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Risk factors associated with congenital clubfoot in children

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Abstract

Introduction Congenital clubfoot is a frequent malformation of the lower extremities. However, the causes of this pathology in children are still unclear. The identification of the factors associated with congenital clubfoot is a relevant problem, the solution of which will allow a prenatal prevention of clubfoot in newborns thus reducing the number of patients with this pathology.

Purpose The search for possible risk factors leading to a violation of foot development in the fetus and their significance in the occurrence of congenital clubfoot in children.

Materials and methods The study was of retrospective nature and was carried out in pairs "Mother-Newborn". It included examination of 149 children. The first group (n = 97) was compiled by the "Mother Newborn" pairs, in which the child had a typical form of congenital clubfoot; the second group (n = 52) were pairs in which the baby was healthy. The data obtained were processed using tables 2×2 and logistics regression.

Results According to the results of the study, it was found that the greatest sensitivity and specificity of congenital clubfoot was associated with the external factor of nicotine dependence in pregnant women (SE = 0.32; SP = 0.90) and the factor of hereditarily burdened congenital foot pathology in close relatives (SE = 0.16; SP = 0.98). An acute respiratory viral infection in the anamnesis, anemia in a pregnant woman or toxicosis did not show statistically significant causal connection with the occurrence of congenital clubfoot according to the analysis using the method of logistics regression ($p > 0.05$) and they should not be used as prognostic ones.

Discussion The data obtained by us on the paramount significance of the two "risk" factors of the congenital clubfoot development (nicotine dependence in a pregnant woman and hereditarily burdened disorder of congenital foot pathology among close relatives) were reflected only in a few scientific sources.

Conclusion The risk factors of the greatest sensitivity, specificity and causal relationship with the congenital clubfoot development were associated with the adverse effects of the external factor of nicotine dependence during pregnancy and burdened heredity associated with congenital foot pathology in close relatives ($p < 0.05$).

Keywords: pregnancy, children, congenital clubfoot, risk factors, nicotine dependence, heredity

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INTRODUCTION

The World Health Organization estimates that more than 100 thousand children worldwide are born with congenital clubfoot every year. Congenital clubfoot is a common malformation of the lower extremities and ranks second among deformities of the musculoskeletal system. The first place in terms of incidence is taken by the pathology of fingers and toes (38.16 %), foot deformities are in the second place (21.95 %), and the third place is taken by congenital deformities of the femur (13.73 %) [1–3]. The incidence of congenital clubfoot among the population of the Russian Federation is average and amounts to 1–3 cases per one thousand newborns [4–6]. There is a tendency of a growing number of children born with congenital clubfoot [7–8].

It should be noted that bilateral congenital clubfoot is more frequent than the unilateral one [9–11]; among males, congenital clubfoot occurs several times more frequently and the ratio to females is from 2.5:1 to 1.1: 1 [12–13]. In 15–30 % of cases, congenital clubfoot is closely related to other developmental anomalies of the musculoskeletal system, such as congenital dislocation of the hip, fusion of fingers and toes, muscular torticollis, amniotic bands of various locations, spina bifida [14–18].

To date, it has been proven that congenital anomalies in fetal development occur much more frequently in pregnant women living in environmentally poor conditions, exposed to dangerous carcinogenic effects at work, experiencing nicotine and alcohol intoxication, and also having sexually transmitted infections such as chlamydia, mycoplasmosis, herpesvirus [19–24]. However, there are very few studies devoted to the role of risk factors in the occurrence of congenital foot deformities [25]. Despite the fact that congenital clubfoot is a disease that has been known for a long time, and significant progress has been made in the treatment of this pathology, the causes of congenital clubfoot in children are still not clear. There is no complete unanimity among researchers on any of the existing theories. At the present stage of the development of medicine, scientists have been discussing various theories of congenital clubfoot occurrence, giving priority to certain factors that, having a negative impact on the body of the expectant mother in the first trimester of pregnancy, can disrupt the proper maturation of the fetus and, in particular, cause abnormal foot development. Data vary on the significance of such external risk factors affecting the fetus and influencing the development of clubfoot, such as smoking, alcohol, diabetes mellitus, acute respiratory infections and others.

Given the frequency of congenital clubfoot among the total number of newborns, severe consequences of the pathological process associated with a high rate of relapses of foot deformities (35–64 %), patients' disability, the detrimental effect of the anatomical defect in the feet on the physical and mental development of the child [26, 27], the search for risk factors causing clubfoot in the fetus is extremely relevant. Identification of risk factors that have the most damaging effect during the formation of organs and systems of the unborn child and lead to congenital clubfoot would enable to carry out prenatal prevention of clubfoot in newborn children thus reducing the number of patients with this pathology.

Purpose To identify possible risk factors leading to foot mal-development in the fetus, and determine their significance in the incidence of congenital clubfoot in children

MATERIALS AND METHODS

During 2017–2022, we examined 97 patients with congenital clubfoot who were admitted for surgical treatment to the children's department of traumatology and orthopaedics of the Privolzhsky Medical Research University (PMRU), and 52 practically healthy children who visited an orthopaedist at the PMRU outpatient clinic. The age of the patients was from 1 to 12 months. The study was retrospective, conducted in pairs "mother-newborn" based on observation (examination) data of 149 children. The method of interviewing mothers was used and the form 113/y (information from the maternity hospital, maternity ward of the hospital about the newborn) was studied. Inclusion criteria were a typical congenital clubfoot diagnosed in the child of the first group of patients; and the second group there was practically healthy children. In both groups, the mother's informed voluntary consent to participate in the study was obtained. Risk factors that were associated with malformations were identified using the "case-control" method based on a comparative analysis of obstetric and gynecological history and data from the form 113/y in two groups. The

first group (n = 97) consisted of "mother-newborn" pairs, in which the child had a typical congenital clubfoot; the second (n = 52) were pairs in which the baby was practically healthy.

The clubfoot grade was determined with the Dimeglio scoring system [28].

In the first group, which included 97 children (150 feet) with congenital clubfoot, all types of congenital clubfoot were represented, depending on the severity of the foot deformity (Table 1).

Table 1

Distribution of clubfoot depending on the severity of the deformity in children with congenital clubfoot

Severity grade	Number			
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	N	%	N	%
Grade I–II	15	15.5	23	15.3
Grade III	33	34.0	47	31.3
Grade IV	49	50.5	80	53.3
Total	97	100	150	100

Statistical processing of the study results was carried out using the Statistika 12.0 application package. In statistical analysis, the objective quantitative characteristics of risk factors were absolute risk (Absolute risk, R), reduction in absolute risk (Atributable risk, AR), relative risk (RR). Specificity (Sp) of the risk factor and sensitivity (Se) were calculated using 2 × 2 tables in the exposed (with the presence of the risk factor) and control (without the risk factor) groups. We determined the odds ratio (OR) and probability (P_+) of developing congenital clubfoot in a newborn according to analysis using the logistic regression method. To test the statistical significance of differences in the compared groups, the Pearson test (χ^2) was used. Differences were considered significant at $p < 0.05$.

RESULTS

The average weight at birth of children with congenital clubfoot was comparable to this indicator in healthy children (p = 0.37). After comparing the average body length in children of the two groups, no statistically significant differences were found (p = 0.31), and no significant differences were found in the average number of Apgar scores (p = 0.13) (Table 2).

The age of mothers at the time of delivery was practically the same in the groups (p = 0.47), and there were also no statistically significant differences in the height of mothers (p = 0.13). There was no significant difference after comparing mothers' weight in the groups (p = 0.08). The difference in the number of pregnancies among the mothers was statistically insignificant (p = 0.16), the number of deliveries was also statistically insignificant (p = 0.17) (Table 3).

Table 2

Average indicators in newborns with congenital clubfoot and practically healthy children (Mann – Whitney test)

Parameter	Group 1 (n = 97)	Group 2 (n = 52)	p-level
Weight at birth, g	3271.75 ± 593.6	3401.27 ± 509.7	0.37
Height at birth, cm	51.04 ± 3.31	51.50 ± 3.06	0.31
Apgar score	7.78 ± 0.74	7.65 ± 0.65	0.13

Table 3

Characteristics and obstetric history of the examined women (Mann – Whitney test)

Parameter	Mothers of children with clubfoot (group 1)	Mothers of healthy children (group 2)	p
Age, years	29.62 ± 5.12	30.23 ± 4.92	0.47
Height, cm	164.73 ± 6.62	166.25 ± 5.13	0.13
Weight, kg	67.16 ± 17.71	63.17 ± 12.93	0.08
Number of pregnancies	2.43 ± 1.54	1.98 ± 1.07	0.16
Number of deliveries	1.80 ± 0.78	1.62 ± 0.74	0.17

Thus, the compared groups did not differ from each other in terms of main indicators and could be used to identify risk factors for congenital clubfoot. Only those factors that could have a direct impact on the intrauterine formation of the fetus were analyzed, with the establishment of cause-and-effect relationships leading to the development of congenital clubfoot (Fig. 1).

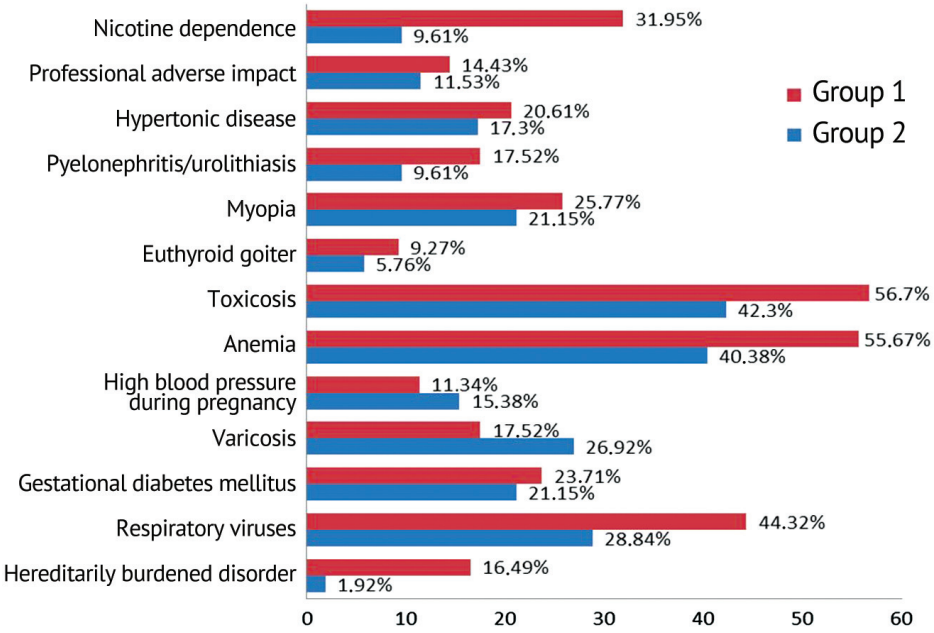

Fig. 1 Incidence of certain identified conditions/diseases and/or complications of pregnancy in mothers of children with congenital clubfoot and in mothers of healthy children

Most of the women of the first and second groups had chronic pathology before the onset of the studied pregnancy. A retrospective analysis of the obstetric anamnesis revealed that the mothers of the examined children in both groups had some pathology during pregnancy. Thus, in the first group, toxicosis was most common in 55 (56.7 %) women, hypertension in 20 (20.6 %) pregnant women. In women of the second group, toxicosis was diagnosed in 22 (42.3 %) cases, pregnancy hypertension in 9 (17.3 %). When studying the genealogical history data, congenital foot pathology in close relatives was revealed in 16 (16.49 %) children of the first group. In the second group, a family history of congenital foot defects was detected in only 1 child (1.92 %).

Using the method of correlation analysis, it was determined that the birth of a child with congenital clubfoot is associated with a number of factors that could serve as risk factors for the occurrence of this disease (Table 4).

Table 4

Determination of factors associated with congenital clubfoot (results of correlation analysis, γ)

Factor	γ	*p*
Professional adverse effects	0.13	0.46
Nicotine dependence in a pregnant woman	0.63	0.001*
Acute respiratory viral infections (ARVI)	0.32	0.006*
Anemia in pregnancy	0.30	0.008*
Toxicosis in pregnancy	0.31	0.005*
Gestational diabetes mellitus	0.07	0.60
Hereditarily burdened disorder	0.81	0.001*
Varicose disease	– 0.26	0.051
High blood pressure in pregnancy	0.14	0.32
Euthyroid goiter	0.24	0.29
Myopia	0.20	0.13
Pyelonephritis/ urolithiasis	0.33	0.054

Note: * — statistically significant ($p \leqslant 0.05$)

There was a correlation between the occurrence of congenital clubfoot and certain risk factors associated with physical health and a number of conditions in pregnant women. Thus, there is a moderate positive correlation of high significance ($\gamma = 0.630666$ at $p = 0.001$) between the occurrence of congenital clubfoot in a child and nicotine addiction in the mother. A moderate positive correlation was determined between the occurrence of congenital clubfoot in a child and anemia in pregnant women ($\gamma = 0.30$ at $p = 0.008$), ARVI ($\gamma = 0.32$ at $p = 0.006$) and toxicosis in pregnant women ($\gamma = 0.31$ at $p = 0.005$).

In the process of correlation analysis, a strong positive relationship of a high degree of significance was revealed between the risk of congenital clubfoot and a family history of congenital foot malformations ($\gamma = 0.81$ at $p = 0.001$). Thus, the identified risk factors may have an adverse effect during the period of intrauterine development of the fetus and be the cause of congenital clubfoot in the newborn.

Risk factors for congenital clubfoot were those associated with a family history of congenital foot deformity in close relatives (RR = 1.53 ± 0.09 [1.28–1.83], $p = 0.007$). Risk factors associated with the adverse effects of external factors during pregnancy: nicotine dependence in women (RR = 1.47 ± 0.10 [1.20–1.80], $p = 0.002$), a history of acute respiratory viral infection (RR = 1.25 ± 0.11 [0.99–1.56], $p = 0.06$). Risk factors associated with the somatic health of pregnant women leading to congenital clubfoot: toxicosis during pregnancy (RR = 1.22 ± 0.12 [0.96–1.55], $p = 0.09$), anemia in pregnant women (RR = 1.23 ± 0.12 [0.97–1.57], $p = 0.07$).

Despite the significant risk indicators, the sensitivity of the occurrence of congenital clubfoot to the action of the identified factors was not high and even low; and noticeably (1.61 times or more) inferior to their specificity. The greatest sensitivity and specificity for the occurrence of congenital clubfoot was for factors associated with the adverse effect of the external factor, namely, nicotine addiction in pregnant women (SE = 0.32; SP = 0.90) during pregnancy, and the factor associated with a family history of congenital foot pathology in close relatives (SE = 0.16; SP = 0.98) (Table 5).

Table 5

Risk factors associated with congenital clubfoot

Risk factor	Group 1 (n = 97)		Group 2 (n = 52)		R_1	R_2	AR	RR ± S [95 % CI]	χ^2	p	Se	Sp
	abs	%	abs	%								
Nicotine dependence	31	31.95	5	9.61	86.1	58.4	27.7	1.47 ± 0.10 [1.20–1.80]	9.22	0.002	0.32	0.90
Acute respiratory virus infections (ARVI)	43	44.32	15	28.84	74.1	59.3	14.8	1.25 ± 0.11 [0.99–1.56]	3.41	0.06	0.44	0.71
Anemia in pregnancy	54	55.67	21	40.38	72.0	58.1	13.9	1.23 ± 0.12 [0.97–1.57]	3.16	0.07	0.55	0.59
Toxicosis	55	56.7	22	42.38	71.4	58.3	13.1	1.22 ± 0.12 [0.96–1.55]	2.81	0.09	0.56	0.57
Hereditarily burdened disorder	16	16.49	1	1.92	94.1	61.4	32.8	1.53 ± 0.09 [1.28–1.83]	7.11	0.007	0.16	0.98

Note: R_1 — absolute risk in the exposed (with the presence of a risk factor) group, R_2 — absolute risk in the control (absence of a risk factor) group, AR — attributable risk, RR — relative risk, S — standard error of the relative risk, [95 % CI] — 95 % confidence interval of the relative risk, χ^2 — Pearson test, p — level of statistical significance of the relative risk, Se — sensitivity to the risk factor, Sp — specificity of the risk factor.

Certain (single) factors among those identified revealed a cause-and-effect relationship in the occurrence of congenital clubfoot in a newborn according to analysis using the logistic regression method: factors associated with the adverse effects of external factors during pregnancy: nicotine addiction in women (OR = 4.41 ± 0 .51 [1.59–12.19], $p = 0.001$). The probability of congenital clubfoot under the influence of this factor was quite high ($P_+ = 0.81$). Factor associated with a family history of congenital foot pathology among close

relatives: (OR = 10.07 ± 1.04 [1.29–78.29], $p = 0.003$), and the likelihood of congenital clubfoot under the influence of this factor was also quite high ($P_+ = 0.90$). A history of acute respiratory viral infection, anemia in pregnant women, and toxicosis in pregnant women did not show a statistically significant cause-and-effect relationship with the occurrence of congenital clubfoot according to analysis using the logistic regression method ($p > 0.05$) (Table 6).

Table 6

Odds ratio and probability of congenital clubfoot in the presence of certain factors (based on logistic regression)

Risk factor	OR ± S [95 % CI]	P_+	B_1	B_0	χ^2	p
Nicotine dependence	4.41 ± 0.51 [1.59–12.19]	0.81	1.48	–3.72	10.29	0.001
Acute respiratory virus infections	1.96 ± 0.36 [0.95–4.04]	0.66	0.67	1.57	3.48	0.06
Anemia during pregnancy	1.85 ± 0.34 [0.93–3.67]	0.64	0.61	–1.00	3.17	0.07
Toxicosis during pregnancy	1.78 ± 0.34 [0.90–3.52]	0.64	0.57	–1.04	3.62	0.06
Hereditarily burdened disorder	10.07 ± 1.04 [1.29–78.29]	0.90	2.30	6.24	9.03	0.003

Note: OR — odds ratio, S — standard error of the odds ratio, [95 % CI] — 95 % confidence interval of the odds ratio; P_+ — probability of congenital clubfoot; B_1 is the regression coefficient of the independent "risk" factor i; B_0 is the free member in the regression equation; χ^2 — Pearson test; p is the level of statistical significance of the regression level

DISCUSSION

Currently, there is no unity in the views on the etiopathogenesis of congenital clubfoot. Proponents of the mechanical theory (intrauterine immobility) of congenital clubfoot explain the occurrence of the deformity by mechanical effects on the fetus during its intrauterine development. Increased intrauterine pressure, oligohydramnios and, as a result, a reduced volume of the uterine cavity lead to excessive immobilization of joints, disruption of tissue trophism, developmental delay and curvature of developing bones [29]. However, a fairly large group of researchers believes that the role of intrauterine pressure as one of the causes of the development of congenital clubfoot has not been proven [30–31].

The theory of congenital defects of the embryo explains the occurrence of congenital clubfoot by a violation of the anlage and delayed development of the foot at one of the stages of embryogenesis [32]. Proponents of the neuromuscular theory believe that the main cause of congenital clubfoot is associated with a malformation of the spinal cord, namely with improper closure of the medullary tube (dysraphism), which ultimately leads to disruption of the innervation of the lateral and, to a lesser extent, the anterior group of muscles of the leg [33 –35]. Patients with congenital clubfoot show a direct relationship between the severity of the deformity and the level of neurological deficit [36–37].

Our studies have shown that the most significant risk factor for the development of congenital clubfoot, associated with the adverse effects of external factors during pregnancy, is nicotine addiction in women.

The study of the risk factors associated with the adverse effects of external factors during pregnancy showed the following results: nicotine dependence in women (RR = 1.47 ± 0.10 [1.20–1.80], $p = 0.002$), acute history of respiratory viral infection (RR = 1.25 ± 0.11 [0.99–1.56], $p = 0.06$). Risk factors associated with the somatic health of pregnant women leading to congenital clubfoot: toxicosis during pregnancy (RR = 1.22 ± 0.12 [0.96–1.55], $p = 0.09$), anemia of pregnant women (RR = 1.23 ± 0.12 [0.97–1.57], $p = 0.07$). Although the risk indicators were significant, the sensitivity of the occurrence of congenital clubfoot to the action of the identified factors was low and noticeably (1.61 times or more) inferior to their specificity, with the exception of such a factor as nicotine addiction (SE = 0.32; SP = 0.90). A number of factors revealed a cause-and-effect relationship in the occurrence of congenital clubfoot in a newborn according to logistic regression analysis: factors associated with the adverse effects of external factors during pregnancy: nicotine addiction

in women (OR = 4.41 ± 0, 51 [1.59–12.19], p = 0.001). The probability of congenital clubfoot under the influence of this factor was quite high (P_+ = 0.81). A history of acute respiratory viral infection, anemia in pregnant women, and toxicosis in pregnant women did not reveal a statistically significant cause-and-effect relationship with congenital clubfoot according to analysis using the logistic regression method ($p > 0.05$).

Our data confirmed a number of works by foreign authors, who also stated the negative impact of nicotine addiction in pregnant women on the development of congenital clubfoot [38–39]. The domestic literature shows a close relationship between mothers's smoking habit during pregnancy and the occurrence of a variety of developmental defects: intrauterine growth retardation, clefts of the hard and soft palate, cardiovascular system defects, etc., but did not indicate a clear relationship between this bad pregnant women;s habit and the birth of a child with congenital clubfoot [41].

The relationship between the birth of a child with congenital clubfoot and nicotine addiction may be due to the teratogenic effect of nicotine and combustion products. Nicotine easily penetrates the placenta and has a direct effect on fetal tissue. The damaging effect of tobacco smoke derivatives is directed directly at the fetus, which leads to the occurrence of congenital pathological anomalies of the fetus [41].

The second most significant risk factor for the development of congenital clubfoot, according to our data, is a factor associated with a family history of congenital foot pathology among close relatives. The risk of congenital clubfoot associated with a family history of congenital malformations was significant (RR = 1.53 ± 0.09 [1.28–1.83], p = 0.007). At the same time, the highest sensitivity and specificity for the occurrence of congenital clubfoot was determined (SE = 0.16; SP = 0.98). A factor associated with a family history of congenital foot pathology among close relatives (OR = 10.07 ± 1.04 [1.29–78.29], p = 0.003), while the likelihood of congenital clubfoot under the influence of this factor was also residually high (P_+ = 0.90).

The relationship we have identified between congenital clubfoot in a child and a family history of foot developmental anomalies in close relatives is reflected in a number of works by foreign authors who put forward a genetic theory of inheritance of this disease [42]. Currently, the genetic theory is the leading one and has gained support among a large group of researchers [43–45].

CONCLUSION

The greatest sensitivity, specificity and cause-and-effect relationship with congenital clubfoot was shown by adverse effects of such external factor as nicotine dependence during pregnancy and association with a family history of congenital foot pathology in blood relatives ($p < 0.05$). These risk factors, having an adverse impact on the formation and development of the fetus, are the cause of congenital clubfoot and can be used in predicting and preventing congenital clubfoot.

Risk factors such as acute respiratory viral infection during pregnancy, anemia in pregnant women, toxicosis during pregnancy, had low sensitivity, poor specificity and did not show a significant cause-and-effect relationship with congenital clubfoot ($p > 0.05$); and they should not be used as prognostic ones.

Conflict of interest *The authors declare no conflict of interest.*

Funding *The study was conducted without sponsorship.*

Ethical statement *The study was conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", as amended in 2013, in compliance with the principles of research safety, awareness, consent, and confidentiality.*

Informed consent *All patients or their legal representatives signed informed consent to participate in the study and publish data without personal identification.*

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