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A MODEL FOR PREDICTING BIRTH DEFECTS OF THE FETUS BASED ON RISK FACTORS IN MOTHERS WITH A HISTORY OF PREMATURE BIRTH

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Abstract. A model for predicting birth defects of the fetus based on risk factors in mothers with a history of premature birth. Mammadzada G. *Birth defects (BD) are an important cause of neonatal mortality and can be associated with premature birth. The study aimed to develop a prognostic model for congenital malformations in mothers with a history of preterm delivery, using logistic regression analysis. The study included 665 mothers of children with BD, of which 432 (65%) had a history of preterm delivery (main group), and 233 (35%) had term delivery (control group). Variables examined included pregnancy history, genetic factors, and biochemical markers. Statistical analysis found significant associations between BD and preterm delivery, intrauterine malformations, miscarriages, MTHFR polymorphism, and HLA antigens. The logistic model showed good predictive performance. The area under the ROC curve was 0.769 for pregnancy history, 0.699 for miscarriages, and 0.630 for intrauterine malformations, indicating moderate predictive ability. A statistical relationship was found between BD risk and pregnancy history, intrauterine malformations, miscarriages, and genetic factors. The resulting logistic model may help predict BD risk in mothers with a preterm delivery history.*

Реферат. Модель прогнозування вроджених вад розвитку плода на основі факторів ризику в матерів з передчасними пологами в анамнезі. Мамед-заде Г. *Вроджені вади розвитку є важливою причиною неонатальної смертності й можуть бути пов'язані з передчасними пологами. Метою цього дослідження була розробка прогностичної моделі вроджених вад розвитку в матерів з передчасними пологами в анамнезі за допомогою логістичного регресійного аналізу. У дослідження було включено 665 матерів дітей з вродженими вадами розвитку, з яких 432 (65%) мали в анамнезі передчасні пологи (основна група), а 233 (35%) – пологи в строк (контрольна група). Змінні, що вивчалися, включали історію вагітності, генетичні фактори та біохімічні маркери. Статистичний аналіз виявив значущі асоціації між вродженими вадами розвитку та передчасними пологами, внутрішньоутробними вадами розвитку, викиднями, поліморфізмом метилентетрагідрофолатредуктази (MTHFR) та лейкоцитарними антигенами людини (HLA). Логістична модель показала хорошу прогностичну ефективність. Площа під ROC-кривою становила 0,769 для історії вагітності, 0,699 для викиднів і 0,630 для внутрішньоутробних вад розвитку, що вказує на помірну прогностичну здатність. Було виявлено статистичний зв'язок між ризиком вроджених вад та анамнезом вагітності, внутрішньоутробними вадами розвитку, викиднями та генетичними факторами. Отримана логістична модель може допомогти в прогнозуванні ризику вроджених вад у матерів з передчасними пологами в анамнезі.*

Birth defects (BD) are a deviation in the structure, functions, and metabolic disturbances of the newborn organism caused by a variety of prenatal influences, resulting in the development of significant physical or mental abnormalities, diseases, or death. According to statistics, birth defects occupy the 2nd-3rd place in the structure of child morbidity, disability, and perinatal and early infant mortality [1]. According to WHO, BD is diagnosed in 4-6% of children, and in 15% of newborns, malformations manifest themselves during the first 5 years of life [2]. The reported risk of abnormalities varies substantially between studies, with estimates ranging from about 2% to more than 10%, which primarily depends on the multifactorial etiology of the defects [3-5].

According to S. Lejeune et al. [6], the clinical manifestations of BD are no less diverse than the causes of their occurrence. For example, these include

both life-threatening diseases (anencephaly, lissencephaly, spina bifida, congenital heart defects (defects of the interventricular and atrial septa of the heart), oesophageal atresia), and relatively favourable BD: cleft lip, cleft palate, but they also lead to deep disability of the child [7]. In addition, birth defects in children substantially affect the likelihood of premature birth and the degree of prematurity [8]. Possible explanations for such variability of BD forms, according to A.G. Mekonnen et al. [4], include differences in the prevalence of risk factors in the examined populations, the presence of genetic mutations at different stages of development and different periods of diagnosis, the inclusion or exclusion of prenatal diagnoses and miscarriages, and the definition of BD itself (for example, limitation of major malformations, exclusion of chromosomal abnormalities, exclusion of conditions associated with prematurity) [3, 4, 5]. Many studies in the field of BD focus on the use of epidemiological data and/or clinical characteristics of the mother and fetus during pregnancy, such as low or polyhydramnios, the number of fetuses, placenta praevia, basal blood flow in the umbilical artery [9].

For example, J.K. Gunn-Charlton [10] reports that there is a link between BD and premature birth. In addition, researchers have identified a link between defects of the nervous system in the third trimester and low gestational age. Thus, in children born before 32 weeks, the brain was more susceptible to further injuries and infections. Therewith, L. Straub et al. [11] used the logistic regression method to predict the impact of pregnancy-related risk factors when assessing the impact of increased BD risk and the intensity of their detection during pregnancy screening. An important conclusion was that the comorbid background of the latter is an important cause of fetal developmental disorders. Notably, extended screening of pregnant women with a history of premature birth is prognostically important. H. Heuvelman et al. [12] also reported that the risk of BD in prematurely born children was much higher, which was manifested by reduced intelligence and delays in psychomotor development in newborns with low gestational age.

An additional determining factor in risk assessment when determining the presence of anomalies is the quality of information and the need to use algorithms that can maximise specificity due to sensitivity [13, 14, 15, 16]. Information based on specific BD risk factors is very important for women of reproductive age, as it can reduce the occurrence of anomalies and develop preventive strategic plans. Therefore, this study aims to design a predictive model for birth defects in mothers with past occurrences of preterm deliveries using logistic regression.

MATERIALS AND METHODS OF RESEARCH

A primary focus was placed on a group of 665 mothers who had given birth to children with birth defects. Additionally, 432 women, who had experienced premature births and whose children had congenital malformations, were also examined, underscoring the significance of prematurity and its associated risks in this study. The Commission on Biomedical Ethics convened a meeting where they established a detailed protocol, which included criteria such as absence of chronic diseases, no history of genetic disorders, and normal prenatal screening results for inclusion in the main study group. Additionally, it was noted that the median age of mothers in the skin care study group was 32 years. The control group consisted of 233 women with the birth of a child during normal gestational age. The average age of the selected patients was 27±6 years. Data on them were collected in various maternity hospitals in Baku.

All studies were conducted in accordance with the ethical standards of the institutional and national research, the Helsinki Declaration of the World Medical Association. Before starting work, all the patients were informed about the research methods used in the study and signed a document of voluntary consent for all examinations necessary for the study.

The literature analysis of the reported BD and their relationship with premature pregnancy was conducted using the Scopus and PubMed databases using foreign and domestic information sources. All sources were selected according to the recommendations of PRISMA. Using PRISMA for original articles can help ensure that key information is adequately reported and allows for better critical appraisal and interpretation of the findings [17, 18]. In this study, we applied relevant PRISMA criteria when selecting and evaluating original research articles to help standardize the literature review process. After the initial set of literature, the latter were subject to strict systematisation regarding the form of the developmental anomaly and the type of source (systematic review, meta-analysis, original work). This approach allowed for avoiding inaccuracies and contributed to a more detailed description of the research methodology. Various aspects were considered to determine the eligibility criteria: accuracy and reliability of the results, ethics and acceptability of the mentioned information. A generalised algorithm was developed to ensure the high quality of the study, which included detailed instructions for conducting the study and analysing the results.

During the information collection, the following variables were considered: age, city/region, childbirth, number of pregnancies, number of abortions,

cases of undeveloped pregnancy, miscarriages, fetal abnormalities, antenatal fetal death, level of methylenetetrahydrofolate reductase (MHTR), alpha-fetoprotein (AFP), human chorionic gonadotropin (CHG), unconjugated estriol (UE), and the frequency of occurrence of HLA-II class antigens. Before calculating the statistical significance between the examined indicators in the examined women, the following null hypothesis was adhered to: the absence of any connection between variables and the development of BD and an alternative hypothesis – there is a connection between variables and the formation of BD.

Statistical analysis was conducted in Statistica 10 (StatSoft, Inc., USA) and Microsoft Excel 2020. For the primary description of the number of patients, descriptive statistics methods were used (calculation of the arithmetic mean, standard deviation). Shapiro-Wilk [19] and Kolmogorov-Smirnov [20] methods were used to calculate the normality of the distribution. With the values of the Shapiro-Wilk criteria $p>0.2$ and Kolmogorov-Smirnov $p>0.05$, the data were considered to be normally distributed. In the normal distribution of data, the method of one-factor analysis of variance ANOVA [21] was used. For variables that were not normally distributed, median and interquartile range were calculated as measures of central tendency and dispersion instead of mean and standard deviation. Kruskal-Wallis H-test [22] or nonparametric analysis of variance was used to compare independent groups with their non-normal distribution. Specificity, sensitivity, and positive and negative predictive value were calculated using the analysis of nominal variables: Pearson's χ^2 criterion ($P\chi^2$) [23], Fisher's reliability criterion, odds ratio (OR), and relative risk [24]. Sensitivity and specificity were assessed using ROC curves and AUC area (ROC analysis) [25]. The results of the study were considered statistically substantial at $p<0.05$.

RESULTS AND DISCUSSION

As a result of initial monitoring and collection of epidemiological data among patients with BD, it was determined that out of 665 mothers who gave birth to children with malformations, 432 (65%) women gave birth earlier than the gestational period (main group), and the remaining 233 (35%) women gave birth on time (control group), which indirectly indicates the influence of premature birth on the development of abnormalities in newborns. In addition, increasing attention is being paid to genetic and epigenetic markers of pathologies, in particular, BD. It was established that mutations in the main human leukocyte antigen (HLA), the *MHTR, DQB1, DRB1*, and *DQA1* genes can have a special influence on the pathogenesis of developmental anomalies, which led to the choice for research and subsequent statistical analysis. In more detail, the results of determining the probability of BD risk in mothers with premature birth, depending on the examined factors of obstetric history, genetic and biochemical data are presented in Table 1.

Table 1

Probability of BD risk depending on the variables examined

Indicators		Gestation factor				$P\chi^2$
		premature		timely		
		abs.	%	abs.	%	
Place of residence	Baku	277	64.1	167	71.7	0.049
	Region	155	35.9	66	28.3	
Childbirth	premature	432	100	0	0	
	timely	0	0	233	100	
Intrauterine malformation factor	Absent	252	58.3	198	85	0
	Present	180	41.7	35	15	
Miscarriage factor	Absent	186	43.1	192	82.4	0
	Present	246	56.9	41	17.6	
Antenatal mortality factor	Absent	335	77.5	197	84.5	0.031
	Present	97	22.5	36	15.5	

Table 1 continuation

Indicators		Gestation factor				$P\chi^2$
		premature		timely		
		Abs.	%		%	
BD factor	**Absent**	**378**		**217**	**90.6**	**0.024**
	Present	**54**	**12.5**	**27**	**93.1**	
MHTR	**CC**	**101**	**49.8**	**92**	**70.2**	**0**
	CT	**82**	**40.4**	**37**	**28.2**	
	TT	**20**	**9.9**	**2**	**1.5**	
DRB1	**Absent**	**44**	**40.4**	**77**	**75.5**	**0**
	Present	**65**	**59.6**	**25**	**24.5**	
DQA1	**Absent**	**32**	**29.4**	**62**	**60.8**	**0**
	Present	**77**	**70.6**	**40**	**39.2**	
DQB1	**Absent**	**47**	**43.1**	**81**	**79.4**	**0**
	Present	**62**	**56.9**	**21**	**20.6**	
HLA	**Absent**	**11**	**10.1**	**52**	**51**	**0**
	1 HLA	**23**	**21.1**	**22**	**21.6**	
	2 HLA	**44**	**40.4**	**20**	**19.6**	
	3 HLA	**31**	**28.4**	**8**	**7.8**	
HLA (sum of any option)	**Absent**	**11**	**10.1**	**52**	**51**	**0**

Notes: abs. – absolute numbers; $P\chi2$ – the value of $\chi2$.

From the results presented in Table 1, the statistical significance of the results obtained was established by analysing all the factors examined ($p<0.001$). In addition, during the analysis of the monitoring results, it was established that mutations in the genes MHTR ($p<0.05$), DRB1 ($p<0.001$), and DQB1 ($p<0.001$) were more often observed among patients with a history of premature birth. Therewith, using the method of discriminant analysis, it was determined that the risk of developing BD factor in the group is possible in 12.5% of cases. The CC MHTR locus was detected in 49.8% of cases ($P\chi^2=0$), the presence of DRB1 – in 59.6% of cases ($P\chi^2=0$), DQA1 – in 70.6% ($P\chi^2=0$), DQB1 – in 56.9% ($P\chi^2=0$), combinations of HLA alleles – in 89.9% of cases ($P\chi^2=0$). In addition, after conducting a statistical analysis of the factors examined and presented in the table for the normality of the distribution using the Shapiro-Wilk and Kolmogorov-Smirnov methods, it was determined that all indicators for subsequent quantitative statistical analysis were normally distributed ($p>0.2$ and $p>0.05$, respectively). Therefore, the next stage of the study was the application of logistic regression analysis to examine the effect of premature birth on the development of BD. In particular, the calculation of the odds ratio (OR) and significance interval (SI) allowed the identification of how the absence or presence of BD is associated with the examined factors and indicators in the group with premature birth (Table 2).

Table 2

Risk factors for BD in the study groups

Factors	Main group					Control group					Odds Ratio (OR)			
	T	+	-	P	+mp	T	+	-	P	+mp	OR	95% CI		p
												lower limit	upper limit	
Age	432	155	277	35.9	2.3	233	66	167	28.3	3	1.42	1	2	<0.05
Gestational period	432	413	19	95.6	1	233	114	119	48.9	3.3	22.69	13.4	38.42	<0.05
Intrauterine malformation factor	432	180	252	41.7	2.4	233	35	198	15	2.3	4.04	2.69	6.07	<0.05
Miscarriage factor	432	246	186	56.9	2.4	233	41	192	17.6	2.5	6.19	4.2	9.12	<0.05
Antenatal mortality factor	432	97	335	22.5	2	233	36	197	15.5	2.4	1.58	1.04	2.41	<0.05
BD factor	432	54	378	12.5	1.6	233	16	217	6.9	1.7	1.94	1.08	3.47	<0.05
MHTR	203	102	101	50.2	3.5	131	39	92	29.8	4.0	2.38	1.5	3.79	<0.05
DRB1	109	65	44	59.6	4.7	102	25	77	24.5	4.3	4.55	2.52	8.22	<0.05
DQA1	109	77	32	70.6	4.4	102	40	62	39.2	4.8	3.73	2.1	6.61	<0.05
DQB1	109	62	47	56.9	4.7	102	21	81	20.6	4	5.09	2.76	9.38	<0.05
HLA total	109	98	11	89.9	2.9	102	50	52	49	4.9	9.27	4.45	19.31	<0.05

Note. T – total.

From the data presented in Table 2, it was determined that in the group with a history of premature birth, according to the OR and p indicator, all variables had statistical significance ($p<0.05$). The highest risk of developing fetal BD was established with an insufficient gestational period (less than 36 weeks) (OR=22.69, $p<0.05$), which indicated its substantial effect on increasing the risk of developing this spectrum of pathologies. In addition, a statistically substantial association with the development of BD was also established with the presence of various variants of HLA alleles (OR=9.27, $p<0.05$), miscarriage factor (OR=6.19, $p<0.05$), with the frequency of DQB1 (OR=5.09, $p<0.05$), and the frequency of DRB1 (OR=4.55, $p<0.05$). Therewith, the low difference in the lower and upper limits of the RI indirectly indicates the high reliability and accuracy of the results obtained. The next stage of the study was the analysis of the influence of the examined risk factors on the prediction of BD development in a child. Due to the fact that the examined quantitative indicators of risk factors were normally distributed, ANOVA multivariate analysis of variance was used to examine the influence of risk factors. The results of the analysis are shown in the table (Table 3).

Due to the conducted research method, the statistical significance was determined when evaluating all the examined risk factors for the development of birth defects ($p<0.05$). According to the analysis of variance, it was established that the maximum value of prognostic significance was during pregnancy – 43.17% ($p<0.001$). The frequency of the combined variant of HLA antigens (24.9%, $p<0.001$), the miscarriage factor (16.77%, $p<0.001$), the frequency of DQB1 (15.99%, $p<0.001$), DRB1 (14.43%, $p<0.001$) also had high prognostic significance for the development of BD. The prognostic significance of the intrauterine malformation factor and MHTR polymorphism was 7.98% ($p<0.001$) and 4.27% ($p<0.001$), respectively. Subsequently, the frequency of various risk factors for BD development in the examined patients was determined. Table 4 shows the quantitative indicators of the examined group of women with premature birth with various risk factors examined. Therewith, out of 665 women, pregnancy factor, abortion, intrauterine malformation, habitual miscarriage and antenatal mortality were observed in 233 patients.

Table 3

Influence of risk factors on prediction of BD in women with childbirth (according to ANOVA analysis of variance)

Markers	R	N	F, %	Degree of influence of the factor on prediction	Lower limit	Upper limit	p	Significance
Place of residence	2	665	3.926	0.59	0.01	1.17	0.048	*
Gestational period	2	665	503.594	43.17	42.84	43.5	0	***
The factor of intrauterine malformation	2	665	57.459	7.98	7.44	8.51	0	***
Miscarriage factor	2	665	133.634	16.77	16.29	17.26	0	***
Antenatal mortality factor	2	665	4.691	0.7	0.13	1.28	0	*
BD factor	2	665	5.163	0.77	0.2	1.35	0	*
MHTR	2	334	14.816	4.27	3.16	5.39	0	***
DRB1	2	211	35.186	14.41	12.82	16	0	***
DQA1	2	211	26.073	11.09	9.44	12.74	0	***
DQB1	2	211	39.773	15.99	14.43	17.55	0	***
HLA total	2	211	69.294	24.9	23.5	26.3	0	***

Note: * – $p<0.05$; ** – $p<0.01$; *** – $p<0.001$.

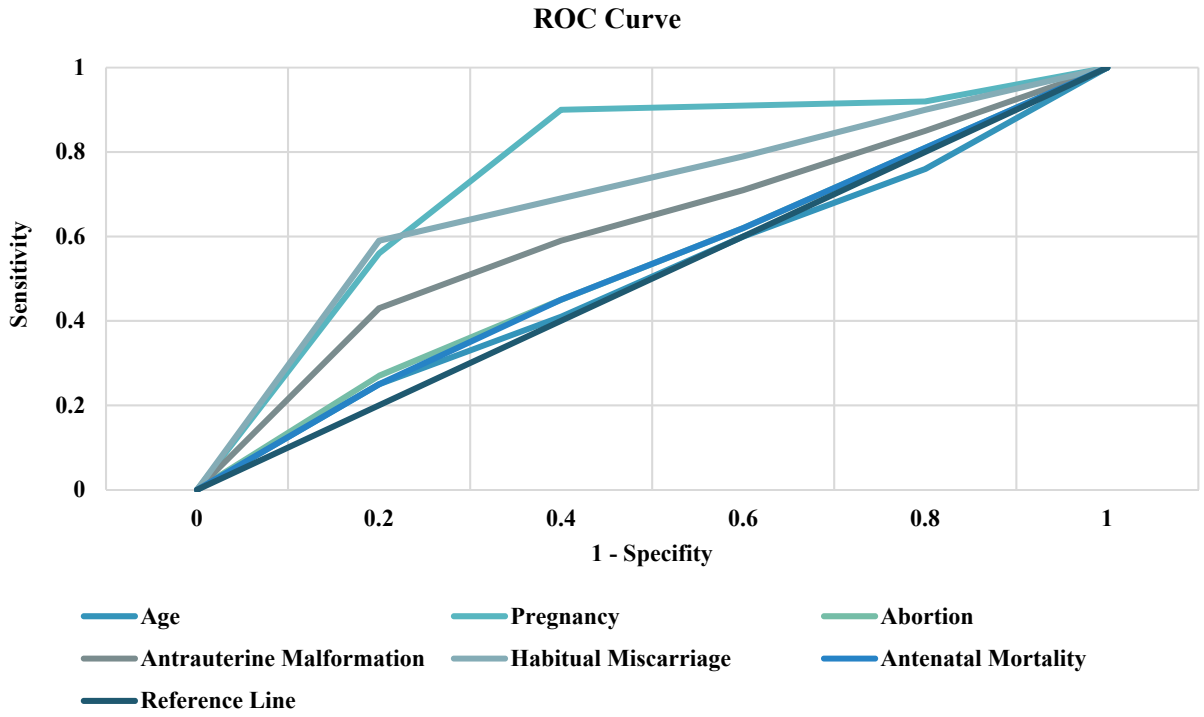
Table 4

Frequency of risk various factors in the examined patients

Indicators		N	M	±m	Standard error	95% CI		Minimal value	Maximum value
						lower limit	upper limit		
Age	absent	432	28.2	5.9	0.3	27.6	28.7	16	46
	present	233	27.8	5.3	0.3	27.1	28.5	16	46
	total	665	28.0	5.7	0.2	27.6	28.5	16	46
Pregnancy	absent	432	3.42	1.25	0.06	3.30	3.53	1	5
	present	233	2.08	1.35	0.09	1.91	2.26	1	5
	total	665	2.95	1.43	0.06	2.84	3.08	1	5
Abortion	absent	432	0.22	0.67	0.03	0.16	0.28	0	5
	present	233	0.14	0.65	0.04	0.05	0.22	0	5
	total	665	0.19	0.67	0.03	0.14	0.24	0	5
Intrauterine malformation	absent	432	0.59	0.88	0.04	0.50	0.67	0	5
	present	233	0.24	0.68	0.04	0.15	0.33	0	5
	total	665	0.47	0.83	0.03	0.40	0.53	0	5
Habitual miscarriage	absent	432	1.29	1.47	0.07	1.15	1.43	0	5
	present	233	0.37	0.94	0.06	0.25	0.50	0	5
	total	665	0.97	1.38	0.05	0.86	1.07	0	5
Antenatal mortality	absent	432	0.30	0.65	0.03	0.24	0.36	0	5
	present	233	0.21	0.56	0.04	0.13	0.28	0	4
	total	665	0.27	0.62	0.02	0.22	0.32	0	5

Note: N – number of patients; M – mean value; ±m – standard deviation; RI – reliability interval.

According to the results obtained (Table 4), and the previously conducted logistic regression analysis, the prognostic significance of the examined risk factors was determined. In particular, by evaluating the effectiveness of using variables such as age, pregnancy, abortion, intrauterine malformation, habitual miscarriage, and antenatal mortality for the group with pregnancy, it was determined that the positive prognostic value was 432, the negative prognostic value was 233. The obtained results were also confirmed by the analysis of ROC curves, which is demonstrated in the figure (Fig.).



Diagonal segments are produced by ties.

ROC-curve of parameters of age, pregnancy, abortion, intrauterine malformation, habitual miscarriage and antenatal mortality for the group with premature birth

According to the results of the analysis of ROC curves (Fig.), the most substantial AUC area was observed under the ROC curve, which displayed the gestational period indicator – 0.769 (95% CI: 0.729-0.809, Asymp. Sig=0), which indicates a large influence of this risk factor on the development of BD in a new-born. In addition, a large AUC area was established among the factors of habitual miscarriage – 0.699 (95% CI: 0.659-0.74, Asymp. Sig=0), intrauterine malformation – 0.630 (95% CI: 0.587-0.673, Asymp. Sig=0). In addition, according to statistical analysis, high sensitivity and specificity of the risk of BD development for the group of women with complicated pregnancy was identified at the gestation period of 1.5 weeks (1.467) and 2.5 weeks (1.384) earlier than the normal gestation period, respectively. In addition, high sensitivity and specificity were identified in the presence of a history of previously born children with intrauterine malformations at 0.5 (1.267) and miscarriages at 0.5 (1.393) and 1.5 (1.237). Consequently, gestation, intrauterine malformation, and early miscarriage had the highest sensitivity and specificity. The results of the values of variables in statistical tests are presented in the table (Table 5).

The Mann-Whitney criterion was used to verify and achieve greater accuracy of future indicators. Therewith, statistically substantial differences were established between the groups concerning factors such as premature pregnancy (F=163.149, p=0), intrauterine malformation (F=27.362, p=0), and the factor of having a habitual miscarriage in the anamnesis (F=73.898, p=0). Consequently, for the group with premature birth, a statistically substantial relationship is identified between the risk of BD formation and the following variables: the place of residence, pregnancy, abortion, intrauterine malformation, intrauterine malformation factor, habitual miscarriage, miscarriage factor, antenatal mortality, antenatal mortality factor, BD factor, BD, of methylenetetrahydrofolate reductase (MTHFR) polymorphism, HLA-DRB1 alleles, DQA1, DQB1, HLA alleles in various variants.

Table 5

Results of statistical analysis of values of variables in the group with childbirth

Variables	Mann-Whitney (U)	Wilcoxon W	Z	Asymptotic value
Age	49168.5	76429.5	-0.491	0.623
Place of residence	46526.5	73787.5	-1.971	0.049
Gestational period	23261.5	50522.5	-11.695	0
Abortion	46361	73622	-3.006	0.003
Intrauterine malformation	37273.5	64534.5	-6.711	0
Intrauterine malformation factor	36918	64179	-7.003	0
Habitual miscarriage	30247.5	57508.5	-9.447	0
Miscarriage factor	30525	57786	-9.766	0
Antenatal mortality	46773	74034	-2.161	0.031
Antenatal mortality factor	46803.5	74064.5	-2.152	0.031
BD factor	47493	74754	-2.257	0.024
BD	47548	74809	-2.209	0.027
MHTR	10286	18932	-4.004	0
DRB1	3606.5	8859.5	-5.143	0
DQA1	3812	9065	-4.579	0
DQB1	3541.5	8794.5	-5.380	0
HLA	2649	7902	-6.811	0
HLA total.	3286	8539	-6.47	0

The focus of this study on mothers with a history of premature birth and the associated increased risk of birth defects is of paramount importance. This emphasis is particularly relevant in light of the findings of Rundell and Panchal [26], which highlighted the necessity of managing and preventing preterm labor as a significant factor in neonatal health. Their work underscores the risks associated with premature births, aligning with our findings that such a history necessitates special attention due to the heightened risk of BD.

Moreover, the study by Chiabi et al. [27], which conducted a cross-sectional analysis of hospital records in Cameroon, further supports our findings by identifying premature births as a key risk factor for BD. This similarity across different geographical regions emphasizes the universal nature of these risk factors and the need for global healthcare strategies to address them. Our study's employment of logistic regression analysis to evaluate the main risk factors for the development of developmental anomalies in patients with a history of premature birth echoes the methodological approach of Daliri et al. [28]. Their systematic review and meta-analysis examined the relationship between neonatal and maternal factors during pregnancy and the prevalence of birth defects in Iran, providing an additional layer of validation to our analytical methods and findings.

The prognostic logistic model developed as part of our study provides a crucial tool for consulting with mothers who have a history of premature births. This model's predictive capability is a significant advancement in prenatal care, as it allows for early identification of risk factors, potentially leading to better management and prevention strategies. Kuhle et al. [29] explored a related area, examining health care utilization in children with fetal growth abnormalities. Their findings, which highlighted the long-term implications of prenatal and perinatal health issues, underline the importance of effective early prediction

models like the one developed in our study. Our analysis also sheds light on the prognostic significance of various risk factors for BD. Kamble et al. [30] conducted a similar exploration into the epidemiology of congenital anomalies, emphasizing the need for early identification and management of risk factors. This aligns with our findings, particularly regarding the importance of understanding the complex interplay of factors like HLA antigens, miscarriage, and MTHFR polymorphisms in the development of BD.

The research by Zhang et al. [31], which investigated how parental predictors jointly affect the risk of offspring congenital heart disease, resonates with our observations on the prognostic significance of specific HLA antigens. Their nationwide multicenter study based on the China birth cohort strengthens our conclusions regarding the broad applicability of these factors in predicting congenital conditions. Furthermore, the study by Modzelewski et al. [32], which looked at large-for-gestational-age diagnoses as a classifier for the risk of adverse perinatal outcomes, provides additional context to our finding regarding the maximum prognostic value during pregnancy. Their research, alongside the work of Rekawek et al. [33], who examined the association of large-for-gestational-age diagnoses during the second-trimester anatomy ultrasound with gestational diabetes and large-for-gestational-age at birth, highlights the criticality of maternal health monitoring throughout pregnancy.

In line with international research findings, our study adds to the body of evidence suggesting no significant ethnic differences in the influence of risk factors on the development of BD. This notion is crucial for the creation of standardized prenatal care guidelines and BD risk management strategies that can be applied globally. The work of Li et al. [34], who developed a prediction model for non-syndromic cleft lip with or without cleft palate, demonstrates the universality of these risk factors and the importance of precision in risk assessment. Our adherence to the PRISMA guidelines in conducting literature analysis, paralleling the systematic approach of Daliri et al. [28], ensured the selection of high-quality, relevant sources. This methodological rigor enhances the credibility of our study and its contributions to the existing literature on BD and prenatal risk factors.

In conclusion, our research significantly contributes to the understanding of BD and their associated risk factors, providing new insights and tools that can aid in better management and prevention. By aligning with and extending upon the findings of international studies, our research not only validates its methodologies and conclusions but also contributes to a more comprehensive understanding of factors influencing BD. This, in turn, can inform future research and clinical practices worldwide, ultimately aiming to improve outcomes in maternal and neonatal health.

CONCLUSIONS

1. Mothers with a history of premature birth deserve special attention, due to a substantial increase in the risk of birth defects in them. In this regard, through logistic regression analysis, the main risk factors for the development of developmental anomalies in such patients were calculated and evaluated.
2. Based on the conducted study, a substantial statistical relationship was identified between the variables: pregnancy, intrauterine malformation, miscarriage, polymorphism of methylenetetrahydrofolate reductase, antigens DRB1, DQA1, DQB1 of the human leukocyte antigen system.
3. The obtained prognostic logistic model can be used when consulting mothers with a history of premature birth.
4. Through the conducted analysis of variance, it was possible to determine the prognostic significance of the above risk factors for the development of birth defects.
5. It was established that the maximum value of prognostic significance was during pregnancy – 43.17% ($p<0.001$).
6. The frequency of the combined variant of the human leukocyte antigens (24.9%, $p<0.001$), the miscarriage factor (16.77%, $p<0.001$), the frequency of DQB1 (15.99%, $p<0.001$), DRB1 (14.43%, $p<0.001$) also had high prognostic significance for the development of birth defects.
7. The results were similar to those of foreign researchers, which confirms the reliability of the results and indicates that there is no ethnic difference in the influence of risk factors on the development of birth defects.

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