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Evaluation of risk factors and modern possibilities for prediction of preterm labour

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The aim is based on the comprehensive examination of pregnant women to determine the risk factors for preterm labor and develop criteria for its prediction.

Materials and methods. In a prospective opened study took part 63 patients at 22–34 weeks of gestation. The study was carried out on the basis of PI "Regional Perinatal Center" ZRC, which is the clinical base of the Department of Obstetrics and Gynecology, ZSMU. The average age of pregnant women was 27.1 ± 0.8 (M ± SD) years. Pregnant women were divided into two groups, depending on the gestation period course. Thus, group I included 44 pregnant women who had TPL (threatened preterm labor), and group II – 19 patients with normal course of pregnancy. In the first day, body mass index was determined and laboratory examinations (progesterone, insulin and cortisol level) were performed.

Results. According to the ROC analysis, we obtained the following distribution points: the age of pregnant women over 35 years (sensitivity 33.3 %, specificity 96.1 %), the area under the ROC curve of 0.542 (95 % CI 0.411–0.668, P = 0.6953); body mass index (BMI) ≤22.95 kg/m² (sensitivity 66.7 %, specificity 84.3 %), the area under the ROC curve 0.694 (95 % CI 0.566–0.804, P = 0.01); insulin >31.36 μMe/ml (sensitivity 41.7 %, specificity 90.2 %), the area under the ROC curve 0.505 (95 % CI 0.376–0.633, P = 0.96); cortisol ≤609.7 ng/ml (75 % sensitivity, 55 % specificity), the area under the ROC curve of 0.694 (95 % CI 0.518–0.765, P = 0.07); progesterone <247.8 ng/ml (sensitivity 41.7 %, specificity 88.2 %), the area under the ROC curve 0.579 (95 % CI 0.448–0.703, P = 0.4).

Conclusions. The results of the conducted research indicate that multivariate logistic regression analysis allows determining the risk factors of preterm labor. Among the established prognostic markers for spontaneous preterm birth, the most comprehensive information is the complex assessment of age, BMI and hormonal profile. The findings suggest that dependent risk factors for preterm birth include: the level of progesterone lower than 139.5 ng/ml, cortisol less than 577.9 ng/ml, BMI less than 24 kg/m² and maternal age of over 25 years. Independent factors should include the maternal age of over 35 years, the level of insulin above 31.36 ng/ml and progesterone less than 247.8 ng/ml. Considering the study results, high specificity and sensitivity of the proposed multivariate models, it would be appropriate to include measurements of progesterone, insulin and cortisol levels in the standard examination complex for pregnant women from 22 to 34 weeks of gestation. It will enable the identification of a risk group for preterm labor and implementation of timely prevention.

Key words: preterm birth, progesterone, insulin, cortisol, prognosis.

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Оцінювання факторів ризику та сучасні можливості прогнозування передчасних пологів

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Мета роботи – на підставі комплексного обстеження вагітних встановити фактори ризику передчасних пологів і розробити критерії їх прогнозування.

Матеріали та методи. У проспективному відкритому дослідженні взяли участь 63 пацієнтки в терміні вагітності 22–34 тижні. Дослідження виконали на базі КЗ «Обласний перинатальний центр» ЗОР, що є клінічною базою кафедри акушерства та гінекології ЗДМУ. Середній вік вагітних – 27,1 ± 0,8 (M ± SD) року. Вагітних поділили на дві групи залежно від перебігу гестаційного періоду. У I групу увійшли 44 вагітні, які мали загрозу передчасних пологів, а в II – 19 пацієнток із нормальним перебігом вагітності. Протягом першої доби всім жінкам встановили індекс маси тіла (IMT) і здійснили лабораторне обстеження (визначення прогестерону, інсуліну та кортизолу).

Результати. У результаті ROC-аналізу отримали такі точки розподілу: вік вагітних понад 35 років (чутливість – 33,3 %, специфічність – 96,1 %), площа під кривою – 0,542 (95 % ДІ 0,411–0,668; p = 0,6593); індекс маси тіла (IMT) ≤22,95 кг/м² (чутливість – 66,7 %, специфічність – 84,3 %), площа під кривою – 0,694 (95 % ДІ 0,566–0,804; p = 0,01); інсулін >31,36 мкМЕ/мл (чутливість – 41,7 %, специфічність – 90,2 %), площа під кривою – 0,505 (95 % ДІ 0,376–0,633; p = 0,96); кортизол ≤609,7 нг/мл (чутливість – 75 %, специфічність – 55 %), площа під кривою – 0,649 (95 % ДІ 0,518–0,765; p = 0,07); прогестерон <247,8 нг/мл (чутливість – 41,7 %, специфічність – 88,2 %), площа під кривою – 0,579 (95 % ДІ 0,448–0,703; p = 0,4).

Висновки. Результати дослідження свідчать, що багатофакторний логістичний регресійний аналіз дає можливість визначити фактори ризику передчасних пологів. Серед встановлених прогностичних маркерів щодо спонтанного розвитку передчасних пологів найбільш інформативним є комплексне оцінювання віку, IMT і гормонального профілю. Встановлені дані свідчать, що залежними факторами ризику передчасних пологів є рівень прогестерону менше ніж 139,5 нг/мл, кортизолу менше ніж 577,9 нг/мл, IMT менше за 24 кг/м² і вік вагітної понад 25 років. Незалежні фактори: вік вагітних понад 35 років, рівень інсуліну понад 31,36 мкМЕ/мл, рівень прогестерону менше ніж 247,8 нг/мл. Враховуючи

Ключові слова: передчасні пологи, прогестерон, інсулін, кортизол, прогнозування.

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результати дослідження, високу специфічність і чутливість запропонованих мультиваріантних моделей, вагітним у терміні 22–34 тижні доцільно в комплекс стандартного обстеження включати визначення рівня прогестерону, інсуліну, кортизолу, що дає змогу виявити групу ризику щодо розвитку передчасних пологів та своєчасно вжити профілактичних заходів.

Ключевые слова: преждевременные роды, прогестерон, инсулин, кортизол, прогнозирование.

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Оценка факторов риска и современные возможности прогнозирования преждевременных родов

А. А. Шевченко, Ю. Я. Круть

Цель работы – на основании комплексного обследования беременных определить факторы риска преждевременных родов и разработать критерии их прогнозирования.

Материалы и методы. В проспективном открытом исследовании приняли участие 63 пациентки в сроке беременности 22–34 недели. Исследование выполнено на базе КУ «Областной перинатальный центр» ЗОС, который является клинической базой кафедры акушерства и гинекологии ЗГМУ. Средний возраст беременных составил 27,1 ± 0,8 (M ± SD) года. Беременных поделили на две группы в зависимости от течения гестационного периода. В I группу вошли 44 беременные с угрозой преждевременных родов, а во II – 19 пациенток с нормальным течением беременности. В первые сутки у всех женщин определили индекс массы тела (ИМТ) и выполнили лабораторное обследование (определение прогестерона, инсулина и кортизола).

Результаты. В результате ROC-анализа получены такие точки распределения: возраст беременных старше 35 лет (чувствительность – 33,3 %, специфичность – 96,1 %), площадь под ROC кривой – 0,542 (95 % ДИ 0,411–0,668; p = 0,6593); индекс массы тела (ИМТ) ≤22,95 кг/м² (чувствительность – 66,7 %, специфичность – 84,3 %), площадь под ROC кривой – 0,694 (95 % ДИ 0,566–0,804; p = 0,01); инсулин >31,36 мкМЕ/мл (чувствительность – 41,7 %, специфичность – 90,2 %), площадь под ROC кривой – 0,505 (95 % ДИ 0,376–0,633; p = 0,96); кортизол ≤609,7 нг/мл (чувствительность – 75 %, специфичность – 55 %), площадь под ROC кривой – 0,649 (95 % ДИ 0,518–0,765; p = 0,07); прогестерон <247,8 нг/мл (чувствительность – 41,7 %, специфичность – 88,2 %), площадь под ROC кривой – 0,579 (95 % ДИ 0,448–0,703; p = 0,4).

Выводы. Результаты свидетельствуют, что многофакторный логистический регрессионный анализ позволяет определить факторы риска преждевременных родов. Среди установленных прогностических маркеров спонтанного развития преждевременных родов наиболее информативной является комплексная оценка возраста, ИМТ и гормонального профиля. Установленные данные показали, что к зависимым факторам риска преждевременных родов относятся уровень прогестерона меньше 139,5 нг/мл, кортизола меньше 577,9 нг/мл, ИМТ меньше 24 кг/м² и возраст беременной более 25 лет. К независимым факторам следует отнести возраст беременных старше 35 лет, уровень инсулина более 31,36 мкМЕ/мл и уровень прогестерона меньше 247,8 нг/мл. Учитывая результаты исследования, высокую специфичность и чувствительность предложенных мультивариантных моделей, беременным в сроке 22–34 недели целесообразно в комплекс стандартного обследования включать определение уровня прогестерона, инсулина и кортизола, что позволит установить группу риска по развитию преждевременных родов и своевременно провести профилактические мероприятия.

For many years, premature delivery (PD) remains one of the main problems of modern practical obstetrics due to high rates of reproductive loss, perinatal morbidity and mortality in preterm infants. Today, positive changes in this area have been achieved through a set of measures within the framework of the National Programs, regionalization of perinatal care and continuous improvement of the conditions for children with a small and extremely low body weight at birth. However, the data from the State Program for “Reproductive Health of the Nation” for the period up to 2018 indicate that direct reproductive losses from PD make up 36–40 thousand unborn wanted children annually and do not have a tendency to decrease, despite the high potential of obstetricians in the implementation of numerous and highly effective diagnostic methods and treatment regimens for pregnancy maintenance. The frequency of PD remains high and ranges between 10–12 % and 20–25 % of the total number of pregnancies [1,2]. More than 30–40 % of perinatal pathology and mortality cases are associated or predisposed to PD [3].

Given the fact that PD is based on both polyetiologic factors and polypathogenetic mechanisms of development, at the present stage, it is considered not as an independent nosological entity, but as a syndrome [4]. PD syndrome covers a combination of processes caused by fibronectin assembly, changes in the cervical length, activation of infection in a pregnant woman, proinflammatory cytokines production in the amniotic fluid, and diseases of the newborn associated with an intrauterine infection [5].

The frequency of preterm birth varies in different regions of the world, for example, in the United States, PD rates are from 12 % to 13 %, while in Europe and other developed countries, official rates range from 5 % to 9 % [6,7]. It should be noted that during the last decade in industrialized countries, the rate of PD is increasing, for example, in the USA this indicator has increased from 9.5 % to 12.8 % (25 %) [7], despite the fact that specialists and scientists have obtained up-to-date knowledge about risk factors and mechanisms of PD development over the last years, as well as a number of social and medical interventions have been developed to reduce the rate of preterm labor [8].

Overall proportion of premature birth in the structure of perinatal mortality is about 75 % and in the structure of long-term morbidity in children – more than 50 % and it is the biggest problem [9]. In addition, most of premature children have an increased risk of developing neurological, respiratory and gastro-intestinal violations [9].

In fact, there are two reasons for inability to reduce the frequency of PD: the lack of both necessary examinations to identify women at high risk and effective measures to prevent these complications. Current conditions dictate the need to find new methods for predicting PD, as well as the use of new more effective methods of pregnancy maintenance.

The aim

The aim is based on the comprehensive examination of pregnant women to determine the risk factors for preterm labor and develop criteria for its prediction.

Materials and methods

In a prospective open study, 63 patients at 22–34 weeks of gestation were included. Pregnant women were involved in the study after signing an informed consent. The study was carried out on the basis of PI "Zaporozhzhia Regional Perinatal Center", which is the clinical base for the Department of Obstetrics and Gynecology, ZSMU (the head of the Department – MD, PhD, DSc, Professor Yu. Ya. Krut). The average age of the pregnant women was 27.1 ± 0.8 (M ± SD) years. The pregnant women were divided into two groups, depending on the gestation period course. Thus, group I included 44 pregnant women who had threatened preterm labor (TPL), and group II – 19 patients with a normal course of pregnancy.

The exclusion criteria were severe somatic diseases. Every pregnant woman was interviewed to determine whether additional methods of examination would be appropriate and gave consent for their performance. The study met the modern moral and ethical standard requirements regarding the ICH/GCP Guidelines, the Helsinki Declaration of 1964, the Council of Europe Conference on Human Rights and Biomedicine, as well as the provisions of the legislative acts of Ukraine.

On the first day, all women were laboratory examined (determination of progesterone, insulin and cortisol) and body mass index (BMI) was calculated.

Statistical processing of materials was carried out using the packages of programs Statistica 6.0 (StatSoft, USA) and MedCalc. The normality of quantitative characteristics distribution was checked with the Shapiro–Wilk 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 were presented as odds ratio and confidence intervals. Cut-off values of the quantitative indicators included in a multivariate logistic regression model were determined using ROC analysis. All statistical tests were two-sided and P values <0.05 were considered statistically significant.

Results

Pregnant women with TPL accounted for 69.8 % (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 19.1 % of the total. Most pregnant women (80.9 %) gave birth to full-term neonates.

According to the study results, pregnant women with TPL had a 57 % (P < 0.05) longer hospital stay after giving birth in comparison to women with normal pregnancy course (6.90 ± 1.27 days versus 3.70 ± 0.33 days). It was due to PD and, in some cases, the need for special medical care for preterm infants and resuscitation measures. In the structure of diseases in 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 prematurity. Two children had a congenital heart disease as an intraventricular septum defect and an atrial septum defect, 2 children had neonatal jaundice.

In order to find out the factors that influence the course of pregnancy and increase the risk of PD, we have conducted an analysis of the results from the monitoring of 63 pregnant women who were observed in the PI "Zaporizhzhia Perinatal Center". Logistic regression analysis was used to determine the cut-off value of quantitative indicators that increase the risk of PD, to construct univariate and multivariate models and to identify dependent and independent risk factors for the spontaneous appearance of clinical symptoms and prematurity.

In the ROC analysis, we obtained the following distribution points (*Table 1*): the age of pregnant women over 35 years (sensitivity 33.3%, specificity 96.1 %), the area under the ROC curve 0.542 (95 % CI 0.411–0.668, P = 0.6593); BMI ≤22.95 kg/m² (sensitivity 66.7 %, specificity 84.3 %), the area under the ROC curve 0.694 (95 % CI 0.566–0.804, P = 0.01); insulin >31.36 μMe/ml (sensitivity 41.7 %, specificity 90.2 %), the area under the ROC curve 0.505 (95 % CI 0.376–0.633, P = 0.96); cortisol ≤609.7 ng/ml (75 % sensitivity, 55 % specificity), the area under the ROC curve 0.694 (95 % CI 0.518–0.765, P = 0.07); progesterone <247.8 ng/ml (sensitivity 41.7 %, specificity 88.2 %), the area under the ROC curve 0.579 (95 % CI 0.448–0.703, P = 0.4).

These factors have been identified as the potential risk predictors for PD using regression logistic analysis. *Table 2* shows the data of the univariate regression analysis.

Consequently, according to the univariate model (*Table 2*), the following indicators were found to be dependent risk factors for PD: maternal >35 years significantly increased the risk of PD in 12.25 times (95 % CI 1.91–78.27; P = 0.008); the risk of PD was also 10.75 times increased in BMI less than 22.95 kg/m² (95 % CI 2.60–44.37, P = 0.001), the insulin level above 31.36 μM/ml significantly increased the risk of PD in 6, 65 times (95 % CI 1,507–28,659; P = 0.01).

At cortisol levels ≤ 609.7 ng/ml, PD was 3.65 times (95% CI 1.50–28.65; P = 0.01) increased. The literary data indicate that the fetus can generate signaling factors that activate the labor activity itself. Hypothalamic-pituitary-adrenal theory is represented as one of these theories. Preparation for labor begins with the fetal adrenal cortex functional activation, which are responsible for the synthesis of major steroids – dehydroepiandrosterone and cortisol [10].

The risk of PD also depends on the level of progesterone, which was convincingly proved by the logistic regression analysis in our study. If progesterone was less than 247.8 ng/ml, the risk of PD was 5.36 times (95 % CI 1.280–22.369; P = 0.02) increased. Progesterone plays an important role in the central and peripheral nervous system regeneration manifesting in multifaceted effects, including soothing, anxiolytic and antidepressant effects at high concentrations, and vice versa, at low levels – anxiety and fear [11–13].

We have constructed three multivariate models (*Table 3*) with the logistic regression analysis. According

Table 1. Distribution point by the ROC analysis for the risk of premature birth

Indicator	Area under ROC curve (AUC)	95 % CI	Significance level, p	Distribution point	Sensitivity, %	Specificity, %
Age, years	0.542	0.411–0.668	0.659	>35	33.3	96.1
BMI, kg / m^2	0.694	0.566–0.804	0.011	≤ 22.95	66.7	84.3
Insulin, μM / ml	0.505	0.376–0.633	0.958	>31.36	41.7	90.2
Cortisol, ng / ml	0.649	0.518–0.765	0.07	≤609.7	75.0	54.9
Progesterone, ng/ml	0.579	0.448–0.703	0.403	<247.8	41.7	88.2

Table 2. Univariate model of the risk of premature delivery

Indicator, units	Univariate model		
	Odds Ratio, OR	Significance level, P	95 % Confidence interval, CI
Age, years	12.25	0.008	1.91–78.27
Insulin, μMe/mg	6.57	0.01	1.50–28.65
Cortisol, ng/ml	3.65	0.073	0.08–15.08
Progesterone, ng/ml	5.35	0.020	1.28–22.36
BMI, kg/m^2	10.75	0.001	2.60–44.37

Table 3. Multivariate models of threatened preterm labor

Indicator, units	Model 1			Model 2			Model 3		
	Odds ratio, OR	Significance level, P	95% Confidence interval, CI	Odds ratio, OR	Significance level, P	95% Confidence interval, CI	Odds ratio, OR	Significance level, P	95% Confidence interval, CI
Age, years	23.87	0.007	2.37–240.45	100.95	0.002	5.42–1877.17	65.12	0.006	3.39–1249.92
Insulin, μMe/mg	10.28	0.02	1.45–72.87				12.23	0.04	1.10–135.69
Cortisol, ng/ml				10.25	0.02	1.38–76.16			
Progesterone, ng/ml	11.81	0.01	1.77–78.59						
BMI, kg/m^2				56.73	0.0009	5.23–615.17	53.82	0.002	4.19–689.89

to the first model, independent risk factors of PD were the following: maternal age over 35 years, serum insulin >31.36 ng/ml and progesterone <247.8 ng/ml.

The combination of these factors significantly increased the odds ratio of PD in comparison with the influence of a particular factor in the univariate model. Thus, in the first multivariate model, maternal age over 35 years increased the risk of PD in 29.3 times (P < 0.01), the level of insulin above 31.36 increased the odds ratio (OR) in 10.3 times (P = 0.01) and progesterone level less than 247.8 ng/ml increased OR in 11.8 times (P = 0.01).

The second model combined such independent risk factors as BMI, age and cortisol level. According to this model, the age proved to be a very powerful factor that the OR was 100 times (P < 0.01) increased, maternal body weight deficiency 56 times (P < 0.01) increased the OR and the cortisol level less than 609.7 ng/ml – in 10 times (P = 0.02).

The third model also combined BMI, age and insulin content. According to our data, the risk of PD was 65 times (P < 0.01) increased in maternal age over 35 years, 54 times (P < 0.01) – in BMI less than 22.96 kg/m^2, 12 times (P = 0.04) in insulin level above 31.36 μMe/mg.

PD can be caused by a variety of factors, including infections, vascular lesions, uterine contractions, violation of mechanisms of allogeneic recognition, stress and other pathological processes [14,15].

It is known that increased activity of endogenous progesterone is required for normal pregnancy development as it can directly reduce the risk of PD due to endocrine and anti-inflammatory mechanisms. In addition, it has been shown that the level of endogenous progesterone withdrawal is involved in the onset of labor. It was followed by numerous studies on the evaluation of exogenous progesterone efficacy for PD prevention.

There are a number of recognized risk factors for PD, including PD in the anamnesis, a short cervix according to ultrasound data in the second trimester of pregnancy, and a high concentration of cervicovaginal fetal fibronectin. The cervical length according to ultrasound data is a powerful and informative prognostic marker for PD, even more significant than the presence of PD in the anamnesis [16,17].

Discussion

So, according to our data, the dependent factors for PD include:

– progesterone less than 139.5 ng/ml increases the OR in 8.23 times (95 % CI 1.06– 63.94; P = 0.043);

– cortisol less than 577.9 ng/ml increases the OR in 10.6 times (95 % CI 1.93–57.68; P = 0.006);

– BMI less than 24 kg/m^2 increases the OR in 12.4 times (95 % CI, 1.89–81.14, P = 0.008);

– age more than 25 years increases the OR in 4.48 times (95 % CI 1.002–20.06, P = 0.049).

Among the independent factors for PD are:

– age over 35 years increases the risk in 29.3 times (P = 0.007);

– the level of insulin over 31,36 μMe/mg increases the OR in 10.3 times (P = 0,01);

– the level of progesterone less than 247.8 ng/ml increases OR in 11.8 times (P = 0.01).

Conclusions

1. The results of the conducted study indicate that multivariate logistic regression analysis allows determining the risk factors for preterm labor. Among the established prognostic markers for spontaneous development of preterm labor, the complex assessment of age, BMI and hormonal profile contain the most comprehensive information.

2. The findings suggest that dependent risk factors for preterm birth include: the level of progesterone lower than 139.5 ng/ml, cortisol less than 577.9 ng/ml, BMI less than 24 kg/m^2 and maternal age of over 25 years. Independent factors should include maternal age of over 35 years, the level of insulin above 31.36 ng/ml and progesterone less than 247.8 ng/ml.

3. Considering the study results, high specificity and sensitivity of the proposed multivariate models, it would be appropriate to include measurements of progesterone, insulin and cortisol levels in the standard examination complex for pregnant women from 22 to 34 weeks of gestation. It will enable the identification of a risk group for preterm labor and implementation of timely prevention.

Prospects for further research. A comprehensive assessment of biochemical markers taking into account the psycho-emotional state of pregnant women with PD is going to be conducted.

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