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PASIESHVILI N.M.
Kharkiv Regional Clinical Perinatal Center

DETERMINATION OF PROGNOSTIC MARKERS OF PREMATURE BIRTH AS WAYS OF PREVENTING PERINATAL COMPLICATIONS

Summary. *The objective of the work — the search and development of modern prognostic markers of preterm birth for the timely implementation of preventive measures aimed at preserving the pregnancy. There were identified the significant differences in endothelial status of pregnant women who subsequently had premature birth from control indicators and women whose pregnancy ended in term of 38–40 weeks. The findings showed that in women with threatened preterm labor there is a high incidence of placental dysfunction and fetal growth retardation syndrome, disorders of immunological and hormonal parameters. Accordingly, it should be noted that disorders in endothelial status of pregnant women can cause pregnancy complications, including preterm birth, and detected signs of endothelial dysfunction can be used as an early prognostic markers for premature termination of pregnancy.*

Key words: *premature birth, endothelial dysfunction.*

Introduction

The challenge of preventing preterm birth (PB) has a great medical and social importance, due to their high frequency, which does not tend to decrease. PB accompanied by perinatal morbidity and mortality, significant economic costs for the treatment of premature infants, including a high percentage of disabled patients with chronic disease [4]. There is such point of view that PB is a syndrome of fetal graft rejection caused by disturbances in cellular and humoral immunity against the backdrop of chorioamnionitis or villusitis [1, 2].

In recent years, the significant role of the immune system, cytokines and factors in the development of endothelial dysfunction anomalies of labor activity was established, but their pathogenic role in the development of PB was not defined [3, 5]. On that basis, the search and development of modern prognostic markers of PB for timely preventive measures, which were aimed at maintaining pregnancy, became the aim of this work.

To achieve this goal we were examined 90 women at 28–40 weeks gestation, they were divided into index group and control set. The index group included 60 pregnant women with threatened PB, who received traditional PB prophylaxis according to the Order of Ministry of Health of Ukraine № 624 03.11.2008. Depending on the delivery term, the index group was divided into 2 groups: 30 women had the preterm delivery, and other 30 pregnant women had the full-term pregnancy. The control set consisted of 30 healthy pregnant women who had no signs of PB. All pregnant women in addition to general clinical and laboratory assessments passed:

- ultrasound scan;
 - determination of hormonal parameters (progesterone, estradiol, cortisone, placental lactogen in blood serum of pregnant women);
 - determination of immunological parameters (total number of T-lymphocytes, T-helper and T-suppressor, B-lymphocytes and natural killers);
 - cytokines status (Immunoregulatory index (IRI) was defined as the ratio of T-helper/T-suppressor, leucocytes-T-cell index (LTI) is the ratio of the absolute number of peripheral blood leukocytes to the absolute T-lymphocytes count. The level of the main classes of G, A, M immunoglobulins in blood serum. Phagocytic activity of neutrophils. Learning the count of interleukins (IL-1 β , IL-2, IL-6, IL-8, IL-10) and tumor necrosis factor (TNF- α));
 - signs of endothelial dysfunction (concentration of vascular endothelial growth factor (VEGF)).
- To determine the condition of fetus we evaluated its biophysical profile (BPhP) according to the scale assessment of fetoplacental system by F.A. Manning (1987).

Results of the research and their discussion

The average age of women with threatened PB was 28.4 ± 5.6 years, in the control set it was 24.3 ± 3.9 years. Women of index group had the aggravated obstetric and gynecological anamnesis (65 %), genital infections (53.3 %), surgery on the pelvic organs (26.7 %).

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43 women (78.3 %) had symptoms of threatened abortion on early terms of pregnancy so they often stayed at obstetric hospitals for treatment. All pregnant of the index group came to KhRPC at the term of 28–34 weeks gestation with complaints on colicky abdominal and labour pains with the appearance of rheuma and spotting. During obstetric and ultrasound examination we determined vesical cervix abbreviation or cervical dilatation on less than 3 cm, which was recognize as a threat of premature birth. All pregnant women of the index group immediately got tocolytic therapy and prevention of respiratory distress syndrome after clinical and laboratory assessment.

According to ultrasound examination, a placental dysfunction was found in 35 cases of index group (58.3 %), 19 (31.7 %) women had a fetal growth restriction. The results indicate that pregnant women with threatened of PB had high incidence of the placental dysfunction and the fetal growth restriction. Doppler research of fetoplacental complex showed hemodynamics abnormality in the index group (41.7 %). The results of uterine, uteroplacental blood flow and fetal indicators Doppler point to increase of vascular resistance in different levels of fetoplacental complex circulatory, which indicated the presence of placental dysfunction.

Evaluating the conditions of fetus, it was found that 25 (41.7 %) women of the index group had pathological character of cardiotocography. Moreover, violation of mild case (8.2 ± 0.3 points) occurred in 31.7 %, medium severity (6.9 and 0.2 points) had 6 (10 %) women. Biophysical Profile Total of pregnant in control set made out 11.8 ± 0.2 points; Biophysical Profile in index group made out 10.0 ± 0.3 points, 8 (13.3 %) women with threatened of PB of biophysical profile was lower (8.8 ± 0.2 points) mainly due to the placental maturity degree and extend of amniotic fluid.

Analyzing the results of hormonal examination it should be noted that women of index group had a hypoprothesteronemia (112.5 ± 14.3 nM/l) in compared with a control set (184.5 ± 10.9 nM/l), indicating a lack of endogenous progesterone production of PB threatened women. The level of estradiol of index group pregnant core was increased in 1.3 times (7.9 ± 0.6 nM/l) compared with control set (5.8 ± 0.5 nM/l). Conspicuous is the fact that there is the increasing of cortisol concentrations index group of women (443.2 ± 15.6 nM/l), while in the control set, these figures were significantly lower (298 ± 15 nM/l) ($P < 0.05$). During the research of placental lactogen, which covers the function of the placenta, it was determined that its concentration in index group (43.4 ± 4.1 nM/l) significantly different from control set markers (65.8 ± 3.2 nM/l) ($P < 0.05$).

Immunological status of pregnant women with threatened PB characterized by disorder of physiological immunosuppression mechanisms, which were shown as reducing the number of T-lymphocytes (CD3+) and their main types (CD4+) — T-helper cells, (CD8+) T-suppressors. The value of IRI in the index group of women was differ (1.23 ± 0.07), than in the control set (1.47 ± 0.03). In addition, there is often

an increase in circulating immune complexes and increased activity of natural killer (NK) — CD 16+. Total number and functional activity of NK-cells in the control set (19.1 ± 1.2 %) were lower than in pregnant women with threatened PB (30.6 ± 1.2 %). In case of physiological pregnancy, there is a sufficient suppression of NK-cell activity of mother's lymphocytes, which helps in child bearing.

It was found that there is a dysimmunoglobulinemia of index group women, which was shown in increasing number of IgM and decreasing concentration of IgA (1.20 ± 0.06 g/l) and (7.7 ± 0.8 g/l) in comparison with control parameters.

The indicators that characterize the phagocytic activity of peripheral blood neutrophils, changed with the threat of abortion: increasing number of phagocytic neutrophils (94.3 ± 4.6 %), the phagocytic number amounted to 5.5 ± 0.7 c.u., index of phagocytosis completeness was decreasing to 0.80 ± 0.07 , which was pointed at digesting ability of peripheral blood neutrophils.

Evaluating the rate of cytokine balance it was found that due to threatened of PB it happens the increasing of IL-1 β to 261.50 ± 14.6 pg/ml in comparison with the index group (128.2 ± 10.3 pg/ml) ($P < 0.05$). Conspicuous is the fact that there was a high concentration of IL-1 β in the first subgroup until childbirth, while in the second group, this marker declined over pregnancy reaching control values over carrying of a pregnancy (139.5 ± 12.3 pg/ml) ($P > 0.05$). The same dynamics of markers was observed in concentration of IL-8 (145.8 ± 16.3 pg/ml and TNF- α (298.3 ± 21.4 pg/ml), which increases in pregnant's blood in the fact of threatened PB and significantly different from the control set (95.1 ± 8.1 pg/ml, 29.7 ± 4.2 pg/ml), especially in the development of labor and delivery ($P < 0.05$). Increasing the number of these cytokines is considered as a factor of vascular endothelial damage, that's why the definition of markers of endothelial dysfunction was the next step in examining of pregnant with the threatened PB.

Studying the count of VEGF in pregnant women with threatened PB, it's level was significantly increased in comparison with control (56.4 ± 5.2 pcg/ml) and ranged from 298.6 to 383.2 pcg/ml, averaging 346.3 ± 28.3 pcg/ml ($P < 0.05$). At the time of further monitoring, the concentration of VEGF varied depending on the flow and subsequent release of pregnancy. With the development of PB, the count of VEGF hardly declined and was within 288.7–345.2 pcg/ml, on average it was about 318.9 ± 15.1 pcg/ml. The second subgroup the concentration of VEGF ranged from 68.6 pcg/ml to 136.3 pcg/ml and was on the average equal to 84.3 ± 9.5 pcg, probably it was no difference in regulatory parameters of women in the control set ($P > 0.05$).

At research of endothelin-1 concentrations it was determined its increasing in the blood serum of the indexgroup to 10.5 ± 1.3 ng/ml in comparison with control marks (1.4 ± 0.5 ng/ml) obtained from women with physiological pregnancy. At the time of further

monitoring of women, whose pregnancy ended in premature birth, it was defined a slight decrease of vasoconstrictive agent to 8.6 ± 1.2 ng/ml, which is significantly exceeded control marks ($P < 0.05$). At the time of pregnancy prolongation the level of endothelin-1 was equal to 2.3 ± 0.8 ng/ml and probably no different from control marks.

Thus, the attention is drawn to significant differences of endothelial status of pregnant women with the further development of PB from the control markers and women whose pregnancy ended in a 38–40 week period.

In addition, the obtain results point at high incidence of placental dysfunction and syndrome of retardation growth, disturbances of the immune and hormonal parameters of pregnant women with threatened PB. On the basis of the foregoing, it should be noted that a disorder of endothelial status of pregnant women may cause pregnancy complications, including preterm delivery and identified issues of endothelial dysfunction can be used as early prognostic markers of early abortion.

Analyzing the results of pregnancy and childbirth of both groups women and state of newborns, we can conclude that because of the application of proposed complex of diagnostics and prediction of pregnancy complications with the use of endothelial status for timely diagnosis of pathogenic changes of preclinical indicators, which were studied, it was possible to improve the gestation course with the threatened PB, reduce the incidence of possible complications of pregnancy and childbirth, and reduce the number of perinatal morbidity and mortality.

Conclusions

1. Premature birth of pregnant women with complicated obstetric-gynecological history, infectious damages against the background of placental insufficiency, fetal growth retardation is the result of immunological and hormonal violations, changes of endothelial system.

2. Revealing of endothelial dysfunction signs can be used as prognostic markers (VEGF, endothelin-1) of premature births, which promoting to make timely therapeutics and preventive measures and reduce perinatal complications.

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Пасієшвілі Н.М.

Харківський обласний клінічний перинатальний центр

ВИЗНАЧЕННЯ ПРОГНОСТИЧНИХ МАРКЕРІВ ПЕРЕДЧАСНИХ ПОЛОГІВ ЯК СПОСІБ ПРОФІЛАКТИКИ ПЕРИНАТАЛЬНИХ УСКЛАДНЕНЬ

Резюме. Мета роботи — пошук та розробка сучасних прогностичних маркерів передчасних пологів для своєчасного проведення профілактичних заходів, що спрямовані на збереження вагітності. Виявлено значні відмінності ендотеліального статусу вагітних із подальшим розвитком передчасних пологів від контрольних показників та жінок, в яких вагітність закінчилася в терміні 38–40 тижнів. Отримані результати вказують, що у вагітних із загрозою передчасних пологів спостерігалися висока частота плацентарної дисфункції та синдрому затримки росту плода, порушення імунологічних та гормональних показників. Виходячи з вищевикладеного, необхідно зазначити, що порушення ендотеліального статусу вагітних може бути причиною ускладнень вагітності, зокрема передчасних пологів, а виявлені ознаки ендотеліальної дисфункції можливо використовувати як ранні прогностичні маркери передчасного переривання вагітності.

Ключові слова: передчасні пологи, ендотеліальна дисфункція.

Пасієшвілі Н.М.

Харьковский областной перинатальный центр

ОПРЕДЕЛЕНИЕ ПРОГНОСТИЧЕСКИХ МАРКЕРОВ ПРЕЖДЕВРЕМЕННЫХ РОДОВ КАК СПОСОБ ПРОФИЛАКТИКИ ПЕРИНАТАЛЬНЫХ ОСЛОЖНЕНИЙ

Резюме. Цель работы — поиск и разработка современных прогностических маркеров преждевременных родов для своевременного проведения профилактических мер, направленных на сохранение беременности. Выявлены значительные отличия эндотелиального статуса беременных с последующим развитием преждевременных родов от контрольных показателей и женщин, у которых беременность закончилась в сроке 38–40 недель. Полученные результаты показали, что у беременных с угрозой преждевременных родов наблюдались высокая частота плацентарной дисфункции и синдрома задержки роста плода, нарушения иммунологических и гормональных показателей. Исходя из вышесказанного, необходимо отметить, что нарушение эндотелиального статуса беременных может быть причиной осложнений беременности, в частности преждевременных родов, а выявленные признаки эндотелиальной дисфункции возможно использовать как ранние прогностические маркеры преждевременного прерывания беременности.

Ключевые слова: преждевременные роды, эндотелиальная дисфункция.