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MODERN POSSIBILITIES OF COMPLEX THERAPY OF PREGNANT WOMEN WITH A THREAT OF PRETERM LABOR

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Today, preterm labor (PL) today is the main problem of obstetrics and perinatology not only in Ukraine but, the whole world. According to the research by Born Too Soon, which was attended by nearly 50 organizations (including the Global Alliance to Prevent Prematurity and Stillbirth – GAPPS), found that one in ten newborns are born prematurely [1, 2, 3]. Investigation of miscarriage problems and understanding of the main links of its pathogenesis are one of priority directions of modern obstetrics. Rate of this pathology makes almost 30 % and doesn’t trend to decrease. It has direct influence on demographic

situation in the country [4, 5]. Annually 15 million premature babies are born in the world [6].

The leading pathogenetic factor in various pathological processes in the body is an increase in the generation of reactive oxygen species as a result of the imbalance of pro- and antioxidant systems and the development of oxidative stress [7, 8]. Oxidative stress is implicated in the pathophysiology of many reproductive complications including infertility, miscarriage, pre-eclampsia, fetal growth restriction and preterm labour. The presence of excess reactive oxygen species can lead to cellular damage of deoxyribonucleic acids, lipids and proteins. [9]. Analysis of biochemical investigations shows that even in conditions of keeping and progression of pregnancy in women with complication such as miscarriage the antioxidant protection is shifted along with activation of peroxidation processes. Such features are the manifestation of oxidative stress in the present group of pregnant women along with deprivation of enzymic and non-enzymic links of protective antioxidant system [10].

With an imbalance in the processes of the oxidation-antioxidant system, free radical oxidation products are able to trigger destructive processes affecting the membranes, the genetic apparatus of cells, upset the regulation of the central mechanisms of the neuroendocrine system that control the delivery process [11, 12].

Analysis of ROS and total antioxidant potential in cord blood from preterm infants demonstrate that preterm infants have significantly decreased antioxidant potential when compared to term counterparts [13].

Since there are still no unambiguous criteria for the prevention and treatment of PB in the world, an important aspect for solving this problem is to prevent them, namely by identification of nonspecific regular reactions of the body that initiate termination of pregnancy.

Object of the work - to assess the effectiveness and impact of complex therapy of pregnant women with risk of preterm labor on biochemical parameters and delivery results.

Examined group and research methods

The research was carried out in Zaporizhia State Medical University, on the basis of MNI «Regional Perinatal Center» ZRC. 121 women with singleton pregnancies were inviloved in the study. The main group included 43 women with risk of preterm birth (RPB), who within 22-34 weeks of gestation, received capsules (active substance - natural micronized progesterone) 200 mg 2 times a day vaginally (course duration was individual and depended on the clinical manifestations of the threat of preterm birth) and suppositories (active substance – thiotriazoline) 200 mg 1 time per day rectally for the first 7-10 days at the same time from the moment of hospitalization. Subsequently, within the absence of clinical manifestations of the threat of preterm birth (TPB), the dose of Utrozhestan was reduced to 200 mg once a day vaginally and continued until 36 weeks of pregnancy. The comparison group included 42 women who received treatment of the TPB under the current Order of the Ministry of Health of Ukraine (№ 624 from 03.11.2008), and with the appointment of progesterone drugs. All pregnant women received prevention

of Respiratory Distress Syndrome of the fetus. The control group are represented by 36 women with physiological course of pregnancy and childbirth. In order to assess the effectiveness of the proposed therapy, before and in the dynamics of treatment (after 14 days), pregnant women underwent a comprehensive assessment of psychoemotional state and biochemical homeostasis, with further analyze of the features of pregnancy, childbirth and newborns.

Markers of oxidative modification of proteins in blood serum were analyzed by spectrophotometric method with wave length of 270 nm (aliphatic aldehydedinitrophénylhydrazones of the main aminoacid residues – APH) and 363 nm (carbonyl dinitrophénylhydrazones of the main aminoacid residues – CPH). Analysis of oxidative modification of proteins was made according to the method of B. Halliwell and its level was expressed in standard units per 1 gram of protein (s.u./g protein). Glutathione level was analyzed by fluorometric method and its level was expressed in mkM/ml [14].

The criteria for including pregnant women with TPB in the groups of study were complaints of irregular, cramping pain in the lower abdomen and buttocks with the appearance of serous-bloody discharge from vagina in combination with a change in the shape and / or location of the cervix without opening. Differences in groups by age, gestational age, social and professional composition were not found ($p > 0.05$). Variational and statistical processing of results was made using STATISTICA 13 – license standard application program packages for multidimensional statistical analysis.

Research results and their discussion

The results of biochemical studies, which are shown in the table, indicate a statistically significant ($p < 0,05$) increase in the level of both spontaneous and stimulated oxidative modification of proteins (OMP) – aldehydephenylhydrazones (AFG) and carboxylphenylhydrazones (CFN) and the lack of reduced glutatione (GSH) in groups of pregnant women with TPB relatively to the control group ($p < 0,05$). These results indicate the activation of oxidative stress reactions, which lead to the development of endothelial dysfunction, circulatory disorders in the mother-placenta-fetus system and, as an consequence, the development of persistent hypoxic disorders in fetal tissues. Hyperproduction of reactive oxygen species and free radicals leads to oxidative modification of protein structures of receptors and their desensitization. One of the mechanisms of formation of receptor desensitization is OMP of receptor structures, formation of carbonyl groups under the action of excess Active forms of oxygen (AFO). Nitrosation of DNA functional groups leads to inhibition of the expression of proteins that are receptors. Such mechanisms underlie the formation of tolerance (mitridatism) to drugs, which may reduce the effectiveness of hormone therapy, which justifies the inclusion in the complex treatment of micronized progesterone (vaginal capsules) and thiotriazoline (suppositories). Thiotriazoline may enhance the activation of the expression of redox-sensitive genes, which are necessary to protect cells from the toxic effects of oxidative stress, by inhibiting the oxidative inactivation of the transcription factor NF-kappa B with an excess of AFO. Thiotriazoline, due to its antioxidant properties, is able to potentiate the pharmacological effects, including cytoprotective, selective modulators of estrogen

receptors [Belenichev I.F. et al., 2020]. The neuroprotective effect of bioidentical progesterone and its active metabolites is the key to protecting the fetal brain from ischemic damage in utero and during childbirth, and respectively, as prevention of postnatal complications [Zhuk S.I. et al., 2019].

Inclusion in the complex therapy of TPB in 22-34 weeks of gestation of micronized progesterone (vaginal capsules) and thiotriazoline (suppositories), contributed the inhibition of both spontaneous and stimulated OMP (indicating a decrease in AFG ($p < 0.05$) and KFG (table 1). Inhibition of stimulated OMP on the background of increased GSH levels in the women's blood with TPB ($p < 0.05$), indicates the activation of their antioxidant status, due to the increased activity of GSH part of the thiol-disulfide system.

Table 1.

Indicators of oxidative modification of proteins and reduced plasma glutathione in pregnant women in the study groups, Me (Q25; Q75)

Indicators	Main group		Comparison group		Conrol group
	Before treatment	In dynamics (after 14 days)	Before treatment	In dynamics (after 14 days)	
AFG (spontaneous), s.u./g of protein	3,6 (3,3; 4,1)	3,2 (2,7; 3,8)	3,7 (3,2; 4,4)	3,8 (3,2; 4,4)	2,6 (2,2; 3,4)
KFG (spontaneous), s.u./g of protein	3,9 (2,7; 4,7)	2,2 (1,9; 3,0)	2,8 (2,2; 3,3)	3,1 (2,2; 3,6)	2,1 (1,8; 2,7)
AFG (stimulated), s.u./g of protein	5,1 (4,3; 6,1)	5,0 (3,9; 5,7)	5,9 (5,2; 6,7)	5,7 (5,0; 6,9)	2,5 (2,1; 3,0)
KFG (stimulated), s.u./g of protein	4,1 (3,3; 6,0)	3,4 (3,3; 6,0)	3,6 (3,0; 4,0)	3,8 (3,2; 6,5)	2,6 (2,4; 3,1)
GSH, mkM/ml	6,4 (5,5; 8,4)	16,9 (10,7; 20,4)	5,5 (4,3; 8,3)	5,9 (5,1; 6,7)	16,2 (15,5; 18,5)

Analyzing the result of the clinical course of childbirth, it was found that the frequency of interm birth in the main group was almost 20% higher than comparison group. In the control group, all children were born in full-term pregnancy. The mean delivery termine among women in the main group was 38.0 ± 1.5 weeks of gestation and was higher than in the comparison group – 36.5 ± 0.6 weeks ($p < 0.05$). In the control group, delivery occurred at 39.5 ± 0.8 weeks of gestation. The frequency of complicated births, which was 25.6% in the main group, was 1.9 times lower than the corresponding indicator in the comparison group – 47.6%. The increase in the percentage of complicated births in the comparison group was due to premature births, the frequency of which was 40.5%. The

corresponding figure in the main group was 2.2 times lower (18.6%). Very early premature births (less than 28 weeks) in the main group, due to timely referral of patients and prescribed treatment, are absent, but in the comparison group 2 (4.7%) of such cases were recorded. The incidence of fetal distress in the main group was 4.7% versus 7.1% in the comparison group. The frequency of abdominal delivery in the main group was lower than in the comparison group and was 11.6% and 16.7% respectively. Among women of control group complications in childbirth were absent. Characterizing the structure and frequency of perinatal pathology, it was found that its percentage in the comparison group was higher than in the main group and was 52.4% vs. 30.2% respectively. These results are due to decrease in the percentage of births of premature infants in the main group (18.6%) relatively to the comparison group (40.5%). Neonatal jaundice and neonatal encephalopathy (33.3% and 14.3%) were leading in the structure of diseases of the comparison group, which were 2 and 3 times higher than these indicators in the main group (16.3% and 4.7%) respectively. The syndrome of respiratory disorders in the comparison group (19.0%) was 2.7 times higher than the corresponding indicator in the main group (7%).

Conclusions

According to the results of the study, it was found that the proposed complex therapy (micronized progesterone – vaginal capsules and tiotriazoline – suppositories) of the threat of premature birth at 22-34 weeks of pregnancy had a positive effect on the psychological state of pregnant women, their oxidative-redox homeostasis and perinatal delivery results. Thus, the frequency of complicated births was 25.6% in the main group and was 1.9 times lower than in the comparison group – 47.6%, due to a decrease in the percentage of premature births (18.6% vs. 40.5%, $p < 0.05$). The proposed complex therapy also affected the reduction of perinatal morbidity in the main group (30.2%) relatively to the comparison group (52.4%), namely - a decrease in birth of premature infants (18.6% vs. 40.5%, $p < 0.05$), neonatal encephalopathy (4.7% vs. 14.3%, $p < 0.05$) and neonatal jaundice (16.3% vs. 33.3%, $p < 0.05$).

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