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Risk factors for cleft lip and palate in the Czech population – a double center study

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Summary

Background: Orofacial clefts (OFC) are common congenital anomalies with complex genetic and environmental etiologies. Although multiple risk factors have been suggested, their role in cleft type and severity remains unclear. **Objective:** This study aimed to assess the relationship between environmental and maternal health factors (body mass index – BMI, parental age, infection, stress, prenatal vitamin supplementation) and the occurrence and severity of cleft types in the Czech population, as well as the effectiveness of prenatal diagnosis by ultrasound. **Methods:** A total of 96 parents of children with nonsyndromic OFC born between 2017 and 2024 in the Czech Republic were surveyed using a custom online questionnaire (RoRis). The data were analyzed using Fisher's exact test ($\alpha = 0.05$). **Results:** The distribution of cleft types in this Czech sample was consistent with international data. Prenatal diagnosis by ultrasound was established in 55% of cases. The highest detection rates were observed for bilateral cleft lip and palate, with 100% of cases diagnosed prenatally, and for unilateral cleft lip and palate, with a 93% detection rate. In contrast, cleft palate only (CPO) was the most frequently missed, with 88% of cases undetected. No significant associations were found neither between the cleft type nor the severity of clefts and parental age, maternal BMI, medication use, infection with fever, or stress during pregnancy. Most mothers had a normal BMI (51%), and 85% reported prenatal supplement use. COVID-19 infection during pregnancy was reported in 13 cases, but no clear link with cleft severity was found. **Conclusion:** While several exogenous factors were studied, no significant associations neither with cleft type nor severity were found. The study highlights the limitations of prenatal screening diagnosis by ultrasound, particularly for CPO, and supports the need for further research into modifiable risk factors.

Key words

orofacial clefts – cleft lip and palate – cleft palate only – risk factors – prenatal diagnosis – BMI – cleft severity

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Introduction

Orofacial clefts (OFC) are the most common congenital craniofacial anomalies, affecting approximately 1.64 in 1,000 live births in the Czech Republic [1]. OFC may adversely affect patients' quality of life in physical, functional, and psychological domains [2]. OFC arise due to disruptions in normal embryonic development. Cleft lip results from a failure of merging between the medial nasal and maxillary prominences during the 5th to 6th week of gestation, while cleft palate results from a failure of fusion of the palatal shelves between the 6th and 12th week of gestation [3].

The etiology of OFC is multifactorial, involving a complex interplay of genetic and environmental factors that influence craniofacial morphogenesis. Understanding these etiological mechanisms is crucial for advancing preventive strategies, early diagnosis, and targeted therapeutic approaches. Genetic predisposition plays a significant role in OFC development, with numerous candidate genes identified through genome-wide association studies and linkage analyses [4]. However, the genetics of OFC is highly heterogeneous, with rare high-penetrance mutations and common low-effect variants contributing to disease susceptibility. Beyond genetic influences, various environmental factors have been implicated in OFC pathogenesis, including parental age, medications during pregnancy, maternal smoking, alcohol consumption, nutritional deficiencies or abundance, teratogenic exposures and others [5,6]. Maternal health conditions such as malnutrition or obesity, infections accompanied by fever or stressful situations have also been linked to an increased risk of OFC [7,8]. Epigenetic modifications, including DNA methylation and histone modifications, may further mediate the interaction between genetic susceptibility and environmental exposures [9].

Prenatal diagnosis of orofacial clefts plays a crucial role in early counseling, treatment planning, and psychological preparation of the parents [10]. These anomalies are typically identified during routine ultrasound screening in the first or second trimester, although the reported sensitivity of prenatal detection varies considerably, depending on the cleft type, the examiner's expertise, and imaging quality [11,12]. Early identification of these anomalies enables a multidisciplinary approach to postnatal care and may reduce parental anxiety by providing timely information about prognosis and therapeutic options.

The aim of this study was to investigate, through a questionnaire-based survey, whether environmental factors and maternal health conditions may influence the occurrence of a specific type of cleft or the severity of cleft involvement in the Czech Republic. Furthermore, this study focused on assessing the rate of prenatal detection of OFC.

Materials and methods

Study design

A detailed questionnaire titled "RoRis" (https://registr-roris.data-warehouse.zone/) was developed for parents of children with orofacial clefts. Ethical approval was obtained in advance from local ethics committees (UH Brno approval number 08-061223/EK, FNKV approval number EK-YPI29I0012024), and the study was conducted in accordance with the Declaration of Helsinki and the applicable legal regulations of the Czech Republic.

The questionnaire was implemented as an internet-based tool by the Institute of Biostatistics and Analyses, Ltd. (IBA), a spin-off company of Masaryk University, Brno. Parents of affected children could access the questionnaire through a time-limited link containing a unique hash code, which was sent to the email address provided during registration or by a leaflet given during the medical appointment.

The questionnaire focused on potential etiological factors contributing to the occurrence of cleft anomalies in children including parental age, maternal pre-pregnancy weight and height (with body mass index (BMI) calculated), medication use during pregnancy, infections accompanied by fever, and stressful situations experienced during pregnancy. Particular attention was given to the intake of prenatal vitamins. Cleft severity was considered when evaluating the associations with parental age, maternal BMI, medication use during pregnancy, infections with fever, and stressful situations during pregnancy. Unilateral cleft lip was considered the least severe and bilateral cleft lip and palate the most severe, while isolated cleft palate was not included in this assessment due to a different embryological mechanism of origin.

Study participants and variables

The questionnaire was distributed to parents of children born between 2017 and 2024 and treated in Prague Cleft Center (PCC) of University Hospital Královské Vinohrady (FNKV) and Cleft Center of the University Hospital Brno (CC UH Brno). All participants were divided into 5 groups according to a cleft type: UCL – unilateral cleft lip, UCLP – unilateral cleft lip and palate, BCL – bilateral cleft lip, BCLP – bilateral cleft lip and palate, CPO – cleft palate only. For evaluation of parents' age at the start of pregnancy mothers and fathers of all participants were divided according to their age into 3 categories according to previous studies [13]: 1) young: up to 25.9 years; 2) middle age: 26–35 years; 3) mature: 35.1 years and more. Mother's BMI at conception was calculated using the mother's weight and height according to standard methods, and the following categories were established: 1) BMI < 18.5: underweight; 2) BMI 18.5–24.9: normal weight; 3) BMI 25–29.9: overweight; 4) BMI > 30.0: obesity.

Statistical analysis

The collected data were statistically analyzed, assessing the null hypotheses that the distributions/central tendency or frequencies between groups do not differ significantly on a significance level of $\alpha = 0.05$. The Fisher's exact test was employed for categorical variables. For statistical analysis, the IBM SPSS Statistics for Windows, Version 23.0 software (Armonk, NY: IBM Corp) was used.

Results

This study presents the results from the first 6 months of data collection, spanning from May 20 to November 20, 2024. Within the PCC 145 parents were contacted by mail, and approx. 35 by a leaflet, while within the CC UH Brno 114 parents were contacted by mail/phone, and approx. 100 by a leaflet. During the first 6 months of data collection, 108 parents completed the questionnaire, a total of 12 questionnaires were excluded due to missing essential information, including the type of cleft and key patient identification data. The whole amount of included study participants was therefore 96 (54 males, 42 females). No patient included in the study had a confirmed syndromic diagnosis.

Prenatal diagnosis of cleft anomaly

Cleft anomaly was diagnosed prenatally by ultrasound in 53 (55%) out of 96 children. All BCLP cases were detected prenatally, and 26 out of 28 UCLP cases (93%) were identified before birth. In contrast, 7 UCL cases (39%) were not diagnosed prenatally. CPO was the most frequently missed in prenatal screening, with 36 cases (88%) going undetected.

Cleft type and gender

The study included a total of 96 patients with a male-to-female ratio of 54 : 42. The distribution of cleft types was as follows: BCLP in 10 patients, UCLP in 28 patients, UCL in 18 patients, and CPO in 41 patients. BCL was not observed in any of the patients included in the study. Regarding the laterality of the unilateral clefts, left-sided UCLP was observed in 20 patients and left-sided UCL in 10 patients, while right-sided UCLP was present in 8 patients and right-sided UCL in 8 patients. Males predominated the sample, especially in the BCLP, UCLP and UCL (Tab. 1), however the male/female ratio for each type of cleft did not differ significantly (P = 0.388). Male-to-female ratio for UCL + UCLP was 1.7 : 1; in CPO it was 0.86 : 1.

Tab. 1. Sample characteristics by type of cleft and gender.

Gender	BCLP	UCLP		UCL		CPO	Total
		left	right	left	right		
male	7	13	5	5	5	19	54
female	3	7	3	4	3	22	42
total	10	20	8	9	8	41	96

BCLP – bilateral cleft lip and palate, CPO – cleft palate only, UCL – unilateral cleft lip, UCLP – unilateral cleft lip and palate

Tab. 2. Association of mothers' age categories with the type of cleft.

Fisher's exact test: P = 0.822	Mother's age (years) < 26	26–35	> 35	Total
BCLP	1 10.0%	8 80.0%	1 10,0%	10 100.0%
UCLP	3 11.5%	19 73.1%	4 15.4%	26 100.0%
UCL	0 0.0%	13 76.5%	4 23.5%	17 100.0%
CPO	4 10.0%	27 67.5%	9 22.5%	40 100.0%
Total	8 8.6%	67 72.0%	18 19.4%	93 100.0%

BCLP – bilateral cleft lip and palate, CPO – cleft palate only, UCL – unilateral cleft lip, UCLP – unilateral cleft lip and palate

Parental age and cleft type

The average parental age was 30 years and 7 months for mothers and 37 years and 8 months for fathers (Tab. 2, 3). Parental age categories showed no association with the type of cleft (P = 0.822; P = 0.808). Furthermore, advancing parental age was not correlated with increased cleft severity (P > 0.005).

Mother's BMI

The average maternal BMI was 25, with 46 mothers within the optimal range (Tab. 4). The maternal BMI category was not associated with the type of cleft in the child, nor was a higher maternal BMI linked to increased cleft severity (P = 0.265).

Medication of the mother during pregnancy

Eighty mothers (85%) reported taking prenatal supplements during pregnancy, starting upon confirmation of pregnancy, including folic acid (N = 35) or prenatal vitamins (N = 45), while 14 mothers (15%) did not take any supplements. The absence of prenatal folic acid intake was not associated with the most severe cleft types (6 CPO, 7 UCLP, and 1 UCL). A total of 30 mothers (31.3%) reported regular medication use during pregnancy, including treatment for asthma, hypertension, hypothyroidism, progesterone supplementation, low molecular weight heparin (LMWH), or allergy medication. Maternal medication use was not associated with the type of cleft in the child, nor did it contribute to increased cleft severity (P > 0.005)

Infections and stressful situations during pregnancy

During pregnancy, 26 women experienced an infection with fever during the first trimester, while 16 reported encountering a stressful situation. Additionally, five women experienced both stress and fever, with cleft types varying among their children. Neither factor was linked to a specific type of cleft in the child, nor did either lead to increased cleft severity (P > 0.005). Thirteen mothers contracted COVID-19 during pregnancy, confirmed by PCR testing, seven of whom were affected in the first trimester.

Discussion

The distribution of cleft types in our sample was consistent with data reported in the literature and well-established epidemiological patterns [14]. Boys were predominant in cases of UCL and UCLP, whereas the male-to-female ratio in CPO was more balanced, with a slight predominance of females. In both genders, left-sided occurrence was more common in UCLP and UCL. Prenatal diagnosis was established in approximately half of all

Tab. 3. Association of fathers' age categories with the type of cleft.

Fisher's exact test: P = 0.808	Father's age (years) < 26	26–35	> 35	Total
BCLP	0 0.0%	6 60.0%	4 40.0%	10 100.0%
UCLP	1 3.8%	15 57.7%	10 38.5%	26 100.0%
UCL	0 0.0%	7 41.2%	10 58.8%	17 100.0%
CPO	3 7.7%	19 48.7%	17 43.6%	39 100.0%
Total	4 4.3%	47 51.1%	41 44.6%	92 100.0%

BCLP – bilateral cleft lip and palate, CPO – cleft palate only, UCL – unilateral cleft lip, UCLP – unilateral cleft lip and palate

Tab. 4. Association of maternal BMI categories with the type of cleft.

Fisher's exact test: P = 0.265	BMI Under-weight	Normal	Over-weight	Obesity	Total
BCLP	1 11.1%	2 22.2%	3 33.3%	3 33.3%	9 100.0%
UCLP	3 11.1%	16 59.3%	6 22.2%	2 7,4%	27 100.0%
UCL	0 0.0%	10 62,5%	5 31,3%	1 6.3%	16 100.0%
CPO	4 10.5%	18 47.4%	7 18.4%	9 23.7%	38 100.0%
Total	8 8.9%	46 51.1%	21 23.3%	15 16.7%	90 100.0%

BCLP – bilateral cleft lip and palate, CPO – cleft palate only, UCL – unilateral cleft lip, UCLP – unilateral cleft lip and palate

children with cleft lip and palate. In our sample, all cases of BCLP and the majority of cases with UCLP were identified before birth, while almost half of the UCL remained undiagnosed prenatally. The fact that more severe forms of clefts are detected more frequently prenatally represents a positive prognostic factor, as it allows for early intervention planning and parental counseling. On the other hand, the high proportion of undiagnosed milder forms of clefts, such as UCL, highlights the limitations of current prenatal screening methods. Notably, the majority of cases with CPO were not detected before birth. These findings also align with previously published results [15].

Advanced parental age has been identified as a contributing factor in cleft development. Both maternal and paternal age have been shown to be associated with an increased risk of cleft lip with or without cleft palate, whereas for CPO, paternal age has been identified as a significant risk factor [16]. Moreover, the risk of complete clefts appears to be higher when both parents are older than 29 years [17,18]. However, no correlation was proven between advanced parental age and the specific type or severity of clefts in our sample. The average maternal age in our sample was consistent with the national average in the Czech Republic, which was reported to be 31 years between 2011 and 2022 [19]. The average paternal age was 3 years higher than the regional average reported for the South Moravian Region [20].

Both maternal malnutrition and obesity have been further on identified as potential risk factors for congenital anomalies, including OFC [21–23]. Malnutrition, particularly deficiencies in essential vitamins such as folic acid, vitamin B6, and vitamin A, has been associated with impaired embryonic development [24,25]. Insufficient intake of these micronutrients affects cellular differentiation, neural crest migration, and tissue fusion, all of which are critical for proper craniofacial development. On the other hand, excessive maternal weight is linked to metabolic disturbances, oxidative stress, and chronic low-grade inflammation, which may interfere with the molecular pathways involved in the fusion of the lip and palate during embryogenesis [26]. Interestingly, both nutritional extremes –malnutrition and obesity – probably share common mechanisms that may increase the risk of OFC. Epigenetic modifications, such as DNA methylation and histone modifications, influenced by maternal nutritional status, have been suggested as possible contributors to cleft formation [9,27]. This highlights the importance of balanced maternal nutrition before and during pregnancy to minimize the risk of congenital anomalies. In our sample, the majority of mothers had a BMI within the normal range, with only 8 classified as underweight and 15 as overweight. This limited variability in BMI distribution is likely the reason why we did not observe a significant correlation between BMI and the severity of the cleft condition.

Fever is a natural physiological response to infection; however, elevated body temperature during the early stages of pregnancy may disrupt normal cellular growth and differentiation. Hyperthermia acts as a stress factor on the developing embryo, potentially impairing cellular signaling pathways and increasing the likelihood of developmental anomalies [28]. In addition, the infection itself represents an independent risk factor, influencing the fetus both directly and indirectly depending on the type of pathogen and the extent of the maternal immune response. While infectious agents can directly interfere with the development of facial and craniofacial structures, the indirect effects of maternal infections during pregnancy are primarily linked to immune system activation, producing inflammatory cytokines and other mediators that may exert toxic effects on the embryo. Severe infections can trigger the release of inflammatory molecules that alter vascular perfusion and compromise placental nutrient and oxygen supply and disrupt epigenetic regulatory mechanisms governing gene expression. In our sample, 26 mothers reported experiencing an infection accompanied by fever during the first trimester. However, no correlation was found between these infections and a specific type of cleft in the child, or its contribution to the cleft severity. Among these cases, nine were confirmed by PCR as SARS-CoV-2. While SARS-CoV-2 primarily targets the maternal respiratory system, the systemic inflammation and immune responses triggered by the infection may have significant consequences for embryonic development. Emerging data suggest that SARS-CoV-2 infection occurring during the one-month preconception period and the first trimester is significantly associated with increased CLP severity [29]. However, further research is needed to establish a direct causal link between maternal COVID-19 infection and the incidence or severity of OFC.

Maternal stress during pregnancy has been investigated as a potential risk factor for OFC, as psychological stress triggers the release of stress-related hormones such as cortisol and catecholamines, which can alter placental function, reducing blood flow, and increasing oxidative stress. While some epidemiological studies have reported a higher prevalence of OFC in infants born to mothers who experienced significant stressors, others have found no such correlation [30,31]. Variability in results may stem from differences in study designs, stress assessment methods, and genetic predisposition among populations. Sixteen mothers reported experiencing stressful situations during the first trimester of pregnancy, but no association was found between these events and a particular type of cleft in the child or its severity.

There is substantial evidence that folate supplementation helps prevent congenital anomalies associated with aberrant neural tube and craniofacial development [32]. Jayarajan et al. concluded that high-dose folic acid intake during the first trimester is associated with a reduced incidence of non-syndromic isolated cleft lip with or without cleft palate, though its protective effect on isolated cleft palate is less pronounced [33]. In our study, 14 out of 96 mothers did not take any form of folic acid during the first trimester, yet none of the most severe cleft defects were observed in their children. Nevertheless, the question remains whether adequate supplementation could have prevented the occurrence of UCL or UCLP clefts in these cases or further reduced their severity.

Conclusion

Our study on exogenous etiological factors in children with orofacial clefts born between 2017 and 2024 indicates that:

- the majority of cleft anomalies involving the primary palate, particularly BCLP, were diagnosed prenatally;
- prenatal diagnosis was effective in only a small proportion of CPO cases;
- the distribution of individual cleft types corresponded to data reported in the literature;
- although exogenous etiological factors cited in the literature were present in our sample, no causal relationship was found between BMI, parental age, infection with fever, or stressful situations and the occurrence of a specific type of cleft or cleft severity.

Limitations: A limitation of this study is the relatively small sample size, which restricts the statistical power and generalizability of the findings. Therefore, the observed associations should be interpreted with caution and require confirmation in studies with larger patient cohorts.

Roles of authors: Wanda Urbanová contributed to the conceptualization of the study, data curation, writing of the original draft, and review and editing of the manuscript. Michaela Večeřová participated in the conceptualization and data curation. Jitka Vokurková contributed to the original draft of the manuscript. Libor Streit was involved in writing the original draft. Jana Vašáková performed data analysis and contributed to the review and editing of the manuscript. Aleš Leger contributed to data analysis and data curation. Olga Košková participated in the conceptualization of the study, data curation, project administration, writing of the original draft, and review and editing of the manuscript.

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