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FEASIBILITY OF OBJECTIVE ASSESSMENT OF THE PROGRESS OF PRETERM LABOR AT DIFFERENT GESTATIONAL AGES

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Aim *To investigate the feasibility of an objective assessment of the progress of preterm labor at different gestational ages.*
Material and methods *This prospective, nonrandomized study comprised 150 women with premature births at various gestational ages and 50 control women with full-term births. The study estimated and differentiated objective factors for predicting preterm labor within 24 hours.*
Results *Based on the discriminant analysis, the predictive significance of various parameters for predicting preterm labor was estimated depending on the gestational age. The risk of childbirth with extensor presentation of the fetal head is established in very early, early and preterm labor.*
Conclusion *To assess the risk of preterm labor, ultrasonic measurements of cervical vascularization index and the fetal head–perineum distance need to be done in addition to routine diagnostic evaluation. In very early, early and premature labor with the extensor presentation of the fetal head, the risks of vaginal birth should be considered together with a neonatologist.*

Keywords: preterm labor, cervical vascularization, extensor presentation of the fetal head.

The authors have no conflicts of interest to report.

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Modern obstetrics sets out the high quality requirements for the timely diagnosis of pregnancy complications [1]. Prematurity, as a result of preterm labor (PL), causes the neonatal morbidity and increases the child's risk of future intellectual and emotional impairment [2]. One of the mechanisms of PL is a breakdown of immune tolerance, which may evolve into maternal anti-fetal rejection [3].

In recent years, efforts have been made to identify reliable predictors and diagnostic markers for the asymptomatic onset of PL. [4-6]. Modern pharmacotherapy provides the opportunity to control the uterine contractile activity in PL [7, 8]. Over the last decades, ultrasound cervicometry has been used to predict PL. Thus, J.D. Iams et al. in 1996 presented an original study investigating the relation between the cervical length and the risk of spontaneous PL [9]. To date, some studies and reviews explored various methods for predicting PL [10-13]. In 2014, the British National Screening Committee (UK NSC) published a guide on screening for preterm labor in asymptomatic, low-risk women. Biochemical markers of spontaneous PL in asymptomatic women have been studied [14].

The present study is aimed to investigate the feasibility of objective assessment of the progress of preterm labor at different gestational ages.

Material and methods

This prospective non-randomized controlled cohort study was conducted between 2012 and 2016 (June) at the Perinal Center, Children's Regional Clinical Hospital of the Ministry of Health of the Krasnodar Krai, which is one of five perinatal centers of the Krasnodar Krai since 2011. Women with PL are referred to this medical institution.

The criteria for the inclusion in the study were: PL (ICD code - O60), first birth, spontaneous pregnancy, spontaneous onset of labor, one fetus, cephalic fetal presentation, front view, intact membranes before onset of labor, delivery within 24 hours from the time of symptom onset. Exclusion criteria: multiple pregnancies, transverse lie and breech presentation, posterior view, placenta previa, premature rupture of membranes, labor occurring later than 24 hours post admission, obstetric, gynecological and extragenital pathology in the decompensated stage that prevents natural delivery or requiring urgent delivery or intensive care. The study comprised 150 women with PL who were divided into four clinical groups depending on the gestational age: I clinical group - very early PL (VEPL group) (22-27 weeks and 6 days, n = 37), II clinical group - early PL (EPL group) (28-30 weeks and 6 days, n = 40), III clinical group - PL group (31-33 weeks and 6 days, n = 38), IV clinical group - late PL (LPL group) (34-36 weeks and 6 days , n = 35). The control group included healthy women with a full-term pregnancy and with physiological births (FT group) (37-40 weeks and 3 days, n = 50). The mean gestational age (M ± SD) was 33.44 ± 2.96 weeks. The mean age of the subjects was 25.67 ± 4.47 years.

All study participants underwent a general clinical examination, including a detailed review of past medical history and the present pregnancy to identify risk factors for PL. Cervical ripening was determined using the Bishop's scale (1964) and ultrasonography (US) (expert class Applio XG SSA-790A, Applio MX SSA-780A and Xario SSA-660A scanners). When assessing the features of fetal head presentation, ultrasound measurements the following presenting diameters of the fetal skull were made: a large oblique (mento-occipitalis); small oblique (suboccipito-bregmatika); middle oblique (suboccipito-frontalis); direct (fronto-occipitalis), and vertical (tracheo-bregmatica). The distance from the perineum to the presenting part of the fetus was determined using transperineal ultrasound measurements, similar to that described by A.F. Barbera et al. (2009) [15]. Power Doppler ultrasound was used to assess blood flow characteristics of the cervix (the number of color voxels in the cervix). The study participants were treated in the maternity ward using appropriate orders and guidelines [16-18].

Statistical analysis was performed using statistical packages Statistica 12.0, Microsoft Excel 2007 [19], and online calculators http://medstatistic.ru/calculators.html. Descriptive statistics were presented as the mean (M), standard deviation (SD), median (Me), lower (Q1), and upper (Q3) quartiles. To assess the differences between mean values of the two samples, the Student's t-test was used. To compare the frequencies of the binary variables in two independent) groups, the χ^2 was used (with the number of observations less than ten — χ^2 with the Yates correction). To represent the results of the binary classification, ROC analysis was used (the area under the curve was estimated as AUC). To interpret the intergroup differences, discriminant analysis was used, Wilk's Lambda, Partial Lambda, F-remove, and Toler.

To determine the relationship between different results, a multiple linear regression method was used. The correlation coefficient (R) and the determination coefficient (R2) were calculated. The strength of correlations was interpreted using the Chaddock scale: at R from 0 to 0.3, the correlation was regarded as very weak, from 0.3 to 0.5 (as weak, from 0, 5 to 0.7 (as average, from 0, 7 to 0, 9 (as strong, from 0.9 to 1 (very strong. When estimating the determination coefficient (R2), we took into account that the closer R2 is to 1.0, the stronger is the relationship between the variables.

Based on the assumption that the dependent variable is a linear function of the independent variables, the multiple linear regression method was used: y = a + b1x1 + b2 x2 + ... + bn xn, where x1 is the value of the independent variables, b1 is the coefficients calculated by estimation of binary logistic regression, and a is a constant.

Results

According to the inclusion criteria, the study participants were primiparous women. The age of women was comparable, averaging (M ± SD) 26.75 ± 7.41, 23 ± 3.6, 25.2 ± 3.19 and 25.83 ± 4.41 years in VEPL, EPL, PL, and LPL groups, respectively.

The readiness of a woman's organism for childbirth in the study groups was compared depending on gestational age (Table 1). Despite the fact that cervical ripening, assessed subjectively by Bishop score in women with VEPL (8.0 ± 1.41 points), EPL (8.55 ± 1.29 points), PL (9.27 ± 1.35 points) and LPL (9,73 ± 1,85 points) was significantly less than in women with full-term pregnancy (10,82 ± 1,78 points), all women progressed to delivery within 24 hours. The subjective feeling of labor contractions at the beginning of observation was noted only in 48.65% of women with VEPL, 60% with EPL, 78.95% with PL. In 100% of women with LPL and FT, labor activity was accompanied by characteristic symptoms. At the onset of regular labor, the fetal head–perineum distance was 60.20 ± 13.03 mm, 63.80 ± 13.35 mm, 61, 50 ± 12.44 mm, and 64.95 ± 10.24 mm in women with VEPL, EPL, PL, and LPL, respectively.

We found a relationship between the degree of cervical ripening Bishop's score and the number of color voxels in the cervix (according to the Doppler US), but not with the fetal head–perineum distance measured by ultrasound (Table 2). The strongest correlation was established for EPL - correlation coefficient R = 0.9350 (p (0.001), coefficient of determination R2 = 0.8742. The weakest correlation was established for PL — correlation coefficient R = 0.4096 (p (0.05), the coefficient of determination R2 = 0.1678. Such a relationship for PL in general, regardless of the gestation age, was comparable to the parameters for a full-term pregnancy. Despite the lack of complete understanding of the mechanism of PL initiation depending on the gestational age, the result suggests that the processes of cervical ripening and transformation in already started active labor during PL and delivery in full-term pregnancy have much in common.

We managed to develop a mathematical model for the hypothetical calculation of the biological cervical ripen ing and the fetal head–perineum distance, taking into account the gestational age, depending on the number of color voxels in the cervix, which can help minimize the number of internal obstetric examinations in parturient women (Table 2).

Based on the discriminant analysis, it was also found that the number of color voxels in the cervix (by US), cervical ripening Bishop's scores, the fetal head–perineum distance

Table 1. Parameters of PL that occurred within 24 hours at different gestational ages

Parameter	All	VEPL	EPL	PL	LPL	FT
	M±SD Me (Q1;Q3)					
Fetal head–perineum distance, mm (by US)	64.24±12.33 67.5 (55;75)	60.20±13.03 60 (50;70	63.80±13.35 70 (52;75)	61.50±12.44 62.5 (50;72,5)	64.95±10.24 67.5 (60-72.5)	70.75±10.67 75 (67.5;80)
The number of color voxels in the cervix (by US)	10.51±4.76 10 (6;14)	6.64±2.38 6 (4;8)	7.64±3.07 8 (5;10)	12.18±3.34 12 (11;15)	10.09±2.91 10 (8-12)	16.0±5.04 16 (15;18)
Cervical ripening, Bishop's score	9.27±1,79 9 (8;11)	8.0±1,41 7 (7;9)	8.55±1.29 9 (7;9)	9.27±1.35 9 (8;11)	9.73±1.85 9 (8-11)	10.82±1.78 11 (10;12)

(by US) fundamentally differentiate (discriminate) the clinical groups, hence, the objective parameters PL risk assessment depending on the gestational age: Lambda Wilk = 0.165274, p = 0.000000) (Fig. 1).

The specific predictive values of the fetal head–perineum distance and the number of color voxels in women with PL were differentiated depending on the gestational ages, which are presented in Table. 3.

The findings of our study showed that at the onset of labor, 29% of women with PL had an extensor presentation of the fetal head (Figure 2). Based on nonparametric statistical analysis using 4x4 tables, we estimated the strength of the connection between the risk of the extensor presentation of the fetal head and PL at various gestational ages. So, VEPL had a strong association with the risk of the extensor presentation of the fetal head (χ^2 with Yates' correction = 13,206, p <0.01). EPL had a relatively strong association with the extensor presentation of the fetal head (χ^2 with Yates' correction = 13,206, p <0.01). For PL this relationship was much less pronounced (χ^2 with Yates' correction = 3.355, p> 0.05). This implies the need for a timely diagnosis of the type of fetal head presentation in preterm pregnancy at the onset of labor. We can assume that small fetuses with the extensor presentation of the fetal head of varying severity and good uterine contractile activity allow labor to progress to delivery, without impeding the progression through the birth

Fig. 1. Relationship between the number of color voxels in the cervix (by US), Bishop's score, fetal head–perineum distance (by US) and gestational age

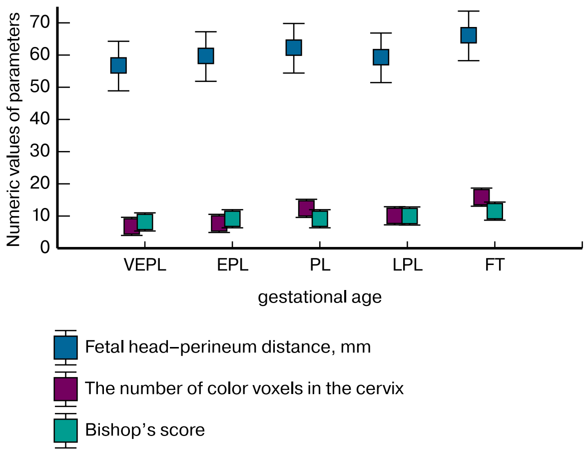

Fig. 2. Incidence of extensor presentation of the fetal head in PL at different gestational ages,%

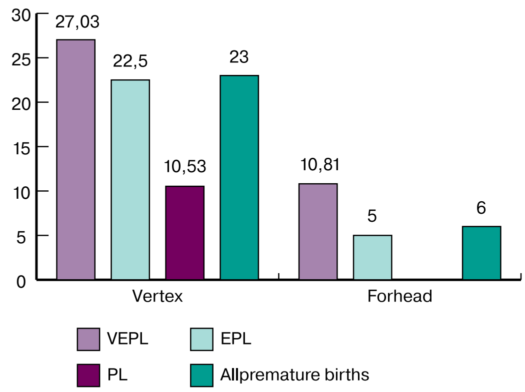

Table 2. The relationship between the number of color voxels in the cervix (by US) and cervical ripening (x) and the fetal head–perineum distance (by US)

Predicted parameter (y)	Correlation coefficient (r)	Determination coefficient (R^2)	Linear regression equation
VEPL			
Bishop's score	**0,6245 (*p*=0,0400)**	0,3900	y=5,5354+0,3714*x
Fetal head–perineum distance, mm (by US)	-0,2806 (*p*=0,4033)	0,0787	y=67,2042-1,6061*x
EPL			
Bishop's score	**0,9350 (*p*=0,00002)**	0,8742	y=5,5423+0,3933*x
Fetal head–perineum distance, mm (by US)	0,5923 (*p*=0,0549)	0,3508	y=37,2192+2,9356*x
PL			
Bishop's score	0,4096 (*p*=0,2109)	0,1678	y=7,259+0,1653*x
Fetal head–perineum distance, mm (by US)	0,1965 (*p*=0,5625)	0,0386	y=52,8355+0,7598*x
LPL			
Bishop's score	**0,6176 (*p*=0,0429)**	0,3814	y=45,9272+1,2955*x
Fetal head–perineum distance, mm (by US)	0,3833 (*p*=0,2446)	0,1469	y=5,773+0,3919*x
Full-term pregnancy			
Bishop's score	0,4685 (*p*=0,1461)	0,2195	y=8,1725+0,1654*x
Fetal head–perineum distance, mm (by US)	-0,4794 (*p*=0,1357)	0,2298	y=84,1768-1,1417*x
R			
Bishop's score	**0,6970 (*p*=0,0)**	0,4858	y=6,5171+0,2622*x
Fetal head–perineum distance, mm (by US)	0,1982 (*p*=0,1469)	0,0393	y=55,0437+0,5322*x

Note: In bold type, the parameters with the moderate strength of the correlation or stronger.

Table 3. Predictive values of objective parameters for assessing the risk of PL within 24 hours at different gestational ages

Predictor	Gestational age					
	VEPL *n*=37	EPL *n*=40	PL *n*=38	LPL *n*=35	FT *n*=50	All *n*=200
Fetal head–perineum distance (M±SD), mm	56.55±13.61	59.64±15.24	62.094±12.92	59.04±9.85	65.91±12.0	60.64±12.77
Number of color voxels in the cervix (M±SD)	6.64±2.34	7.64±3.08	12.18±3.34	10.09±2.91	16.0±5.04	10.51±4.76

Note: FT – full-term pregnancy.

canal, especially with tocolysis and anesthesia. The effect of PL with the extensor presentation of the fetal head on the outcomes of the newborns in the short and long terms requires further investigation.

We could not compare the findings of the assessment of the progress of Pl at different gestational ages with the duration of labor. The duration of labor was calculated conditionally, as in some women the characteristic symptoms of labor occurred when they had the ripe cervix and the fetal head was engaged in the small pelvis. Nevertheless, the duration of labor in the EPL group (331.67 ± 5.7 min), PL (404 ± 10.54 min) and LPL (346.71 ± 3.72 min) was significantly less than in the control group (435.14 ± 3.82 min) and in the group with VEPL (432.5 ± 13.39 min).

Nevertheless, the duration of labor in the EPL, PL and LPL groups was 331.67 ± 5.7, 404 ± 10.54 and 346.71 ± 3.72 min, respectively, which was significantly shorter than in the control group (435.14 ± 3.82 min) and VEPL group (432.5 ± 13.39 min).

An attempt to find the relationship between the different parameters of the progress of PL and the newborn's gender was unsuccessful. According to our data, girls were more likely to be delivered prematurely except the VEPL group (50% boys, 50% girls). In the EPL, PL, LPL and FT groups, proportions of boys and girls were 33/66, 40/60, 30/70, and 40/60%, respectively.

There were no significant differences in maternal age ($p = 0.770323$), gestational age ($p = 0.608136$), estimated fetal weight ($p = 0.952708$), duration of the first stage of labor ($p = 0.97545723$), maternal blood loss ($p = 0.556954$), the fetal 1 minute and 5 minute Apgar scores ($p = 0.510382$ and $p = 0.558377$, respectively). The constructed ROC curve showed no significant associations between newborns' gender and the factors studied (maternal age, the length of labor, postpartum maternal blood loss, the estimated fetal weight, the transfer of the newborn to the intensive care unit, Apgar score, the severity of the general state of newborns, asphyxia at birth) (the AUC was less than 0.6). Also, in the general discriminant analysis, comparable PL predictors were obtained, differentiated according to gender: maternal age at the birth of girls was 26.4 years, at the birth of boys — 26.2 years (Wilks' Lambda = 0.516184, F = 0.725339, p = 0.422575, Toler = 0.509919); the gestational age at birth was 34 weeks for girls, 35 weeks for boys at birth (Wilks' Lambda = 0.570132, F = 1.532746, p = 0.255610, Toler. = 0.108102); the estimated fetal weight at the birth of girls was 2385 g, at the birth of boys - 2520 g (Wilks' Lambda = 0.475330, F = 0.113907, p = 0.745634, Toler. = 0.184834).

This result cannot be considered definitive, can be explained by the design of this study and requires further similar studies with appropriate research methodology. The findings of our study suggest the need to investigate the progress of PL depending not only on the gestational age, as in this study, but also on fetal gender, the number of fetuses, fetal head size and presentation, the amount of amniotic fluid, and the duration of the anhydrous span.

Conclusion

The study findings expand our understanding of the features of the progress of PL characteristics at different gestational ages and require further investigation to assess their practical significance. In the framework of this study, it was not possible to establish a relationship between the state of the newborn and the presence of an extensor presentation of the fetal head, the duration of tocolytic therapy, the tocolytic drug, the duration, and type of anesthesia at various gestational ages. Moreover, these issues require a joint study with neonatologists in the long term. Further studies are needed to evaluate the outcome for newborns resulting from the extensor presentation of the fetal head into the plane of the pelvic inlet. It is impossible to calculate whether the biomechanism of labor leading to the transfer of the fetal head from the extensor to the occipital presentation affects the long-term outcome for premature newborn infants; whether gestational age, the use of tocolysis of various types affects this outcome; whether tocolysis prevents fetal head flexion, etc.

The findings of this study and suggested diagnostic criteria should be implemented in local protocols for PL management, which will allow for timely referral of pregnant women to a hospital of the appropriate level, to begin prophylaxis of the fetal respiratory distress syndrome and tocolysis to reduce the incidence of PL and perinatal complications.

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