02.2011-12.2015).

According to the purpose, the patients were divided into two groups: Group I, the main group (MG) - 40 pregnant women with signs of imminent abortion, especially the presence of bloody discharge or RCH, and Group II, the control group (CG) - 44 pregnant women without complications in the first trimester of pregnancy. There were no women who worked at night among the patients.

The following research methods were used in the study: general clinical (determination of complaints, taking anamnesis, general somatic medical examination) and obstetric examination, special research methods to determine the amount of MT, CG, ultrasound to determine the condition of the fetus, the size of RCH.

Preparation of patients for melatonin determination according to general rules. Time of sampling: 8.00-9.00 a.m., material: blood serum.

Melatonin ELISA kits are used for determination of melatonin level in blood of pregnant women. The principle of analysis is based on enzyme-linked immunosorbent assay. The mean value of MT in serum: 03:00 18.5-180 pg/ml, 08:00 3.8-80.4 pg/ml.

Statistical analysis was performed using generally accepted methods of variance statistics. Reliability was assessed using Student's t-test. Differences were considered significant at a significance level of $p \leq 0.05$.

The study was approved by the Bioethics Committee of the Bukovinian State Medical University (Ukraine). Personal data were processed after obtaining informed consent from the patients.

Research Results and Discussion

To determine the effect of MT on the course of pregnancy and childbirth, the incidence of complications, we performed its determination in pregnant women of the main and control groups. To determine the fetal condition, we also determined CG.

Taking into account that pregnant women with a risk of abortion were of different gestational age, and pregnant women in the CG were within 10-12

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weeks, we formed three subgroups in the study group. The expediency of forming three subgroups is due to qualitative statistical analysis and dynamic observation of changes in blood MT depending on gestational age. Thus, the 1st subgroup of the study group (1SG of the study group) included 23 pregnant women at 10-12 weeks of gestation, the 2nd subgroup of the study group included 13 pregnant women at 8-9 weeks of gestation, and the 3rd subgroup of the study group included 4 pregnant women at 5-6 weeks of gestation. Three subgroups were formed during the study because it is known that the level of MT should increase with gestational age due to synthesis in the chorion-placenta. Since the data in the literature are contradictory, we determined MT during the first trimester, starting at 5 weeks of pregnancy.

It is known from the medical history that in MG the pregnancy was the first in 20, repeated in 20, in CG the first in 23, repeated in 21, previous pregnancies were complicated by miscarriage in MG: in 5 cases spontaneous miscarriage, 4 stillbirths, 1 premature birth, in CG: in 3 cases spontaneous miscarriage, 4 stillbirths. Thus, there was no significant difference in the history of miscarriage (Table 1).

As a result of the study, it was found that the MT level depends on the size of RCH, so we calculated MT with hematoma size up to 1 cm, more than 1 cm and the third group where there was marginal chorionic detachment (Table 2).

Table 1

Medical history of pregnant women in main and control groups

Medical history	Main group (n=40)	Control group (n=44)
Spontaneous miscarriage	5	3
Stillbirth	4	4
Premature birth	1	0

It was found that RCH up to 1 cm was observed almost twice as often as more than 1 cm at 8-12 weeks and twice as rarely at 5-6 weeks. There was a slight trend towards marginal detachment.

The next step of the study was to determine the MT in pregnant women with different sizes of RCH. A significant decrease in MT was found in all subgroups of the main group. A decrease in MT was also found with increasing gestational age, which can be used as a prognostic marker for pregnancy complications in the first trimester. A significant decrease in MT was observed in hematomas up to 1 cm, but not in hematomas larger than 1 cm, which are more dangerous for pregnancy. The data may indicate a compensatory increase in MT in threatening conditions to further preserve the pregnancy.

Table 2

Size of retrochorionic hematoma in the main group depending on gestational age

Subgroups	Up to 1 cm, n (%)	More than 1 cm, n (%)	Marginal detachment, n (%)
10-12 (n=23)	15 (65,2)	6 (26,1)	2 (8,7)
8-9 (n=13)	7 (53,8)	5 (38,5)	1 (7,7)
5-6 (n=4)	1 (25)	2 (50)	1 (25)
Total	23	13	4

In 1SG of MG, in case of RCH up to 1 cm, 7 (44.7%) i.e. less than a half, had a normal pregnancy and delivery, in all other cases, pregnancy and delivery were complicated, in case of RCH more than 1 cm in 50% had a normal pregnancy and delivery.

In case of RCH up to 1 cm with subsequent normal course of pregnancy and delivery we have a significantly lower level of MT 60.06 pg/ml, in case of complicated pregnancy and delivery 66.07 pg/ml. In this case, in the presence of RCH, the determination of MT can be a prognostic sign for further pregnancy management.

Table 3

Comparative characteristics of melatonin level in the main and control groups and at different sizes of retrochorionic hematoma (pg/ml)

	Control group (n=44)	Main group	Up to 1 cm	More than 1 cm	Marginal detachment
Control group	124,27±9,12	-	-	-	-
Main group 10-12 weeks	-	(n=23) 79,03±9,61**	(n=15) 63,61±12,08**	(n=6) 93,98±14,52*	(n=2) 92,08±10,39*
Main group 8-9 weeks	-	(n=13) 84,69±23,11*	(n=7) 59,31±10,32**	(n=5) 127,7±52,04	(n=1) 47,3
Main group 5-6 weeks	-	(n=4) 93,78±17,44*	(n=1) 78,59	(n=2) 103,51±57,22	(n=1) 89,51

Note: **p < 0,05*
***p < 0,001*

In 3 (50%) cases of RCH more than 1 cm with subsequent normal course of pregnancy and labor, the MT level is significantly lower than 85.15 pg/mL, in complicated pregnancy 102.77 pg/mL ($p < 0.05$).

In 2SG of MG, in the case of RCH up to 1 cm with further normal course of pregnancy and delivery in 2 (28.6%) we have a lower level of MT 50.22 pg/ml, where pregnancy and delivery were complicated in 5 (71.4%), MT 62, 94 pg/ml, in case of RCH over 1 cm with further normal course of pregnancy and delivery in 1 (20%) low level of MT 57.8 pg/ml, where pregnancy and delivery were complicated in 4 (80%), MT 145.17 pg/ml ($p < 0.05$).

In 3SG of MG in the case of RCH up to 1 cm in 1 (33.3%) MT 78.59 pg/ml, foot presentation, over 1 cm in 2 (66.7%) cases, normal course MT 71.18 pg/ml, pathological MT 135.84 pg/ml.

In the case of marginal detachment, two women had a normal course of pregnancy and delivery: at 6 weeks, MT 89.51 pg/ml and at 8 weeks, MT 47.3 pg/ml, and complicated at 11-12 weeks, MT 92.08 pg/ml.

Thus, in all cases of complicated pregnancy and delivery in the presence of RCH, there is a tendency to an increased level of MT.

Chorionic gonadotropin: in pregnant women of 1SG of MG 53.63 ng/ml, CG 45.85 ng/ml. In pregnant women of 2SG of MG 47.68 ng/ml, 3SG of MG 40.55 ng/ml. Thus, no significant difference was found despite the presence of RCH. Also, no significant difference was found in the subsequent normal and complicated course of pregnancy.

Normal CG levels may be evidence of chorionic function and pregnancy preservation despite a significant decrease in MT. An increase in MT levels in RCH over 1 cm may be due to an increase in synthesis in both the chorion and the CNS as a stress response to compensate and normalize the fetal state under extreme conditions of impaired blood supply and further development of the pregnancy. That is, increased sleepiness and fatigue in the first trimester of complicated pregnancy are important for compensatory increase in MT, which should be considered in the management of such patients and provide them with appropriate recommendations for adequate rest and sleep.

The results of pregnancy and delivery are quite interesting. We considered the CG as a group of healthy pregnant women whose first trimester of pregnancy was uneventful, but the results of further pregnancy and delivery in both groups are not encouraging. The presence of placental dysfunction and fetal growth retardation syndrome is striking, confirming our hypothesis of a compensatory increase in MT in threatening conditions, as well as an increased number of complications in MG. It is also noteworthy that the control group had an increased level of MT in the presence of other complications.

Conclusions

1. Melatonin level in the presence of retrochorionic hematoma in the first trimester is significantly lower, with the development of pregnancy decreases to 16%, which may be a prognostic sign and is different from chorionic gonadotropin, whose changes are unreliable.

2. In the case of retrochorionic hematoma up to 1 cm at any gestational age up to 12 weeks, a significantly lower level of melatonin is observed ($p < 0.001$) than in hematoma over 1 cm, where no significant difference was found.

3. Instead, during complicated pregnancy and childbirth, melatonin levels are higher than during normal pregnancy, which can be seen as a compensatory increase to maintain the pregnancy.

4. Since melatonin levels are higher in complicated pregnancy and delivery and in hematoma over 1 cm and do not differ significantly from the control group, it can be concluded that melatonin has a regulatory effect on the further course of pregnancy.

Prospects for further research

Future plans include studying serotonin levels and determining the relationship between melatonin, serotonin, and chorionic gonadotropin to predict and prevent pregnancy complications.

Conflict of interest. The authors declare no conflict of interest.

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Table 4

Results of pregnancy and delivery

	Main group (n=40)	Control group (n=44)
Normal delivery	17 (42,5 %)	21 (47,7%)
Early rupture of membranes	8 (20 %)	4 (9,1 %)
Labor anomaly	3 (7,5 %)	2 (4,5 %)
Polyhydramnios	2 (5 %)	1 (2,3 %)
Preterm delivery	2 (5 %)	3 (6,8 %)
Premature detachment of the of the normal placenta	1 (2,5 %)	2 (4,5 %) (рівень МТ достовірно знижений у одному випадку)
Placental dysfunction	3 (7,5 %)	-
Fetal growth retardation syndrome	1 (2,5 %)	-
Distress in labor	1 (2,5 %)	4 (9,1 %)
Abnormal labor activity		7 (15,9 %)
Gestosis	2 (5 %)	1 (2,3 %)
Gestational diabetes	1 (2,5 %)	

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РОЛЬ МЕЛАТОНІНУ ПРИ УСКЛАДНЕНОМУ ПЕРЕБІГУ ВАГІТНОСТІ

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Резюме

Вступ.

За останні роки відбулися значні зміни в розумінні гормону мелатоніну (МТ). Підтверджено, що процеси зачаття, вагітність та дітонародження безпосередньо залежать від ритму і рівня секреції МТ, проте загальної концепції, яка могла б в деталях описати механізми впливу на онтогенез, не існує.

Мета дослідження. Оцінити МТ у крові вагітних з ретрохоріальною гематомою (РХГ) до 12 тижнів вагітності.

Матеріали та методи дослідження. Сформовано дві групи: І основна – 40 вагітних з РХГ, ІІ контрольна – 44 здорових вагітних. Проведено акушерське дослідження, імуноферментне для визначення МТ, УЗД.

Статистичний аналіз виконували за загальноприйнятими методами варіаційної статистики. Достовірність оцінювали за t-критерієм Стьюдента. Відмінності визнавали істотними при рівні значимості $p \leq 0,05$.

Схвалення наукової роботи було отримано від Біоетичної комісії Буковинського державного медичного університету (Україна). Обробку персональних даних здійснювали після отримання інформованої згоди пацієнтки.

Робота є фрагментом науково-дослідної роботи «Профілактика, діагностика та лікування розладів перинатального періоду та репродуктивної системи жінок і дівчат-підлітків» (№201110Н, номер державної реєстрації 0111U006499).

Результати дослідження. Виявлено достовірне зниження МТ у основній групі і залежність його рівня від розмірів РХГ: у випадку гематом до 1 см МТ (59,31±10,32 пг/мл) ($p < 0,001$), чого не спостерігається при гематомах більше 1 см, які є більш небезпечними для вагітності, де МТ 93,98±14,52 пг/мл, що може свідчити про компенсаторне підвищення; та терміну вагітності (у 10-12 тижнів МТ 79,03±9,61 пг/мл ($p < 0,05$), у 5-6 тижнів МТ 93,78±17,44 пг/мл).

Висновки. За наявності РХГ до 1 см кількість МТ з розвитком вагітності знижується, що можна використовувати як прогностичний маркер діагностики ускладнень вагітності. Зростання кількості МТ при розмірах РХГ більше 1 см можна розцінювати як компенсаторне підвищення для збереження вагітності та регулюючий вплив на подальший перебіг вагітності.

Ключові слова: мелатонін; ретрохоріальна гематома; загроза переривання вагітності.

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