EFFECT OF MELATONIN ON THE LEVEL OF CYTOKINES IN PREECLAMPSIA

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Summary

Introduction. The literature reports a decrease in melatonin levels in preeclampsia, when the degree of decrease correlates with the severity of the process, as well as a decrease in the expression of melatonin receptors in the placental tissue in case of fetal growth restriction.

Regarding changes in the cytokine profile in PE: there is evidence that the levels of proinflammatory cytokines, namely TNF-α and IL-6, increase in preeclampsia, while the concentrations of anti-inflammatory cytokines, namely IL-4 and IL-10, decrease. Melatonin, on the contrary, reduces the secretion of proinflammatory cytokines, in particular TNF-α, and increases the production of anti-inflammatory cytokines, namely IL-10. Therefore, normalization of melatonin levels may be a promising direction in the treatment of PE in pregnant women.

Objective of the study. Assess the pathogenetic mechanisms of complications arising from a decrease in melatonin, and, in particular, find out more about the changes in melatonin, IL-6 and IL-10, determine the correlation between them.

Material and research methods

The study conducted at the Department of Pregnancy Pathology of the Chernivtsi Regional Perinatal Center, involved 32 women whose pregnancy was complicated by preeclampsia. The control group consisted of 33 women with uncomplicated pregnancies observed in the antenatal clinic of the Chernivtsi Regional Perinatal Center.

The patient's informed consent form and the patient's examination card were approved by the Biomedical Ethics Committee of Bukovinian State Medical University (BSMU) of the Ministry of Health of Ukraine (Chernivtsi). The work was guided by the general provisions of the Declaration of Helsinki “Recommendations for Physicians for Biomedical Research Involving Human Subjects” (1964), the World Medical Association on Ethical Principles for Scientific Medical Research Involving Human Subjects (1964-2000), considering the requirements of Directive 2001/20/EC of the European Parliament and of the Council, ICH GCP, the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009.

Statistical data were calculated using MedCalc software developed by MedCalc Software (Ostend, Belgium). The results were evaluated using the Mann-Whitney U-test for small groups. The P value of <0.05 was considered valid. Correlation and regression statistical evaluations were also performed using the aforementioned software.


Research results. The level of melatonin in venous blood taken from women with diagnosed PE was significantly lower (p=0.029), as well as levels of placental growth factor PI GF (p<0.0001), compared to healthy women. In our study we also found that the concentrations of both proinflammatory IL-6 and anti-inflammatory IL-10 were elevated in women with PE compared to women with uncomplicated pregnancies. We performed a prognostic assessment of the impact of the biochemical parameters we studied on the outcome of pregnancies in the examined patients. Melatonin, if present in the blood of a pregnant woman in a concentration higher than the threshold values we established (6.71 pg/ml), reduces the chances of clinical manifestations of severe preeclampsia with a high degree of reliability (p=0.00173). We assume that placental dysfunction in particular leads to impaired synthesis of the antioxidant melatonin, which causes disorders in the tissues of the mother, placenta and fetus and, as a result, provokes clinical manifestations of preeclampsia. The condition of the placenta also worsens the subclinical inflammatory process, as evidenced by an increase in IL-6 levels in patients with diagnosed preeclampsia; an increase in IL-10 in the study group, in our opinion, is a kind of compensatory reaction that prevents preterm labour. In women with pregnancies complicated by preeclampsia, melatonin is a prognostic criterion for delivery before 38 weeks of gestation, and this delivery is mainly associated with the progression of preeclampsia to its severe stage. In the group of patients with uncomplicated pregnancy, proinflammatory interleukin-6 is predictive of spontaneous onset of labour before 38 weeks of gestation. Placental growth factor PI GF was a predictor of the birth of children with a body weight of less than 3000 g in both study groups.

Conclusions. Concentrations of melatonin and of placental growth factor in venous blood in women whose pregnancy was complicated by preeclampsia in the third trimester of pregnancy are significantly lower compared to uncomplicated pregnancies. On the other hand, the levels of proinflammatory IL-6 and anti-inflammatory IL-10 were significantly increased in the group of patients with diagnosed preeclampsia compared with normal pregnancy.

Key words: Melatonin; PI GF; Cytokines; Preeclampsia.
**Introduction**

Preeclampsia (PE) is a systemic disease of the mother-placenta-fetus system typical for pregnancy [1]. PE is characterized by the appearance of arterial hypertension, proteinuria, which is first detected during pregnancy after 20 weeks, as well as damage to other organs, primarily the kidneys, liver dysfunction, changes in blood count, and often fetal growth restriction [2]. A key link in the pathogenesis of preeclampsia is placental dysfunction. Placental damage is associated with excessive secretion of antiangiogenic molecules by the placental tissue [3] and insufficient proangiogenic molecules, in particular, placental vascular growth factor PlGF [4, 15]. Thus, massive endothelial dysfunction occurs in the mother's body, which progressively leads to increased peripheral vascular resistance and activation of procoagulant mechanisms and immune response [2], in particular, to an increase in the production of proinflammatory cytokines and a decrease in anti-inflammatory cytokines, namely IL-4 and IL-10, and progression of systemic multiorgan failure [7].

Oxidative stress is a key factor in placental disorders [8], so many researchers consider melatonin as a potentially useful option for the treatment of PE [1, 9]. Melatonin is a natural antioxidant that acts directly and indirectly. The direct pathway consists in the effective removal of atomic oxygen species from cells directly by the melatonin molecule, while the indirect pathway involves the activation of endogenous antioxidant enzymes, namely glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase [1]. During normal pregnancy, melatonin levels progressively increase [10, 11]; there is evidence of co-expression of melatonin and oxytocin receptors in the myometrium before and during labour [12]. The literature reports a decrease in melatonin levels in preeclampsia, when the degree of decrease correlates with the severity of the process [13], as well as a decrease in the expression of melatonin receptors in placental tissue in case of fetal growth restriction [14].

In pregnant women with PE, there is a decrease in nighttime melatonin concentrations compared to healthy pregnant women [11], which may indicate a dysfunction of the pineal gland. However, a decrease in melatonin levels in this pathology is caused not only by changes in the pineal gland: it is known that the expression of two of the most important enzymes necessary for the synthesis of melatonin, namely aralkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase, which is significantly reduced in the placental tissue of women diagnosed with PE, as well as the expression of melatonin receptors of both types (M1 and M2); therefore, insufficient melatonin synthesis by the placenta in this case is quite accurately confirmed [20].

Regarding changes in the cytokine profile in PE: there is evidence that the levels of proinflammatory cytokines, namely TNF-α and IL-6, increase in preeclampsia, while the concentrations of anti-inflammatory cytokines, namely IL-4 and IL-10, decrease [21]. Melatonin, on the contrary, reduces the secretion of proinflammatory cytokines, in particular TNF-α [22], and increases the production of anti-inflammatory cytokines, namely IL-10 [23]. Therefore, normalization of melatonin levels may be a promising direction in the treatment of PE in pregnant women. As the key immunosuppressive cytokine, IL-10 is secreted primarily by Th2 cells, macrophages, natural killer cells, granulocytes, dendritic cells, and autoantigen-stimulated B cells; normal pregnancy is characterized by a shift in immunity toward Th2 over Th1; this is commonly referred to as "Th2 polarization," which is reversed in the case of PE [34]. Inhibition of IL-10 during the second half of pregnancy in mice resulted in restricted fetal growth but did not affect gestational age or fetal outcome, illustrating the critical but not essential role of IL-10 in fetal growth [35, 36].

Due to melatonin deficiency, oxidative stress in PE increases, leading to a high amount of circulating reactive oxygen species and reactive nitrogen species; both species play an important role as secondary messengers in many intracellular signaling cascades, but they can also have a critical impact on pathological processes in pregnant women [26]. One of the most important signaling pathways activated by reactive oxygen and nitrogen species is the induction of neutrophil adhesion to the endothelium, accompanied by the release of cytokines and activation of signaling pathways associated with the inflammatory response [26-28]. In addition, poor trophoblast invasion, which has been confirmed as one of the main pathological aspects of PE [29], leads to placental hypoxia, accelerating the apoptotic cascade in the villous trophoblast; the production of several other factors, including leukocyte and platelet membrane particles, cytokines, growth factors, and angiogenic factors, is also altered in the case of abnormal trophoblast invasion, and these factors will then interact with the maternal vascular endothelium, which may already be damaged [29].

The role of placental growth factor in preeclampsia is undoubtedly proven: it is known that the deficiency of the secretory activity of this pro-angiogenic molecule causes massive endothelial dysfunction in the mother's body, which progressively leads to an increase in the resistance of peripheral vessels and the activation of procoagulant mechanisms [39]. Regarding the relationship between the levels of melatonin and the placental growth factor PlGF, which is key in the pathogenesis of the development of preeclampsia, there is very little data in the modern literature; however, one of the recent studies found that the levels of both melatonin and the placental growth factor decrease in umbilical cord blood collected during childbirth in women whose pregnancy was complicated by fetal growth restriction [32].

Hence, PE is a complex pathological process, a significant role in the development of which is played by a decrease in melatonin levels, which is a consequence of pituitary and placental dysfunction.

The purpose of this study was to assess the pathogenetic mechanisms of complications arising from melatonin deficiency, and in particular - to determine changes in melatonin, IL-6 and IL-10 and the correlation between them.

**Material and research methods**

R&D "Preservation and restoration of reproductive health of women and girls in obstetric and gynecological pathology». State registration number:

The study, which was conducted at the Department of Pregnancy Pathology of the Chernivtsi Regional Perinatal Center, involved 32 women whose pregnancy was complicated by preeclampsia. The presence of preeclampsia was diagnosed by systolic blood pressure $\geq 160$ mm Hg or diastolic blood pressure $\geq 110$ mm Hg, confirmed by a second blood pressure measurement within 10 minutes, as well as proteinuria $\geq 300$ mg per 24-hour urine collection [37]. All women in the study group had a gestational age of 30-32 weeks, confirmed by calculating the labour date based on the first day of the last menstrual period, and the first trimester ultrasound (11-13 weeks).

The control group consisted of 33 women with uncomplicated pregnancies who were observed in the antenatal clinic of the Chernivtsi Regional Perinatal Center.

Patients with extragenital diseases (chronic arterial hypertension, obesity, pregestational and gestational diabetes, endocrine diseases, anemia, etc.) were excluded from both the study and control groups.

Melatonin and PIGF concentrations were determined using an ELISA kit manufactured by IBL (Germany), and concentrations of proinflammatory (IL-6) and anti-inflammatory (IL-10) cytokines were determined using diagnostic kits manufactured by Vector Best (Ukraine). The study was performed in venous blood, all analyzes were collected by vein puncture at the same time: 9:00 am on an empty stomach.

Statistical data were calculated using MedCalc software developed by MedCalc Software (Ostend, Belgium). The results were evaluated using the Mann-Whitney U-test for small groups. The P value of $<0.05$ was considered valid. Correlation and regression statistical evaluations were also performed using the aforementioned software.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Women with PE (n=32)</th>
<th>Control group (n=33)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>28.6±3,7</td>
<td>31.2±6,6</td>
<td>0.053</td>
</tr>
<tr>
<td>Woman's weight, kg</td>
<td>74.0±6.6</td>
<td>65.6±8.7</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Due date of labour, weeks</td>
<td>38.0±0.8</td>
<td>38.7±1.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Note:** Data are presented as arithmetic mean ± standard deviation

We conducted a prognostic assessment of the impact of the biochemical parameters we studied on the pregnancy outcomes of the patients examined. To do this, we used the method of constructing a "curve of errors", also known as a ROC-curve. This technique is widely used in clinical practice to make a diagnosis on a "yes/no" basis ("1/0", diagnosis is/is not present). The methodology also allows calculating threshold values of quantitative indicators used in a diagnostic and/or prognostic model [33]. The result of a diagnostic test is often based on whether the value of the marker selected by the researcher exceeds the threshold value. In this case, the diagnosis for a particular patient is "positive" (present), and if the threshold value is not exceeded, it is "negative" (absent) [34]. The most important aspect in this case is the correct choice of the quantitative variable on which the qualitative indicator "1/0" will depend (or not). We chose the following qualitative indicators that characterized the end of pregnancy in the examined patients: delivery before 38 weeks of gestation, which is usually due to the progression of preeclampsia, as well as the birth of children with a body weight below 3000 g, which is most often due to placental dysfunction. To build ROC curves, we used the "ROC curve analysis" computational block of the MedCalc software package produced by MedCalc Software Ltd, Ostend, Belgium. The results were taken into account only if $p<0.05$.

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Women with PE (n=32)</th>
<th>Control group (n=33)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child's body weight at birth, g</td>
<td>3176.5 ± 274.4</td>
<td>3164.0 ± 405.9</td>
<td>0.88</td>
</tr>
<tr>
<td>Height at birth, cm</td>
<td>50.3 ± 1.7</td>
<td>51.5 ± 2.7</td>
<td>0.037</td>
</tr>
<tr>
<td>Apgar score (1ˢᵗ min), points</td>
<td>7.7 ± 0.45</td>
<td>7.8 ± 0.69</td>
<td>0.49</td>
</tr>
<tr>
<td>Apgar score (5ᵗʰ min), points</td>
<td>8.1 ± 0.46</td>
<td>8.4 ± 0.66</td>
<td>0.038</td>
</tr>
</tbody>
</table>

**Note:** Data are presented as arithmetic mean ± standard deviation

The patient's informed consent form and the patient's examination card were approved by the Biomedical Ethics Committee of Bukovinian State Medical University (BSMU) of the Ministry of Health of Ukraine (Chernivtsi). The work was guided by the general provisions of the Declaration of Helsinki "Recommendations for Physicians for Biomedical Research Involving Human Subjects" (1964), the World Medical Association on Ethical Principles for Scientific Medical Research Involving Human Subjects (1964-2000), taking into account the requirements of Directive 2001/20/EC of the European Parliament and of the Council, ICH GCP, the Council of Europe Convention on Human Rights and Biomedicine (04.04.1997), Order of the Ministry of Health of Ukraine No. 690 of 23.09.2009.
Study results and discussion

Here is a brief clinical and statistical description of the study groups (Table 1).

The mean age in the main group was 28.59 years (95% confidence interval for the average 27.3 - 29.88 years), in the control group - 31.24 (28.97 - 33.51) years, this indicator did not differ significantly between the groups (p=0.053). Instead, as can be seen from Table 1, the average weight of patients whose pregnancy was complicated by preeclampsia was significantly higher compared to healthy pregnant women (p<0.0001). Births in the study group occurred significantly earlier (p=0.01), at an average of 38.09 weeks (in the control group – at 38.67 weeks).

All patients gave birth naturally at a gestational age of more than 37 weeks. Cases of severe fetal distress that required cesarean section, obstetric vice or vacuum fetal extraction were excluded from the study.

The results of pregnancies of women included in the study groups are presented in Table 2.

The data presented in Table 2 show that the average birth weight of children at birth did not differ significantly between the groups (p=0.88), while the height of newborns was significantly higher in the control group (p=0.037). In addition, the Apgar score of newborns at the 5ᵗʰ minute of life was 0.3 points higher in the group of patients with uncomplicated pregnancy (p=0.038).

The analysis of biochemical parameters revealed a significant decrease in melatonin in women with PE compared with patients with uncomplicated pregnancy (Table 3), which is also confirmed by other studies [11, 20].

As can be seen in Table 3, the level of melatonin in venous blood taken from women with diagnosed PE was significantly lower (P=0.029) compared to healthy women. Thus, we can conclude that in the case of PE, the level of melatonin in the mother's venous blood decreases during pregnancy.

The levels of PlGF in venous blood taken from the patients of the studied groups are represented in Table 4.

It’s been established that the concentration of PlGF in venous blood taken from women with diagnosed preeclampsia was more than 5 times lower than in women who had uncomplicated pregnancies, p<0.0001.

The next step was to determine the consequent pathogenic chain, in particular proinflammatory IL-6 and anti-inflammatory IL-10, as the literature on this issue is different and contradictory in its results. A recent study suggests that endothelial cells in PE produce significantly more IL-6 and its receptor gp130 in soluble form, which is a signal of inflammatory changes in the endothelium [32], but much less IL-10. For example, a study of a preeclampsia model in rats with reduced uterine perfusion showed that placental ischemia was associated with decreased IL-10 levels and endothelial cell dysfunction [33]. Some human studies have shown that individual levels of IL-10 did not differ significantly between patients with preeclampsia and normotensive patients [35, 36].

In our study, we found that the concentrations of both proinflammatory IL-6 and anti-inflammatory IL-10 were elevated in women with PE compared with women with uncomplicated pregnancies (Table 5). In our opinion, this fact can be explained by the inclusion of women with PE, confirmed proteinuria and hypertension in the study group, as well as the exclusion of patients with fetal restriction and fetal distress; thus, IL-10 clearly plays a protective role for the fetus in PE.

The data in Table 5 show a clear difference in cytokine concentrations between the two groups. In the group with PE, we found an increase in the concentration of both IL-6 and IL-10 compared to patients with uncomplicated pregnancies.

To build a prognostic model using the ROC curve, which will be used to predict the selected qualitative indicators in pregnant women with preeclampsia, we analyzed the quantitative variables we monitored.

The results of building ROC curves and the predictive models developed on their basis are shown in Figure 1.
Let's take a closer look at the findings. Thus, we were able to build prognostic ROC curves for predicting the following events during pregnancy complicated by preeclampsia: delivery before 38 weeks by melatonin concentration (Figure 1a), and birth of a child weighing up to 3000 g by placental growth factor concentration (Figure 1b).

First of all, let's pay attention to the prognostic model "Melatonin - delivery before 38 weeks" (Figure 1a). Indications for delivery before 38 weeks of gestation in women with preeclampsia: signs of severe preeclampsia (blood pressure 160/110 mmHg and above and/or proteinuria 3 g per day or more).

Parameters of our prognostic model for women with preeclampsia "Melatonin – delivery before 38 weeks":
- is the area under the AUC curve: 0.781,
- is the standard deviation: 0.118,
- reliability criterion: \( p = 0.0173 \),
- associated threshold criterion: \( \leq 6.71 \text{ pg/ml} \),
- sensitivity: 75.00%,
- specificity: 87.50%.

The prognostic model was developed for the following tasks and conditions: predicting the onset of severe preeclampsia during pregnancy if the level of melatonin measured in fasting venous blood at 8 am in pregnancy complicated by preeclampsia is \( \leq 6.71 \text{ pg/ml} \).

Regarding the prediction of births below 3000 g in women whose pregnancy was complicated by preeclampsia: we were able to reveal the prognostic value of the studied levels of placental growth factor (PlGF) for predicting the birth of a child with such a birth weight (Figure 1b).

The prognostic model for women with preeclampsia "PlGF - birth weight less than 3000 g" has the following parameters:
- is the area under the AUC curve: 0.799,
- is the standard deviation: 0.132,
- reliability criterion: \( p = 0.0239 \),
- sensitivity: 75.00%,
opinion, the direction of predicting future adverse blood sampling by a medical professional. In our invasive medical intervention - venipuncture and of a pregnant woman. Secondly, the model involves when predicting the likelihood of severe preeclampsia the strict conditions (described above) that must be met the part of the placental tissue. Therefore, melatonin, placental tissue. The progression of preeclampsia to a protective effect on the mother and fetus and on the our prognostic models as follows. As demonstrated at up to 38 weeks' gestation if the level of the pro-inflammatory interleukin IL-6 (Figure 1d).

The parameters of the prognostic model for women with uncomplicated pregnancy "PlGF - birth weight less than 3000 g":
- is the area under the AUC curve: 0.800,
- is the standard deviation: 0.017,
- reliability criterion: p = 0.0051,
- associated threshold criterion: ≤ 66.6 pg/ml,
- sensitivity: 70.00%,
- specificity: 95.65%.

The prognostic model was developed for the following tasks and conditions: predicting the birth of a child with a birth weight below 3000 g if the level of placental growth factor PlGF measured in fasting venous blood at 8 am in pregnancy complicated by preeclampsia is ≤ 12.88 pg/ml.

For women with uncomplicated pregnancies (control group), we were able to build prognostic ROC curves to predict the following events: the birth of a child weighing up to 3000 g - by the concentration of placental growth factor PlGF (Figure 1b) and delivery before 38 weeks - by the concentration of IL-6 (Figure 1d).

Parameters of the prognostic model for women with uncomplicated pregnancy "PlGF - birth weight less than 3000 g":
- is the area under the AUC curve: 0.800,
- is the standard deviation: 0.017,
- reliability criterion: p = 0.0051,
- associated threshold criterion: ≤ 66.6 pg/ml,
- sensitivity: 70.00%,
- specificity: 95.65%.

The prognostic model was developed for the following tasks and conditions: predicting the birth of a child with a birth weight below 3000 g if the level of placental growth factor PlGF measured in fasting venous blood at 8 am in an uncomplicated pregnancy is ≤ 66.6 pg/ml.

The parameters of the prognostic model for women with uncomplicated pregnancy "IL-6 - delivery before 38 weeks" are as follows:
- is the area under the AUC curve: 0.932,
- is the standard deviation: 0.448,
- reliability criterion: p < 0.0001,
- associated threshold criterion: > 294.69 pg/ml,
- sensitivity: 100.00%,
- specificity: 85.71%.

The prognostic model was developed for the following tasks and conditions: prediction of labor at up to 38 weeks' gestation if the level of the pro-inflammatory cytokine IL-6 measured in fasting venous blood at 8 am in an uncomplicated pregnancy is > 294.69 pg/ml.

We explain the data we obtained in developing our prognostic models as follows. As demonstrated throughout our study, melatonin is a hormone that has a protective effect on the mother and fetus and on the placental tissue. The progression of preeclampsia to it's severe form is a manifestation of maladaptation on the part of the placental tissue. Therefore, melatonin, if present in the blood of a pregnant woman in a concentration higher than the thresholds we have established (6.71 pg/ml), reduces the chances of clinical manifestations of severe preeclampsia with a high degree of reliability (p=0.00173). However, this prognostic model has its drawbacks. Firstly, these are the strict conditions (described above) that must be met when predicting the likelihood of severe preeclampsia based on the level of melatonin in the venous blood of a pregnant woman. Secondly, the model involves invasive medical intervention - venipuncture and blood sampling by a medical professional. In our opinion, the direction of predicting future adverse obstetric events based on changes in salivary melatonin concentrations is promising. Such a study is non-invasive, economically more feasible, can be performed on an outpatient basis, and the patient can donate biological material for it herself. This may be the focus of further research.

To develop prognostic models to calculate the probability of having a child with a birth weight below 3000 g in both groups, the indicator PlGF (placental growth factor) was used.

Placental vascular growth factor is an angiogenic protein whose expression is most pronounced during pregnancy. Its concentration correlates with placental function well. Placental growth factor (PIGF) belongs to the vascular endothelial growth factor (VEGF) family of proteins. It is known that PIGF exerts its angiogenic effects through both direct and indirect mechanisms, causing receptor dimerization and phosphorylation. PIGF directly activates endothelial cells, macrophages, and hematopoietic progenitor cells by binding to a membrane receptor known as fms-like-tyrosin-kinase-1 (Flt-1), and in doing so, not only triggers angiogenesis itself, but also increases the cell's sensitivity to the vascular endothelial growth factor VEGF. PIGF acts indirectly by displacing vascular endothelial growth factor from receptors, while the soluble form of the mentioned receptor, soluble fms-like-tyrosin-kinase-1 (sFlt-1), which is actively expressed by the placenta in preeclampsia has antiangiogenic potential because it binds to PIGF and VEGF in the blood, reduces their bioavailability, and thus interaction with membrane proangiogenic receptors [35]. Thus, PIGF has a proangiogenic effect in the maternal-fetal complex; it is widely known as a predictor and diagnostic marker of preeclampsia [36]. At the same time, this molecule attracts the attention of many researchers in placental insufficiency or fetal distress. For example, Larissa N. Bligh, Ristan M. Greer, Sailesh Kumar (2016) found that reduced PIGF levels were associated with lower Apgar scores, abnormal fetal heart rate changes in labor, and pH changes in the umbilical cord arteries, which are characteristic of fetal hypoxia [37]. In our study, PIGF had a prognostic value for the birth of children with a birth weight below 3000 g at a threshold value of ≤ 12.88 pg/ml (p = 0.0239). We believe that this is due to the delivery of patients with signs of severe preeclampsia, as well as manifestations of placental dysfunction accompanying the development of preeclampsia. However, the prognostic value of PIGF for this qualitative parameter was also observed in the group of women with uncomplicated pregnancy at a threshold value of ≤ 66.6 pg/ml (p = 0.0051). Also in our study, we noted the prognostic value of proinflammatory interleukin IL-6 for predicting the delivery of women with uncomplicated pregnancy at a time earlier than 38 weeks of gestation (associated threshold criterion > 294.69 pg/ml, p < 0.0001), which, in our opinion, is associated with a subclinical inflammatory response in the placental tissue, which, along with other factors, causes spontaneous onset of labor.

Conclusion. Concentrations of melatonin and of placental growth factor in venous blood in women whose pregnancy was complicated by preeclampsia in the third trimester of pregnancy are significantly lower compared to uncomplicated pregnancies. On
the contrary, the levels of proinflammatory IL-6 and anti-inflammatory IL-10 are significantly increased in the group of patients with diagnosed preeclampsia compared to normal pregnancies. We assume that placental dysfunction, in particular, leads to impaired synthesis of the antioxidant melatonin, which causes disorders in the tissues of the mother, placenta and fetus, and, as a result, provokes clinical manifestations of preeclampsia. The condition of the placenta also worsens the subclinical inflammatory process, as evidenced by an increase in IL-6 levels in patients with diagnosed preeclampsia; an increase in IL-10 in the study group, in our opinion, is a kind of compensatory reaction that prevents preterm birth. In women with pregnancies complicated by preeclampsia, melatonin is a prognostic criterion for delivery before 38 weeks of gestation, and this delivery is mainly associated with the progression of preeclampsia to severe preeclampsia. In the group of patients with uncomplicated pregnancy, proinflammatory interleukin-6 is predictive of spontaneous onset of labor before 38 weeks of gestation. Placental growth factor PlGF was a predictor of the birth of children with a body weight of less than 3000 g in both study groups.

Prospects for further research. In the future, it is planned to continue to elucidate the role of melatonin in preeclampsia combined with extragenital pathology.

Conflict of interest: none

Sources of funding: self-financing


ВПЛИВ МЕЛАТОНІНУ НА КІЛЬКІСТЬ ЦИТОКІНІВ ПРИ ПРЕЕКЛАМПСІІ

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Резюме
Вступ. У літературі є повідомлення про зниження рівня мелатоніну при прееклампсії, коли ступінь зниження корелює з тяжкістю процесу, а також про зниження експресії різних рецепторів мелатоніну в плантарній тканині у випадку затримки розвитку плода.

Щодо змін у цитокіновому профілі при прееклампсії: є дані про те, що рівні прозапальних цитокінів, а саме TNF-α та IL-6, підвищаються при прееклампсії, тоді як концентрації протизапальних цитокінів, а саме IL-4 та IL-10, зменшуються. Мелатонін, навпаки, знижує секрецію прозапальних цитокінів, зокрема TNF-α, і збільшує продукцію протизапальних цитокінів.

Мета дослідження. Оцінити патогенетичні механізми ускладнень, що виникають при зниженні мелатоніну, зокрема, з’ясувати зміни мелатоніну, IL-6 та IL-10, визначити кореляцію між ними.

Матеріал і методи дослідження. У дослідженні, яке проводили в Чернівецькому обласному перинатальному центру, брали участь 32 жінки, вагітність яких ускладнилася прееклампсією. Керування група склали 33 жінки з неускладненим перебігом вагітності, які спостерігалися у відділенні жіночої консультації Чернівецького обласного перинатального центру.


Статистичні дані розраховували за допомогою програмного забезпечення MedCalc, розробленого компанією
"MedCalc Software" (Остенде, Бельгія). Результати оцінювали за допомогою U-тесту Манна-Уітні для маліх груп. Значення P < 0,05 вважалося достовірним. Кореляційні та регресійні статистичні оцінки також проводили за допомогою згаданого програмного забезпечення.

НДР «Збереження та відновлення репродуктивного здоров'я жінок та дівчат при акушерській і гінекологічній па

Результати дослідження. Рівні мелатоніну у венозній крові, взятій у жінок з діагностованою прееклампсією, був достовірно низьким (p=0,029), порівняно зі здоровими жінками. У нашому дослідженні ми встановили, що концентрації як прозапального IL-6, так і противапального IL-10, були підвищені у жінок з прееклампсією порівняно з жінками з неускладненою вагітністю. Нами було проведено прогнозистичну оцінку впливу виникнення нами біохімічних показників на результати вагітностей обстежених пацієнток. Мелатонін, якщо він присутній в крові вагітної жінки в концентрації, вищій за встановлені нами порогові значення (6,71 pg/ml), з високим ступенем довірочності (p=0,00173) визнає шанси на появи клінічних проявів тяжкої прееклампсії. Ми припускаємо, що плазматична дисфункція, зокрема, призводить до порушення синтезу антиоксидантну мелатоніну, що спричиняє порушення в тканинах матері, плаценти та плода та, як наслідок, провокує клінічні прояви прееклампсії. Стан плаценти також погіршує субклінічне запальний процес, пов'язаний з виникненням рівня IL-6 у хворих з діагностованою прееклампсією; підвищення IL-10 в досліджуваній групі, на нашу думку, є своєрідною компенсаторною реакцією, яка запобігає передчасним пологам. У жінок з вагітністю, що удосконалилася прееклампсією, мелатонін є прогностичним критерієм розродження до 38 тижнів гестації, причому це розродження переважно пов'язане з прогресуванням прееклампсії до тяжкої. В групі пацієнток з неускладненим перебігом вагітності прогностичне значення щодо спонтанного початку пологової діяльності в терміні до 38 тижнів має прогностичний інтерлейкін-6. Плацентарний фактор росту PlGF виступив предиктором народження до 38 тижнів гестації, причому це розродження переважно пов'язане з прогресуванням прееклампсії до тяжкої. В групі пацієнток з прееклампсією, мелатонін є прогностичним критерієм розродження до 38 тижнів, причому це розродження переважно пов'язане з прогресуванням прееклампсії до тяжкої. В групі пацієнток з неускладненим перебігом вагітності прогностичне значення щодо спонтанного початку пологової діяльності в терміні до 38 тижнів має прогностичний інтерлейкін-6. Плацентарний фактор росту PlGF виступив предиктором народження до 38 тижнів, причому це розродження переважно пов'язане з прогресуванням прееклампсії до тяжкої. В групі пацієнток з неускладненим перебігом вагітності прогностичне значення щодо спонтанного початку пологової діяльності в терміні до 38 тижнів має прогностичний інтерлейкін-6. Плацентарний фактор росту PlGF виступив предиктором народження до 38 тижнів, причому це розродження переважно пов'язане з прогресуванням прееклампсії до тяжкої. В групі пацієнток з неускладненим перебігом вагітності прогностичне значення щодо спонтанного початку пологової діяльності в терміні до 38 тижнів має прогностичний інтерлейкін-6. Плацентарний фактор росту PlGF виступив предиктором народження до 38 тижнів, причому це розродження переважно пов'язане з прогресуванням прееклампсії до тяжкої.