ГИНЕКОЛОГИЯ

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Melatonin levels and fetal growth restriction: Clinical insights and analytical approaches

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Fetal growth restriction is a prevalent complication of pregnancy. Fetal growth restriction entails the pathological restriction of fetal growth, leading to heightened perinatal risks. Placental histopathology in fetal growth restriction typically involves incomplete invasion and transformation of spiral arteries, as well as impaired uteroplacental blood flow. Often, fetal growth restriction is comorbid with preeclampsia. Several theories propose the beneficial role of melatonin in reducing fetal growth restriction and preeclampsia. Studies suggest that melatonin may enhance neoangiogenesis and oxygenation, crucial processes in pregnancy. Melatonin's expression throughout pregnancy in the human placenta underscores its importance in placental function and pregnancy outcomes. This research aims to study clinical and anamnestic data in women with fetal growth restriction compared to a control group and analyze urinary melatonin levels in both groups. The study, conducted between 2018 and 2021, included 66 pregnant women (34 with fetal growth restriction, 32 controls). Enzyme immunoassay of urine revealed significantly lower melatonin levels in the fetal growth restriction group compared to controls. In conclusion, fetal growth restriction remains a significant challenge, warranting new therapeutic approaches. Lower urinary melatonin levels in fetal growth restriction patients suggest its potential role in disease pathogenesis. Further research into

melatonin's mechanisms and therapeutic applications is essential for preventing or mitigating fetal growth restriction's clinical manifestations.

Keywords: pregnancy, fetal growth restriction, preeclampsia, melatonin, enzyme immunoassay.

Introduction

The main criterion assessing the effectiveness of socio-economic development and a marker of the reproductive and demographic situation in the country is infant mortality [1]. Fetal growth restriction (FGR) is a common complication of pregnancy affecting the fetus, it is 5–10 %, with a burdened obstetric-gynecological history and complicated pregnancy — 10–25 % [2]. FGR characterizes a pathologically small fetus that has not reached its growth potential and has a high risk of perinatal complications. The incidence of FGR is inversely proportional to the term of gestation and can reach 60 % among premature births, increasing the morbidity and mortality of fetuses [3].

In FGR, placental histopathology is characterized by incomplete invasion of the placenta, incomplete transformation of the spiral arteries, and impaired uteroplacental blood flow. FGR is often combined with preeclampsia (PE), especially with the early development of the pathology described above, and at the onset of PE it is necessary to exclude FGR[1]. One of the causes of maternal mortality is PE. According to WHO, every 16 seconds there is one case of stillbirth in the world, and the presence of FGR in pregnant women makes a significant contribution to this statistics.

Theories have been put forward about the positive effect of melatonin on reducing the incidence of FGR and PE. At the same time, it is important to note that the described studies of melatonin indicate an improvement in neoangiogenesis and oxygenation [4–8]. It is known that the manifestations of the threat of termination of pregnancy and the severity of PE and FGR in later stages are directly related to the processes occurring in the placenta. It has been proven that melatonin is expressed in the human placenta throughout pregnancy and contributes to the formation of syncytium, which indicates the essential role of this indolamine and its precursors in the functioning of the placenta and the favorable development of pregnancy [9]. In addition, melatonin has also been shown to protect embryos from various exogenous hazards [10].

Melatonin can have a protective effect on the placenta and fetus in the presence of unfavorable factors for their development, as well as improving their adaptive capabilities [4, 11].

The objectives of our research:

— study clinical and anamnestic data in women with FGR and in the control group;
— analyze the level of melatonin in urine in two groups of patients.

Materials and methods

The clinical study was performed from 2018 to 2021 on the basis of the antenatal and maternity departments of the D. O. Ott Research Institute of Obstetrics, Gynecology

[1] Clinical recommendations for insufficient fetal groth requiring maternal medical care (fetal growth restriction) // Minzdrav RF. Available at: https://cr.minzdrav.gov.ru/recomend/722_1 (accessed: 11.02.2022). (In Russian)

and Reproductology, St. Petersburg and on the basis of the antenatal and maternity departments of the St. Petersburg State Budgetary Healthcare Institution Maternity Hospital no. 9, St. Petersburg. A prospective analysis of clinical observations for the period 2019–2021 was carried out, the study is not continuous in terms of coverage.

The main group — women with fetal growth restriction (n = 34); control group — women without FGR (n = 32).

Inclusion criteria: age from 18 to 45 years; established diagnosis of FGR, detected before 34 weeks; single pregnancy; comparable therapy within group.

Exclusion criteria: multiple pregnancies; pregnancy that occurred with the help of assisted reproductive technologies; chromosomal abnormalities of the fetus or its malformations; acute infectious diseases during pregnancy; obesity established before pregnancy; chronic alcohol and/or nicotine intoxication; somatic pathology (bronchial asthma, chronic obstructive pulmonary disease, antiphospholipid syndrome, diabetes mellitus, rheumatoid arthritis, neurodegenerative diseases).

Methods of clinical research: clinical and anamnestic; general clinical examination; Ultrasound: fetometry, assessment of amniotic fluid, Dopplerometry; cardiotocographic monitoring; laboratory methods, including enzyme immunoassay of urine for melatonin levels.

Pregnant women collected the first morning portion of urine into a vessel in a dark room with dim yellow lighting. The time of falling asleep and waking up for each patient was recorded. After collection, the resulting urine volume was measured to calculate the results. The entire volume of urine was collected and mixed in one container, without adding a preservative. After which it is poured into two 5 ml eppendorfs and immediately frozen to a temperature of –20 °C, avoiding premature defrosting.

Most circulating melatonin is metabolized in the liver to 6-hydroxymelatonin sulfate and then to 6-sulfatoxymelatonin, which is excreted in the urine. The concentration of 6-hydroxymelatonin sulfate in urine correlates well with the average daily level of melatonin in the blood [12].

Enzyme immunoassay of urine to determine the level of hourly excretion of melatonin sulfate was performed using a Microtiter plate reader capable of reading absorbance ft 450 nm (and a reference filter of 600–650 nm). An enzyme immunoassay kit was used for the in vitro quantitative determination of human melatonin sulfate in human urine.

The determination of melatonin sulfate is based on the method of solid-phase competitive enzyme immunoassay.

Melatonin sulfate (MeSO4) conjugated with horseradish peroxidase and MeSO4 contained in the sample compete with each other for a limited number of binding sites of antibodies sorbed in the wells of the tablet.

Methodology for determining the level of melatonin in urine in the main and control groups:

1. Preparation of samples for analysis included complete defrosting of the material, after which mixing using a FUGE VorteX centrifuge, then taking 500 μl of material. Automatic pipette for 500 μl, Multipette Eppendorf.
2. Centrifuge for 5 minutes at 3000 rpm using an orbital shaker.
3. Preparation of reagents from concentrated components.
4. Preparation of standards, controls, samples.

5. Dilution of all standards, controls, samples: 500 μl of Working Buffer + 10 μl of each standard, control, sample.

6. Mixing.

7. We dig up a concentration of 1:40.

8. 50 ml of freshly prepared conjugate + 50 ml of standard, control, sample + 50 ml of antiserum to Melatonin sulfate in all wells.

9. Cover the tablet with adhesive film. Incubate for 2 hours at room temperature (18–25 °C) on an orbital shaker (500 rpm).

10. Remove the adhesive film from the plate and remove the incubation solution. We wash each well with a working solution of Wash Buffer 4 × 250 μl. Remove the remaining Wash Buffer by tapping the inverted tablet on the filter paper.

11. To add the Substrate Solution and Stop Solution, we use an 8-channel dispenser. We apply solutions in the same sequence and at the same speed.

12. Add 100 μl of TMB Substrate Solution to each well.

13. Incubate for 30 minutes at room temperature (18–25 °C) on an orbital shaker (500 rpm).

14. Stop the reaction by adding 100 μl of TMB Stop solution to all wells, gently shaking the plate before measurement.

15. We measure the optical density (OD) in the wells at 450 nm on a tablet photometer for microtiter plates (reference wavelength 600–650 nm) no later than 60 minutes after adding the Stop solution.

In the laboratory, groups were recruited to determine the range of normal values (melatonin levels in healthy people), which coincided with the specified norms.

Formula for calculation:

$$\text{Hourly Excretion} = \frac{\text{6COMT concentration} \times \text{Urine volume}}{\text{Number of hours}} : 1000.$$

Results and their discussion

According to the results of an enzyme immunoassay of urine to determine the level of hourly excretion of melatonin sulfate in urine, it was found that in the control group the level of melatonin was 1877.17 ± 283.36 μg/day, while in the study group the level was 1040.99 ± 344.50 μg/day, the difference between these groups was statistically significant, $p < 0.05$. A significant difference in melatonin levels was noticed within the group with FGR; the analysis revealed that in patients who were diagnosed with PE, the melatonin level was 527.27 ± 234.90 μg/day, which is significantly less than in patients with FGR and without PE 1397.04 ± 520.47 mcg/day, $p < 0.05$. When comparing melatonin levels in the subgroup of patients with PE and in the control group, the differences were even more convincing $p < 0.01$ and is presented in Fig. 1. The literature describes [5, 8, 11] that melatonin levels vary significantly in different age groups. In our study, in women with FGR under the age of 35 years, the level was 1043.44 mcg/day, in the same group aged 36 years and older, it was 1029.526 mcg/day, $p > 0.05$, which does not disprove the null hypothesis. The null hypothesis was not refuted in the control group either: in patients in the age group under 35 years old — 1828.68 mcg/day, and from 36 and older — 2562.41 mcg/day, $p > 0.05$.

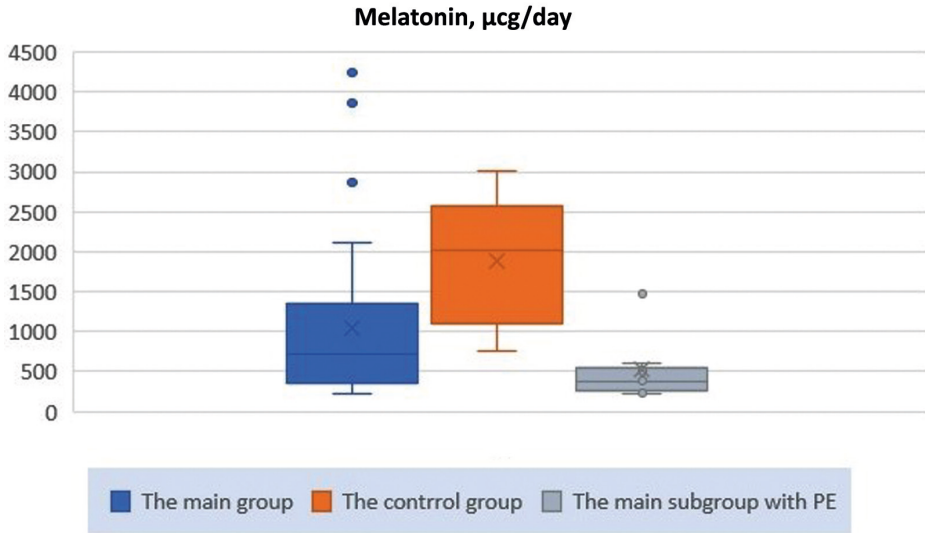

Fig. 1. The level of hourly urinary excretion (ELISA)

Among the compared clinical groups of patients, no statistically significant differences were found in age and height. The weight of pregnant women with FGR was significantly lower, which is confirmed by $p = 0.003$. The distribution of blood groups and Rh factor did not differ from the average in the population. Primigravidas of women with FGR accounted for 38.23 %, and women without the pathology under study — 46.87 %, were compared with each other, $p > 0.05$; $\chi^2 = 0.3$. Also, primiparas in the main group were 58.82 %, in the control group 59.375 %, $p > 0.05$; $\chi^2 = 0.73$. This is statistically insignificant.

There were no statistically significant differences between the groups in terms of obstetric and gynecological history: endometriosis; uterine fibroids or myomectomy; cicatricial deformity of the cervix; polycystic ovary syndrome; history of miscarriage or infertility; narrow pelvis.

The hypothesis of a difference between groups cannot be rejected for such somatic nosologies as arterial hypertension, urolithiasis, pyelectasia, hydronephrosis, varicose veins, biliary dyskinesia, subclinical hypothyroidism and euthyroidism.

It is interesting that in pregnant women without FGR, the total weight gain during pregnancy was significantly greater and equal to 14.2 ± 0.95 kg, while in pregnant women with FGR it was 10.7 ± 0.79 kg, $p = 0.007$. On the one hand, this is due to the timing of delivery, but when calculating women with comparable dates in different groups, the statistical difference remained.

In the control group, 50 % of women had no edema, 30 % had slight swelling of the extremities, and 20 % had edema of the extremities, while in the group with FGR, only 10 % had no edema, 32 % had slight edema of the hands and legs, and 58 % had edema of the extremities, the difference between the groups is confirmed statistically, $p = 0.0002$ and is presented in Fig. 2.

An increase in blood pressure figures was recorded in 41 % of pregnant women with FGR, while in the control group hypertension was not recorded, $p < 0.00001$, $\chi^2 = 0.00001$.

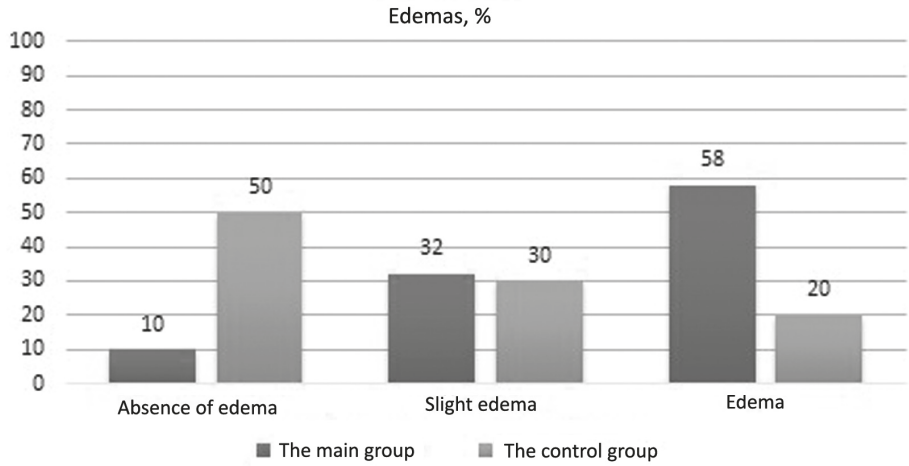

Fig. 2. Distribution of edema among the studied

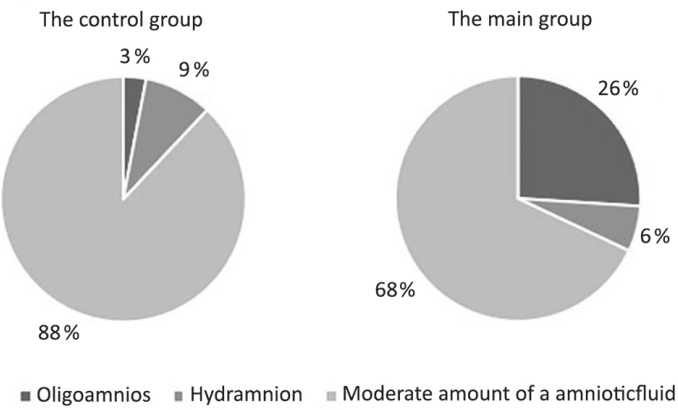

Fig. 3. The amount of amniotic fluid

PE in the group with FGR occurred in 44.1 % of cases, while in the control group in only 6.25 % of cases, $p < 0.001$.

Assessing the amount of amniotic fluid (AF), statistically significant differences were found, which are clearly shown in Fig. 3. In the control group, oligohydramnios was diagnosed in only one woman — 3.125 %, while polyhydramnios was 9.37 %, a moderate amount of amniotic fluid in 87.5 %. In the main group, 26.5 % had oligohydramnios, 5.8 % had polyhydramnios, and 67.7 % had moderate amounts of water, which refutes the null hypothesis, $p = 0.02$.

The average amniotic index studied during pregnancy in the main group was 10.5 ± 0.9, while in the control group it was 13.9 ± 0.7; these indicators were significantly different from each other, $p < 0.005$.

The incidence of pregnancy anemia and thrombocytopenia were calculated in the study and control groups. There were no statistically significant differences between them. Leukocytosis was noted only among patients in the control group. Increased levels of fibrinogen and proteinuria were more common in the group of women with FGR, however, when statistically processed, these differences were not significant.

Table 1. **Indicators of Dopplerometry the mother-placenta-fetus system, with FGR / without FGR**

Artery	Systolic-diastolic ratio	Resistance index	Ripple index
Umbilical cord	3,56 ± 0,8 / 2,41 ± 0,07 (p < 0.05)	0,59 ± 0,02 / 0,55 ± 0,01 (p < 0.05)	1,19 ± 0,06 / 0,8 ± 0,16 (p < 0.05)
Middle cerebral	4,1 ± 0,24 / 4,43 ± 0,4 (p > 0.05)	0,73 ± 0,02 / 0,74 ± 0,02 (p > 0.05)	1,5 ± 0,08 / 1,6 ± 0,29 (p > 0.05)
Right uterine	2,66 ± 0,16 / 1,87 ± 0,05 (p < 0.001)	0,57 ± 0,02 / 0,45 ± 0,02 (p = 0.0005)	1,08 ± 0,09 / 0,6 ± 0,08 (p < 0.05)
Left uterine	2,29 ± 0,1 / 1,98 ± 0,06 (p < 0.05)	0,54 ± 0,02 / 0,48 ± 0,01 (p < 0.05)	0,98 ± 0,07 / 0,71 ± 0,1 (p > 0.05)

Table 2. **CTG indicators (beats per minute) in the studied groups**

Indicator	Group with FGR	Group without FGR	p-value
Basal fetal heart rate	137,88 ± 1,39	132,2 ± 1,04	p < 0.05
Myocardial reflex	19,92 ± 0,58	23,43 ± 0,53	p < 0.01
Oscillations	6,96 ± 0,13	8,06 ± 0,19	p < 0.01

The location of the placenta does not affect the risk of developing FGR. The placenta was located on the posterior wall in 58.6 %, on the anterior wall in 41.4 % of women without FGR. In women with FGR, the placenta was on the posterior wall in 46.7 %, anterior — 53.3 %, p = 0.18; $\chi^2 = 0.35$.

During ultrasound, the fetometric indicators of the control group were within 10 ‰ for the corresponding gestational age, while in the main group 58.8 % had signs of FGR.

According to a Doppler study of hemodynamics in the mother-placenta-fetus system, the indicators in the main group were outside the normal range, while no violations were detected in the control group. The data is shown in Table 1.

In fetuses of women with FGR, the basal fetal heart rate was higher than in the control group, while oscillations and myocardial reflex in the group with the studied pathology were significantly lower. The data is shown in Table 2.

All women without FGR gave birth at term, while in the group with FGR, three patients had preterm birth, which amounted to 8.25 %.

In the control group, 31.75% of pregnant women were delivered by cesarean section, in the main group 58.82% of patients p < 0.05. Indications for cesarean section in 14 patients with FGR were associated with the presence of placental insufficiency and fetal hypoxia, two underwent surgery based on the opinion of an ophthalmologist, one due to incompetent scar on the uterus, one due to cicatricial deformity of the cervix, the information is clearly presented on Fig. 4.

Among the postpartum women with FGR, there were the following complications of childbirth: two had rapid labor, two underwent transfusion of fresh frozen plasma, one had primary weakness of labor, one had asphyxia of the newborn, one patient underwent abdominal drainage. During vaginal delivery, perineotomy was performed in 5 women and manual examination of the uterine cavity was performed in one due to retained placenta.

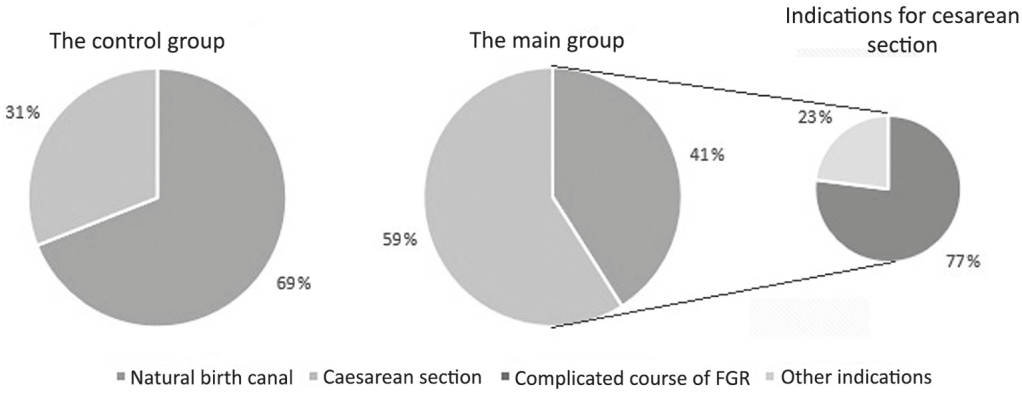

Fig. 4. Method and indications for delivery

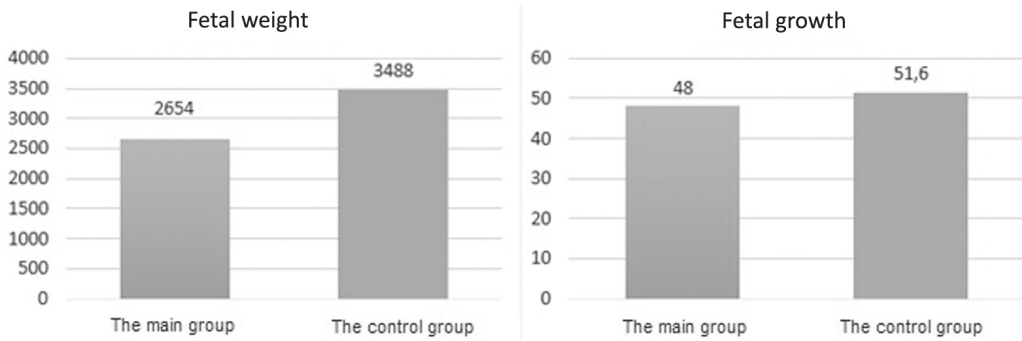

Fig. 5. Fetal parameters

In the postpartum women from the control group, complications of childbirth were: three had incoordination of labor, two had drainage installed in the abdominal cavity during a caesarean section, and one had asphyxia of the newborn. In addition, 12 parturients underwent perineotomy and two underwent manual examination of the uterine cavity and isolation of the retained placenta.

The average term of delivery in women with FGR was 38.0 weeks, and without FGR — 39.75, which refutes the null hypothesis, $p < 0.0000001$.

Women in the control group gave birth to boys in 64.5 % of cases and girls in 35.5 %; in the main group, 52.9 % gave birth to girls and 47.1 % to boys, $p > 0.05$.

The average weight of fetuses born to women with FGR was 2654 ± 85 g, which was significantly lower than that of conditionally healthy women 3488 ± 68 g, $p < 0.00000001$, which certainly reflects the presence of a deficiency in fetal weight as the leading component of FGR. The average height of fetuses in the main group was 48 ± 0.54 cm, which was statistically less than in the control group 51.6 ± 0.37 cm, $p < 0.001$. These data are shown in Fig. 5.

Indicators: head circumference, chest circumference, umbilical cord length, placenta weight, placenta dimensions are given in Table 3.

Fetal hypoxia in women with FGR was in 27.3 %, in women without the pathology under study in 18.75 % of cases, $p = 0.21$; $\chi^2 = 1.17$.

Table 3. **Fetal and placental sizes**

Parameter	Group with FGR	Group without FGR	p-value
Head circumference	33,8 ± 0,28	35,2 ± 0,24	< 0,001
Chest circumference	31,4 ± 0,45	33,9 ± 0,25	< 0,0001
Umbilical cord length	62,4 ± 1,7	63,8 ±1,7	> 0,05
Placenta weight	489,3 ± 22,8	613,1 ± 21,6	< 0,001
Placenta area	278,8 ± 21,8	337,1 ± 14,0	< 0,05

Women without the pathology under study had the following Apgar scores 1 minute after birth: 9 points — 9.375 %, 8 points — 81.25 %, 7 points — 6.25 %; 5 points — 3.125 %. The scores for patients of the main group were as follows: 8 points — 64.7 %, 7 points — 32.35 %; 6 points — 2.95 %. Apgar values had statistically significant differences between groups at 1 minute, $p < 0.05$, while at 5 minutes after birth no differences were detected, $p > 0.05$. Apgar 5 minutes after birth in the control group: 9 points — 31.25 %, 8 points — 62.5 %, 7 points — 3.125 %; 6 points — 3.125 %. For the main group: 9 points — 44.1 %, 8 points — 47.1 %, 7 points — 8.8 %.

Blood loss during surgery did not differ significantly between the groups: in the main group, the average volume of blood lost was 582 ± 20 ml, in the control group 630 ± 16 ml, $p > 0.05$. Also, no differences were found during natural childbirth. The average blood loss in postpartum women with FGR was 227 ± 12 ml, without FGR 247 ± 20 ml, $p > 0.05$.

FGR occurred with PE in 44 % of cases. The severe course of this disease in 58 % of cases led to surgical delivery, on average 2 weeks earlier than in the control group. All this confirms the need for new treatment and prevention regimens for FGR.

Conclusion

Today, FGR remains an extremely pressing problem, which is confirmed by high rates of perinatal mortality and morbidity of fetuses diagnosed with obstetric pathology.

In accordance with the objectives of our study, an analysis was carried out on 66 pregnant women, 34 of whom had FGR. Having analyzed the general anamnestic data for all criteria, no statistically significant differences were identified, which confirms the possibility of comparing these groups. The exception was body weight; in women with FGR it was significantly lower. This fact can probably be associated with genetic and physiological characteristics in patients with FGR, however, further research in this direction is necessary to confirm these assumptions. Lower body weight in patients in the main group probably explains the fact that the total weight gain during pregnancy in these patients was reduced by a quarter of the average value than in the control group, which is confirmed by the refutation of the null hypothesis

Edema, increased blood pressure, and preeclampsia were significantly more common in the main group, and this defines the above criteria as predictors of FGR. When we talk about FGR, we should think about PE; these data are consistent with the opinion of foreign authors [13–15].

Oligohydramnios, low-weight fetus at term, Doppler measurements and CTG are the conditions that make it possible to verify FGR, and this was confirmed in our study.

Among the studied women with FGR, 8.25 % had preterm birth; the average delivery date for patients with the pathology under study was almost 2 weeks earlier than in the control group. In the main group, 58.2 % were delivered by CS surgery, of which 77.8 % were due to the deterioration of the clinical situation for the main disease of FGR, which in two cases led to complications such as transfusion of fresh frozen plasma, in one case there was asphyxia of the newborn and Another patient had drainage installed in the abdominal cavity. The average weight of fetuses born to mothers with FGR was 834 g less than in the control group; such parameters as height, head and chest circumference, weight and area of the placenta were also lagging behind; as a result, such fetuses had lower Apgar scores. All of the above demonstrates a pessimistic picture and the ineffectiveness of the approaches used, confirming the need to develop new areas of therapy for FGR.

In our study, there were no statistically significant differences in urinary melatonin levels by age, as reported by other authors, likely due to undersampling of age subgroups. It was reliably established that with FGR, the level of melatonin in pregnant women is significantly lower than in the comparison group. It is especially interesting that there was a significant difference in patients with PE compared to the control group. Our data make the hypothesis about the possible influence of melatonin on the development of PE and FGR promising; we can talk about the need to continue to study the mechanisms of development of this disease and develop new treatment regimens, since currently there is no method that would guarantee a complete cure. The effects of melatonin in FGR are mediated by its influence on the development of the placenta and fetus and, obviously, the use of melatonin during pregnancy will ultimately lead to the prevention of FGR or a decrease in the severity of clinical symptoms of this obstetric pathology.

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Клинические и аналитические аспекты взаимосвязи мелатонина и задержки роста плода

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Задержка роста плода является распространенным осложнением беременности, влекущим за собой патологическое ограничение роста плода, что приводит к повышенному перинатальному риску. Плацентарная гистопатология при этом обычно включает неполную инвазию и трансформацию спиральных артерий, а также нарушение маточно-плацентарного кровотока. Часто задержка роста плода сочетается с преэклампсией. Несколько теорий предполагают полезную роль мелатонина в снижении задержки роста плода и преэклампсии. Исследования показывают, что мелатонин может усиливать

неоангиогенез и оксигенацию, важнейшие процессы во время беременности. Экспрессия мелатонина в плаценте человека на протяжении всей беременности подчеркивает его важность для функции плаценты и исходов беременности. Целью исследования явилось изучение клинических и анамнестических данных у женщин с задержкой роста плода в сравнении с контрольной группой и анализ уровня мелатонина в моче в обеих группах. В исследовании, проведенном в период с 2018 по 2021 г., приняли участие 66 беременных женщин (34 чел. с задержкой роста плода и 32 чел. в контрольной группе). Иммуноферментный анализ мочи выявил значительно более низкие уровни мелатонина в группе с задержкой роста плода по сравнению с контрольной группой. Исследованная патология остается серьезной проблемой, требующей новых терапевтических подходов. Более низкие уровни мелатонина в моче у пациенток с задержкой роста плода позволяют предположить его потенциальную роль в патогенезе заболевания. Дальнейшие исследования механизмов и терапевтического применения мелатонина необходимы для предотвращения или смягчения клинических проявлений данного осложнения беременности.

Ключевые слова: беременность, задержка роста плода, преэклампсия, мелатонин, иммуноферментный анализ.

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