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## CURRENT OPPORTUNITIES FOR DETERMINING OF PREDICTORS OF THREATENED PRETERM LABOR

**The aim of the study** – to ascertain predictors of a threat of premature birth.

**Materials and Methods.** 63 patients participated in the gestation period of 22–34 weeks in a prospective open study. Pregnant women were divided into two groups. Thus, the group I included 44 pregnant women, with the threat of PL, and the group II included 19 patients with normal course of pregnancy.

All women were tested for body mass index (BMI), progesterone, insulin and cortisol on the day of admission.

Statistical processing of materials was carried out by using the software package "Statistica 6.0" (StatSoft, USA) and MedCalc. 10.2.0.0. To determine the predictors of the occurrence of a TPL, the method of binary logistic regression analysis was used. All statistical tests were two-sided; the  $p < 0.05$  level was considered as significant.

**Results and Discussion.** An analysis of the results of the observation of 63 pregnant women was provided. In 12 women, pregnancy ended in preterm labor, which was 19 % of the total. The following indicators fell to the dependent predictors of TPL occurrence: body mass index (BMI)  $\leq 24$  kg/m<sup>2</sup> significantly increased the odds ratio (OR) of TPL 7.76 times; insulin level  $< 8.65$   $\mu$ MO/ml significantly increased OR of TPL 5.14 times; OR of TPL increases in 7.02 times, in case that the level of cortisol is less than 577.9 ng/ml; progesterone  $< 139.5$  ng/ml increases the odds ratio of TPL in 4.39 times. Taking into account the data of univariate regression analysis, multivariate models of independent predictors of TPL were created. According to the first model ( $p = 0.0001$ ), independent risk factors for miscarriage include: the age of pregnant women over 25 years, an insulin level more than 8.7  $\mu$ MO/ml, and the level of cortisol less than 577.9 ng/ml. According to the second model ( $p < 0.0001$ ), independent risk factors which increase the risk of TPL occurrence are: BMI less than 24 kg/m<sup>2</sup>, insulin level more than 8.7  $\mu$ MO/ml, cortisol level less than 577.9 ng/ml. However, the most interesting is the third model ( $p < 0.0001$ ) of independent risk factors for TPL. It includes four indicators: the level of progesterone, less than 139.5 ng/ml, the level of cortisol, less than 577.9 ng/ml, the BMI, less than 24 kg/m<sup>2</sup> and the age of pregnant, more than 25 years.

**Conclusions.** It was found that in pregnant women with a threat of preterm birth the age and BMI are the most informative, and in combination with the hormonal examination of women are of primary importance. The obtained results indicate the expediency of inclusion to the standard examination of pregnant women with a threat of premature birth, a comprehensive determination of the level of progesterone, insulin and cortisol, which will enable to identify the risk group for this complication in time and to propose preventive measures.

**Key words:** threat of preterm labor; progesterone; insulin; cortisol; prediction.

### СУЧАСНІ МОЖЛИВОСТІ ВИЗНАЧЕННЯ ПРЕДИКТОРІВ ЗАГРОЗИ ПЕРЕДЧАСНИХ ПОЛОГІВ

**Мета дослідження** – встановити предиктори загрози передчасних пологів.

**Матеріали та методи.** У проспективному відкритому дослідженні взяли участь 63 пацієнтки у терміні вагітності 22–34 тижні. Вагітні були розподілені на дві групи. Так, до I групи увійшли 44 вагітні, які мали ЗПП, а до II – 19 пацієнток із нормальним перебігом вагітності. У першу добу усім жінкам виконали визначення індексу маси тіла (ІМТ) і визначення прогестерону, інсуліну та кортизолу. Статистичне опрацювання матеріалів здійснювали із застосуванням пакетів програм «Statistica 6.0» (StatSoft, США) та MedCalc. 10.2.0.0. Для визначення предикторів виникнення ЗПП використали метод бінарного логістичного регресійного аналізу. Усі статистичні тести були двобічними, значущим вважали рівень  $p < 0,05$ .

**Результати дослідження та їх обговорення.** Проведено аналіз результатів спостереження за 63 вагітними. У 12 жінок вагітність завершилась передчасними пологами, що становило 19 % від загальної кількості. До залежних предикторів виникнення ЗПП потрапили такі показники: індекс маси тіла (ІМТ)  $\leq 24$  кг/м<sup>2</sup> достовірно збільшував відношення шансів (ВШ) ЗПП у 7,76 раза; рівень інсуліну  $< 8,65$  мкМО/мл вірогідно підвищував ВШ ЗПП у 5,14 раза; ВШ ЗПП зростало у 7,02 раза за умови, що рівень кортизолу був менший за 577,9 нг/мл; прогестерон  $< 139,5$  нг/мл збільшував відношення шансів ЗПП у 4,39 раза. Зваживши дані уніваріантного регресійного аналізу, були створені мультіваріантні моделі незалежних предикторів ЗПП. Відповідно до першої моделі ( $p = 0,0001$ ), до незалежних факторів ризику невиношування вагітності належать: вік вагітної понад 25 років, рівень інсуліну понад 8,7 мкМО/мл, рівень кортизолу, менший за 577,9 нг/мл. Згідно з другою моделлю ( $p < 0,0001$ ), незалежними факторами ризику підвищення ризику виникнення ЗПП є: ІМТ, менший за 24 кг/м<sup>2</sup>, рівень інсуліну понад 8,7 мкМО/мл, рівень кортизолу, менший за 577,9 нг/мл. Проте найбільш цікавою є третя модель ( $p < 0,0001$ ) незалежних факторів ризику ЗПП. До неї увійшли чотири показники: рівень прогестерону, менший за 139,5 нг/мл, рівень кортизолу, менший за 577,9 нг/мл, ІМТ, менший за 24 кг/м<sup>2</sup>, та вік вагітної понад 25 років.

**Висновки.** Було встановлено, що серед вагітних із загрозою передчасних пологів найбільш інформативними є вік та ІМТ, а в комплексі з гормональним обстеженням жінок мають першочергове значення. Включення до стандартного обстеження вагітних із загрозою передчасних пологів комплексного визначення рівня прогестерону, інсуліну та кортизолу дасть можливість своєчасно виявити групу ризику і запропонувати профілактичні заходи.

**Ключові слова:** загроза передчасних пологів; прогестерон; інсулін; кортизол; прогнозування.

### СОВРЕМЕННЫЕ ВОЗМОЖНОСТИ ОПРЕДЕЛЕНИЯ ПРЕДИКТОРОВ УГРОЗЫ ПРЕЖДЕВРЕМЕННЫХ РОДОВ

**Цель исследования** – установить предикторы угрозы преждевременных родов.

**Матеріали і методи.** В проспективному відкритому дослідженні прийняли участь 63 пацієнтки в строку вагітності 22–34 тижнів. Вагітні були розділені на дві групи. Так, в I групу вошли 44 вагітні з загрозою ПР, а во II – 19 пацієнток з нормальним теченням вагітності. В перші сутки всім жінкам виконали визначення індексу маси тіла (ІМТ), прогестерона, інсуліну і кортизола. Статистичка обробка матеріалів здійснювалась з використанням пакетів програм «Statistica 6.0» (StatSoft, США) і MedCalc. 10.2.0.0. Для визначення предикторів виникнення загрози ПР використовували метод бінарного логістичного регресійного аналізу. Всі статистичні тести були двосторонніми, значимим вважали рівень  $p < 0,05$ .

**Результати дослідження і їх обговорення.** Проведено аналіз результатів спостереження за 63 вагітними. У 12 жінок вагітність завершилась преждевременними родами, що становило 19 % від загальної кількості. До незалежних предикторів виникнення УПР потрапили наступні показники: індекс маси тіла (ІМТ)  $\leq 24$  кг/м<sup>2</sup> достовірно збільшував відношення шансів (ОШ) УПР в 7,76 разів; рівень інсуліну  $< 8,65$  мкМЕ/мл достовірно підвищував ОШ УПР в 5,14 разів; ОШ УПР зростає в 7,02 разів при умові, що рівень кортизола менше 577,9 нг/мл; прогестерон  $< 139,5$  нг/мл підвищує відношення шансів УПР в 4,39 разів. Приймаючи до уваги дані уніваріантного регресійного аналізу, були створені мультиваріантні моделі незалежних предикторів УПР. Згідно першої моделі ( $p = 0,0001$ ), до незалежних факторів ризику невиношування вагітності належать: вік вагітної більше 25 років, рівень інсуліну більше 8,7 мкМЕ/мл, рівень кортизола менше 577,9 нг/мл. Згідно другої моделі ( $p < 0,0001$ ), незалежними факторами ризику підвищення ризику виникнення УПР є: ІМТ менше 24 кг/м<sup>2</sup>, рівень інсуліну більше 8,7 мкМЕ/мл, рівень кортизола менше 577,9 нг/мл. Однак найбільш цікавою є третя модель ( $p < 0,0001$ ) незалежних факторів ризику УПР. В неї потрапили чотири показники: рівень прогестерона менше 139,5 нг/мл, рівень кортизола менше 577,9 нг/мл, ІМТ менше 24 кг/м<sup>2</sup> і вік вагітної більше 25 років.

**Висновки.** Було встановлено, що у вагітних з загрозою преждевременних родов найбільш інформативними є вік і ІМТ, а в комплексі з гормональним обстеженням жінок мають первостепенне значення. Включення в стандартне обстеження вагітних з загрозою преждевременних родов комплексного визначення рівня прогестерона, інсуліну і кортизола дає можливість своєчасно виявити групу ризику і запропонувати профілактичні заходи.

**Ключові слова:** загроза преждевременних родов; прогестерон; інсулін; кортизол; прогнозування.

**INTRODUCTION.** One of the critical problems in preserving reproductive capacity is preventing of pregnancy loss. Premature babies make up the main "contribution" to the indicators of perinatal morbidity and mortality. Their share accounts for about 60–75 % of this pathology. More than 30–40 % of the cases for perinatal pathology and mortality are associated with or caused by premature birth [1]. Today, preterm labor (PL) 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 [2–4]. Despite the progress of modern medicine and the introduction of modern perinatal technologies, the frequency of PL and the birth of premature infants is constantly increasing and ranges from 4.0 % to 15.0–20.0 %. In Ukraine, the frequency of PL ranges from 3.0 % to 12.0 % in different years, this corresponds to the average world trend [5, 6]. In 2018, it was 3.7 % in the Zaporizhzhia region, and according to the statistical data of the Zaporizhzhia Regional Perinatal Center – 13.0 %. However, it should be noted that the high rate at this medical institution is due to the specific orientation and the contingent of patients seeking for medical care. This is why the problem of stillbirth requires a detailed study of how to prevent as miscarriages, as PL and birth of children with low birth weight [1].

**THE AIM OF THE STUDY** – to ascertain predictors of a threat of premature birth.

**MATERIALS AND METHODS.** In a prospective open study, 63 patients at 22–34 weeks gestation were included. Pregnant women were involved in the study after signing voluntary consent information. The research was carried out on the basis of Zaporizhzhia Regional Perinatal Center, which is the clinical base for the Department of Obstetrics and Gynecology of ZSMU (the head of the department is MD,

Professor Yu. Ya. Krut). The average age of the pregnant women was  $(27.1 \pm 0.8)$  ( $M \pm SD$ ). The pregnant women were divided into two groups, depending on the course of the gestation period. Thus, group I included 44 pregnant women who had threatened preterm labor (TPL), and group II – 19 patients with a normal course of pregnancy.

On the first day, all women underwent an examination of the body mass index (BMI) and laboratory examination (determination of progesterone, insulin and cortisol).

Statistical processing of materials were carried out using the packages of programs "Statistica 6.0" (StatSoft, USA) and MedCalc. The normality of the distribution of quantitative characteristics was analyzed using the Shapiro-Ulyka test. The method of binary logistic regression analysis was used to determine the predictors of TPL. Factors that had a probable predictive value in one factor analysis were included in the multivariate model by the inverse step-by-step method for the determination of independent predictors. The data is presented as a ratio of odds and their confidence intervals. Cut-off values of the quantitative indicators included in the multi-factor logistic regression analysis were determined using ROC analysis. All statistical tests were bilateral, meaning that the level  $p < 0.05$  was considered significant.

**RESULTS AND DISCUSSION.** Pregnant women with TPL accounted for 70 % (44 out of 63 pregnant women) of the total number of patients involved in the study. For 12 women, pregnancy ended with preterm birth, accounting for 19 % of the total. Most pregnant women (81 %) gave birth in the term of full-term pregnancy.

According to the results of the study, pregnant women with TPL had a 57 % ( $p < 0.05$ ) greater duration of hospital stay after germination in comparison with women with normal course of pregnancy ( $6.9 \pm 1.27$ ) days versus ( $3.7 \pm 0.33$ ) days). This was due to the premature birth and in some cases the need for special medical care for preterm infants and resuscitation measures. In the structure of diseases of preterm

infants, the leading ones were: hypoxic-ischemic injury of the central nervous system with inhibition syndrome, neonatal jaundice, respiratory distress syndrome, predominantly type I, intraventricular cerebral hemorrhages and retinopathy of preterm ones. Two children had a congenital heart disease as an intraventricular septum defect and an atrial septum defect, 2 children had neonatal jaundice. Proved is the fact that the consequences of non-carrying of pregnancy for the mother's organism are infection of the uterus, associated with it courses of antibiotic therapy, disorders of lactation regulation, etc. [7]. Thus, according to scientific literature, TPL and prolongation of stay in a hospital due to premature births, preterm infants who require high-quality medical care from the first minutes of life are associated with the lack of a perfect scheme of therapy, prevention of TPL and the premature births itself [8]. Significance of the absence of a unified treatment scheme for TPL can be underlined by the high level of occurrence for this pathological condition, prolongation of the length of stay in the hospital, the need for intensive care, complications and (indirectly) an increase in the cost of treatment. PL is the main cause of perinatal morbidity and mortality, which accounts for up to 80 % of deaths of newborns. Among these infants in the group, the highest risk are those who were born with early PL. However, a high mortality rate persists among those, who were born in 32–36 weeks of gestation. In children born prematurely, survivors are determined by a number of adverse neonatal diseases: chronic pulmonary disease, retinopathy of preterm newborns, traumatic brain injury, necrotic enterocolitis and neonatal sepsis.

In the future, such children often have motor and sensory impairments, learning difficulties and behavioral problems.

In spite of the continuous improvement of neonatal services, which constantly increase the survival rate of early premature children, it is possible to influence the incidence and mortality of infants only by early detection, formation of a risk group of TPL among pregnant women and the selection of an effective prevention strategy for this condition.

In order to find out the factors that influence the course of pregnancy and increase the risk of premature birth, we

conducted an analysis of the results from the monitoring of 63 pregnant women who were observed in the Zaporizhzhia Perinatal Center. To determine the cut-off value of quantitative indicators that increase the risk of TPL, ROC analysis was used. We obtained the following distribution points for a number of indicators (Table 1): the age of pregnant women over 25 years (sensitivity 70.5 %, specificity 68.4 %, area under the ROC curve 0.638 (95 % CI 0.507–0.755,  $p = 0.0594$ )); body mass index (BMI)  $\leq 24$  kg/m<sup>2</sup> (sensitivity 47.7 %, specificity 89.5 %, area under the curve 0.623 (95 % CI 0.492–0.742,  $p = 0.1207$ )); Insulin  $> 8.65$   $\mu$ Me/ml (75 % sensitivity, specificity 63.2 %, area under the curve 0.665 (95 % CI 0.535–0.779;  $p = 0.02$ ), cortisol  $\leq 577.9$  ng/ml (sensitivity 56.8 %, specificity 84.2 %, area under the curve 0.665 (95 % CI 0.524–0.770,  $p=0.05$ ), progesterone  $\leq 139.5$  ng/ml (sensitivity 34.1 %, specificity 89.5 %), area under the curve of 0.572 (95% CI 0.441–0.606;  $p = 0.37$ )).

By using logistic regression analysis, predictors of the threat of premature birth were identified. Factors that had a probable predictive value in one-factor analysis were further included in the multivariate model for the determination of independent predictors. Table 2 shows the data of a univariate and multivariate logistic regression analysis.

Consequently, all the above-mentioned indicators were included in the dependent predictors of the occurrence of TPL. They were: Body Mass Index (BMI)  $\leq 24$  kg/m<sup>2</sup> significantly increased the odds ratio (OR) of TPL at 7.76 times (95 % CI 1.598–37.683;  $p = 0.011$ ); the level of insulin  $< 8.65$   $\mu$ M/ml significantly increased OR of the TPL in 5.14 times (95 % CI 1.62–16.328;  $p = 0.004$ ); the OR of TPL increased in 7.02 fold (95 % CI 1.784–2612;  $p = 0.001$ ) in case that the cortisol level was less than 577.9 ng/ml; the progesterone level  $< 139.5$  ng/ml increased the odds ratio of TPL in 4.39 times (95 % CI 0.8945–21.608;  $p=0.0683$ ).

According to the models of multivariate logistic regression analysis (Table 2), independent factors which increase the risk of TPL are: age of pregnant women over 25 years, body mass index  $\leq 24$  kg/m<sup>2</sup>, blood insulin level  $> 8.65$   $\mu$ Me/ml, blood cortisol in serum  $\leq 577.9$  ng/ml and progesterone  $\leq 139.5$  ng/ml.

Table 1. Distribution point according to ROC analysis for the threat of preterm labor

Indicator, units	Area under ROC curve (AUC)	95% CI	Level of certainty, p	Distribution Point	Sensitivity,%	Specificity,%
Age, years	0.638	0.507- 0.755	0.05	> 25	70.5	68.4
BMI, kg/m <sup>2</sup>	0.623	0.492- 0.742	0.12	$\leq 24$	47.7	89.5
Insulin, $\mu$ M/ml	0.665	0.535- 0.779	0.02	> 8.65	75.0	63.2
Cortisol, ng/ml	0.665	0.52– 0.770	0.05	$\leq 577.9$	56.8	84.2
Progesterone, ng/ml	0.572	0.441– 0.696	0.37	$\leq 139.5$	34.1	89.5

Table 2. Univariate risk analysis of the threat of premature birth

Indicator, units	Univariate analysis		
	The odds ratio, OR	Certainty, p	95 % confidence interval, CI
BMI, kg/m <sup>2</sup>	7.76	0.011	1.59- 37.68
Age, years	5.17	0.005	1.61–16.54
Progesterone, ng/ml	4.39	0.068	0.89–21.60
Insulin, $\mu$ M/ml	5.14	0.005	1.61–16.32
Cortisol, ng/ml	7.02	0.005	1.78–27.61

Consequently, the TPL association with the age of pregnant women over 25 years significantly increases the odds ratio of premature infusion in 5.17 times, which may be the result of gradual depletion of maternal body, aging of the sex cells, prolonged influence of pathogens and toxic substances, and the presence and exacerbation of chronic pathology.

According to some authors, primipara women of the older age group, namely at the age over 35, have a high risk of PL, untimely rupture of amniotic membranes, clinically contracted pelvis, soft tissue ruptures, pathological blood loss in labor and a very high risk of development of discoordination of the delivery forces and asphyxia of newborns (A. N. Rybalka, V. A. Zabolotnov, N. A. Timofeeva, Yu. K. Pamfamirov, Yu. A. Kucherenko, F. Sh. Khuramshin, 2010).

Interesting is the fact that weight deficiency, concretely BMI  $\leq$  24 kg/m<sup>2</sup>, significantly increases the risk of non-carrying of pregnancy in 7.76 times (Table 2).

According to our data, the unconditional effect on TPL results insulin level in serum. So, according to our study, an increase of insulin level more than 8.65  $\mu$ M/ml increases the odds ratio of TPL in 5.14 times (Table 2).

It is known that during the action of extreme factors on the organism nonspecific stress reactions are primarily aimed on stimulating of energy metabolism and providing of adaptive reactions and processes. By activating catabolic processes, catecholamines and glucocorticosteroids lead to hyperglycemia – one of the initial reactions of substrate energy supply. By activating catabolic processes, catecholamines and glucocorticosteroids lead to hyperglycemia – one of the initial reactions of substrate energy supply. As a result, the level of insulin in blood increases for some time. This physiological mechanism prevents the next teratogenic effect of glucose, which circulates in the bloodstream and reduces the level of stress [9, 10].

The odds ratio of TPL, according to our results, increases in 7.02 times in case that the reduction of cortisol level is

below the limit of 577.9 ng/ml, appears is, namely the initial increase in the content of cortisol with subsequent inhibition of its level on the background of the depletion of energy reserves. In our opinion in pregnant women, who are in a state of chronic stress, this fact is combined with a two-phase response of the adrenal glands on the pathological stress effect, namely the initial increase of cortisol with subsequent inhibition of its level against the background of the depletion of energy reserves.

After weighing the data of the univariate regression analysis, multivariate models of independent predictors of TPL were created (Table 3).

According to the first model ( $p = 0.0001$ ), independent factors of risk of miscarriage include:

- the age of a pregnant woman over 25 years – increases the OR of TPL in 4.2 times (95 % CI, 1.12–15.50,  $p = 0.03$ );
- the insulin level more than 8.7 – increases the OR of TPL in 4.4 times (95 % CI 1.16–16.24;  $p = 0.03$ );
- the cortisol level less than 577.9 – increases the OR of TPL in 5.1 times (95 % CI 1.35–25.80;  $p = 0.02$ ).

According to the second model ( $p < 0.0001$ ), independent risk factors for increasing the risk of TPL are:

- BMI less than 24 kg/m<sup>2</sup> – increases the chance of a risk of threatening in 24.8 times (95 % CI 3.00 – 204.01;  $p = 0.002$ );
- the level of insulin more than 8.7 – increases the OR of a threat of non-carrying of pregnancy in 11.2 times (95 % CI 2.02 – 62.37;  $p = 0.005$ );
- the level of cortisol is less than 577.9 – increases the chances of a risk of miscarriage in 13.1 times (95 % CI 2.19 – 77.95;  $p = 0.004$ ).

However, the most interesting is the third model ( $p < 0.0001$ ) of independent risk factors for TPL of course. It includes four indicators:

- the level of progesterone less than 139.5 – increases the chances of TPL in 8.2 times (95 % CI 1.06 – 63.94;  $p = 0.043$ );

Table 3. Multivariate analysis of the risk of threatened preterm labor

Indicator, units	The odds ratio, OR	Certainty, p	95 % confidence interval, CI
Model 1			
BMI, kg/m <sup>2</sup>			
Age, years	4.2	0.03	1.12–15.50
Progesterone, ng/ml			
Insulin, $\mu$ M/ml	4.3	0.03	1.16–16.24
Cortisol, ng/ml	5.9	0.02	1.35–25.80
Model 2			
BMI, kg/m <sup>2</sup>	24.8	0.002	3.00–204.01
Age, years			
Progesterone, ng/ml			
Insulin, $\mu$ M/ml	11.2	0.005	2.02–62.37
Cortisol, ng/ml	13.1	0.004	2.19–77.95
Model 3			
BMI, kg/m <sup>2</sup>	12.4	0.008	2.02–62.37
Age, years	4.5	0.05	3.0077–204.01
Progesterone, ng/ml	8.2	0.04	2.19–77.95
Insulin, $\mu$ M/ml			
Cortisol, ng/ml	10.6	0.006	3.00–204.01

– the level of cortisol less than 577.9 – increases the odds ratio of chances of the risk of miscarriage in 10.6 times (95 % CI 1.93 – 57.68;  $p = 0.006$ );

– BMI less than 24 kg/m<sup>2</sup> increases the OR of risk of threatening of pregnancy in 4.5 times (95 % CI 1.89 – 81.14;  $p = 0.008$ ).

**CONCLUSIONS.** The results from the conducted research clearly show that the use of multivariate logistic regression analysis allowed to determine the predictors of threatened premature birth. Taking into account the obtained data, it was found that among pregnant women with a threat of preterm labor the most informative are age and BMI, and

in combination with the hormonal examination of women are of primary importance.

The obtained results indicate the expediency of inclusion to the standard examination of pregnant women with a threat of premature birth, a comprehensive determination of the level of progesterone, insulin and cortisol, which will enable to identify the risk group for this complication in time and to propose preventive measures.

**PROSPECTS FOR FURTHER RESEARCH.** Results of the study indicate the advisability of further research in this area. It is planned to assess the importance of independent and dependent predictors in accordance with the logistic regression analysis to assess the risk of premature birth.

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