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Serotonin in pregnancies complicated by intrahepatic cholestasis

Serotonina w ciążach powikłanych cholestazą wewnątrzwątrobową

Intrahepatic cholestasis of pregnancy is most common liver disorder in pregnancy (1). Its pathogenesis is unknown (7). The characteristic symptom is itching (*pruritus gravidarum*) which involves the trunk, extremities, palms and soles. Generalized pruritus develops after the 30th week of gestation, may be severe and usually is relieved after delivery (1, 7).

Intrahepatic cholestasis is associated with an increased risk of perinatal complication, including prematurity, stillbirth and a higher incidence of meconium passage, abnormal intrapartum fetal heart rate patterns, an increased perinatal mortality and postpartum bleeding (7).

The cause of the stillbirth and the mechanism of meconium passage in intrahepatic cholestasis of pregnancy is unknown (1, 2, 3, 4, 5). *In vitro* studies have shown that umbilical vein constriction may cause an acute reduction in the umbilical blood flow leading to fetal hypoxia, meconium passage and fetal death (1, 2, 3).

Schworer et al. (12) suggested that serotonin may participate in the generation and/or sensation of cholestatic pruritus. On the basis of successful treatment of cholestatic itch with 5-hydroxytryptamine subtype 3 receptor antagonists the role of serotonin in intrahepatic cholestasis is discussed (9, 11). Serotonin is the potent vasoconstrictor and may be involved in the control of vascular tone in the umbilicoplacental circulatory bed in normal and/or pathological conditions. All these observations and literature data were inspiration to conduct this study.

OBJECTIVE

The purpose of this study was to compare maternal serum serotonin (5-HT) levels and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in 24-hour urine collection in singleton pregnancies complicated by intrahepatic cholestasis with those of appropriate controls.

MATERIAL AND METHODS

The study was carried out on 7 patients with singleton pregnancy complicated by intrahepatic cholestasis between the 30th and 36th weeks of gestation (group C). The diagnosis of intrahepatic cholestasis of pregnancy was based on the presence of generalized pruritus in the absence of other skin or medical conditions that could produce pruritus.

Patients with viral hepatitis and obstructive gallstones were excluded from the study.

The control group (group K) were 7 healthy normotensive patients with singleton uncomplicated pregnancy without intrahepathic cholestasis of pregnancy and normal with laboratory tests.

All studied patients were non-smokers.

The serum serotonin level was estimated in blood taken between 6 and 8 a.m. using spectrophotometry. Blood was also taken for the estimation of serum urea, creatinine, uric acid, alanine and aspartate aminotransferases, alkaline phosphatase and the serum bilirubin concentration. The elimination of 5-hydroxyindoleacetic acid was evaluated in 24-hour urine collection using Mac Farlane method (8).

The obtained data were statistically analysed. The elements of descriptive statistics and one-sided Student's t-test were employed. The level of statistical significance was established as $p<0.05$.

RESULTS

There were no statistically significant differences in patient profiles between the two groups in gravidity, parity, maternal age and gestational age. Systolic and diastolic blood pressure and mean arterial blood pressure (MAP) were higher in the control group, but these differences were not statistically significant. All arterial blood pressure measurements in both groups remained normal and did not exceed 135/85 mm Hg. Diastolic blood pressure was recorded as the fourth Korotkoff sound in all pregnant women.

None of the patients suffered from proteinuria (Table 1). Mean platelet count in the study group was 231371/μL +/- 24116/μL (range between 194000/μL and 270000/μL. No a prolonged prothrombin time was observed in the study and in the control groups. Mean

Table 1. Maternal blood pressure

	Group C (n=7)	Group K (n=7)	p value.
Systolic blood pressure (mmHg).	102.50 +/–13.06	109.46 +/–11.44	NS
Diastolic blood pressure (mmHg).	65.00 +/–10.18	71.25 +/–84	NS
MAP (mmHg).	77.50 +/–10.61	83.98 +/–8.92	NS

Data presented as mean +/–SD

serum bilirubin concentration in the study group was 1.08 +/– 0.65 mg/dL (range between 0.4 mg/dL and 2.5mg/dL). Mean level of alkaline phosphatase was 20.16 +/– 4,22 IU in the study group. The mean level of aspartate aminotransferase was 156.88 +/– 99.62 IU, while the mean level of alanine aminotransferase was 397.88 +/– 335.31 IU.No hepatic dysfunction was observed in the control group. In the control group alanine and aspartate aminotransferases, bilirubin concentration and alkaline phosphatase were normal. No renal dysfunction in the study and in the control groups was observed. Creatinine, uric acid and urea levels were normal in all patients. In the study group creatinine level was 0.64 +/– 0.07mg/dL on average while urea level 16.50 +/– 3.20mg/dL and uric acid 3.16 +/– 0.45 mg/dL. Elevated serotonin levels in blood serum in the study group of cholestatic patients were found to be higher in comparison with the control group. The mean values were 0.726 +/– 0.048 μg/mL respectively in group C versus 0.572+/– 0.088 μg/mL in the control group ($p<0.005$). It was also found that 24-hour elimination of 5-hydroxyindoleacetic acid was higher in the group C than in the control group. These values were 8.560 +/– 0.907 mg/24h versus 6.840 +/– 1.157 mg/24h respectively. This difference was statistically significant ($p<0.02$) (Table 2).

Table 2. Analysis of obtained results

	Group C (n=7)	Group K (n=7)	p value
5-HT(μg/mL)	0.726 +/–0.048	0.572 +/–0.088	p<0.005*
5-HIAA (mg/24 hours)	8.560 +/–0.907	6.840 +/–1.157	p<0.02*

Data presented as mean +/–SD

*Statistical significance

DISCUSSION

Intrahepatic cholestasis of pregnancy is related to a high incidence of perinatal complication and the poor pregnancy outcome. This disease is related to a higher incidence of stillbirth and meconium passage, ab-

normal intrapartum fetal heart rate pattern and increased perinatal mortality (7).

The cause of these complications in intrahepatic cholestasis of pregnancy are unknown (1, 2, 3, 4, 5). The most likely explanation for fetal death in pregnancies complicated by intrahepatic cholestasis is an acute anoxic (1). Umbilical vein constriction may cause an acute reduction in the umbilical blood flow leading to fetal hypoxia, episodes of fetal bradycardia necessitating an immediate operative delivery, meconium passage and fetal death (1, 2, 3).

Serotonin plays a role in hemostasis and interactions between platelets and vascular endothelium, is the potent vasoconstrictor and may be involved in the control of vascular tone in the umbilicoplacental circulatory bed. This biogenic amine may also take part in placental and fetal development (6). The elevated concentrations of serum serotonin in pregnant patients may evoke vasoconstriction of umbilical artery and enhance vasoconstrictory properties of catecholamines.

Rothlin et al. (10) observed that minimal effective concentrations of serotonin are able to produce an increase or "amplification" in the contractile response in the human umbilical artery. In their study the response to noradrenaline was enhanced by previous treatment with minimal effective doses of serotonin. The role of serotonin in intrahepatic cholestasis and generation of cholestatic pruritus is discussed (11, 12).

Our study revealed elevated levels of serotonin in maternal blood serum and 5-hydroxyindoleacetic acid in 24-hour urine output in patients. The obtained results indicate the increased activation of blood platelets and increased release of serotonin in pregnant patients with intrahepatic cholestasis of pregnancy. At the same time the elevated values of 24-hour elimination of 5-hydroxyindoleacetic acid indicate hyperserotoninemia, that does not result from decreased monoamine oxidase activity nor impaired serotonin metabolism in this disease, but rather from its increased release from blood platelets, resulting from their activation.

Changes observed in our study are not related to impaired renal function, because creatinine and urea concentrations in patients with and without intrahepatic cholestasis of pregnancy were comparable and within normal limits. These conditions may result in disorders in placental-fetal circulation and influence the development of placenta and fetus. It is very important in pregnancy and may have clinical consequences during pregnancy, especially pregnancy complicated by intrahepatic cholestasis.

Our results point out the significant role of serotonin and platelet activation in the pregnancy complicated by intrahepatic cholestasis.

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STRESZCZENIE

Wewnątrzwątrobowa cholestaza ciężarnych jest związana ze zwiększonym ryzykiem perinatalnym. W naszych badaniach stwierdziliśmy podwyższone poziomy serotoniny w surowicy krwi i kwasu 5-hydroksyindolooctowego w moczu dobowym u kobiet z ciążą powikłaną cholestazą wewnątrzwątrobową. Uzyskane wyniki wskazują na wzmożoną aktywację płytek krwi i zwiększone uwalnianie serotoniny w grupie badanych kobiet. Zaobserwowane zmiany mogą być następstwem uszkodzenia śródbłonka naczyń, co może być przyczyną zmian w krążeniu łożyskowo-płodowym i wpływać na rozwój łożyska i płodu.