MATERNAL EMPLOYMENT STATUS AND ISOLATED OROFACIAL CLEFTS IN HUNGARY

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SUMMARY

Aims: To study the role of maternal employment status as indicator of socioeconomic status in the origin of isolated orofacial clefts (OFC) and in the use of periconceptional folic acid/multivitamin supplementation.

Methods: 1,975 cases with OFC (1,374 cases with cleft lip ± palate and 601 cases with posterior cleft palate), 38,151 population controls without any defects and 20,868 patient controls with other isolated defects were compared in the population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA), 1980–1996.

Results: The proportion of professionals and managerials was lower, while the proportion of unskilled workers, housewives and others was higher in the mothers of cases with OFC compared with the population control group. However, the comparison of OFC and patient control groups did not show any difference in the employment status of mothers. A lower level of folic acid supplementation occurred in the professional and skilled worker mothers of cases with OFC compared with the population control group. This difference was confirmed by the comparison of folic acid used by mothers of cases with OFC compared with patient controls. An infrequent multivitamin use was displayed in the studied groups.

Conclusions: The prevalence of OFC at birth shows a slightly lower maternal employment status as indicator of socioeconomic status than in the population control group. The higher level of maternal education does not imply a higher rate of folic acid supplementation in the group of OFC.

Key words: cleft lip, cleft palate, employment status, folic acid, multivitamins

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INTRODUCTION

Orofacial clefts (OFCs) are among the most extensively studied congenital abnormalities (CAs) due to their visibility and common prevalence at birth (1 child is born with an OFC in approximately 750 births) (1, 2). In 1942 in his pioneer work Paul Fogh Andersen (3) demonstrated that isolated cleft lip with or without cleft palate (CL±CP) and posterior cleft palate (PCP) are distinct entities with different genetic background. It is necessary to differentiate cases with Robin sequence (RS) (previously it was called Pierre Robin syndrome) from cases with PCP (4). Finally, a pathogenetic distinction was made between isolated or non-syndromic OFCs and multiple or syndromic OFCs (5, 6, 7). Most cases with non-syndromic CL±CP are caused by the interaction between genetic and environmental factors (8), while a considerable proportion of cases with PCP and RS are due to monogenic entities (4, 9).

The possible association between the socioeconomic status (SES) and OFC have been mentioned several times but as Mossey and Little (2) stated: "The overall conclusion of SES in OFC is not well studied". An association between lower SES and higher prevalence of OFC was found in Malaysia and Thailand (10, 11, 12). Womersley and Stone (13) examined the prevalence of OFCs at birth within Greater Glasgow (Scotland) by housing and employment features. They found a higher rate of OFC in unemployed couples, poor housing and unskilled workers. The lowest rates were found in affluent areas with high rates of professional and nonmanual workers in high-quality housing. The majority of cases examined were PCP, and there appeared to be less variation in CL±CP cases. In contrast, a small study in the United Kingdom (14), found no association between CL±CP or PCP and SES (Carstairs Deprivation Index), however this study included only 44 cases of CL±CP and 29 cases of PCP. A recent Scottish study (15) investigated the relationship between the same Carstairs Deprivation Index as an indicator of SES and the prevalence of OFC at birth between 1989 and 1998 and they found that the prevalence of OFC increased with increasing deprivation.

The two objectives of our study dealing with the analysis of the data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA), 1980–1996 (16) are the following:

1. To check the possible association between maternal employment status as an indicator of SES in Hungary and isolated CL±CP and PCP (without RS). This possible relation is based on (i) the comparison of these two OFC groups and population controls without any CAs (representing the Hungarian newborn population) and on (ii) the comparison of two OFC groups and patient controls affected with all other CAs – studied to clarify whether the SES has an effect specifically on OFC only or it is a characteristic of all CAs.
2. To study the possible association between maternal employment status and periconceptional folic acid/multivitamin supplementation.

METHODS

Cases with isolated CL±CP and PCP, in addition patient controls with other isolated CAs were selected for the HCCSCA from the population-based Hungarian Congenital Abnormality Registry (HCAR) (17). Notification of cases with CAs is mandatory by physicians in Hungary. Most reports are received from obstetricians as practically all deliveries occur in inpatient obstetric clinics, or from paediatricians in the neonatal units of inpatient obstetric clinics and various inpatient and outpatient paediatric clinics. Autopsy was required for all infant deaths, and was frequently performed for stillborn fetuses. Pathologists sent a copy of every autopsy report to the HCAR if defects were identified. Reported fetal defects from antenatal diagnostic centres have been included in the HCAR since 1984. Thus, the period from the second trimester of gestation to the end of first postnatal year was covered with respect to the study population. The prevalence of total recorded cases (birth + fetal) with diagnosed CAs was 35 per 1000 informative offspring (liveborn infants, stillborn and malformed fetuses from electively terminated pregnancies) (17). About 90% of major CAs and 96% of isolated OFCs were reported to the HCAR during 17 years of the studied period (4).

We identified OFC cases and patient controls for the HCCSCA reported to the HCAR within the first three months after birth or termination of pregnancy between 1980 and 1996. This short interval between the birth or pregnancy termination and data collection increases the accuracy and effectiveness of the information about the history of pregnancies since 77% of cases were reported during this time window to the HCAR.

We defined population controls as newborn infants without CAs matched to each case with CA by sex, week of birth in the year when the case was born, and district of parent's residence from the National Birth Registry of the Central Statistical Office. In general two controls were selected for every case.

The necessary personal and exposure data were collected from three sources. First, we sent a post-paid structured questionnaire to the parents. Information was requested on their personal data including the employment status of mother, occupational exposures, maternal diseases and medicines (drugs and pregnancy supplements) taken during pregnancy, by gestational months. The average time between the end of pregnancy and the return of questionnaire was 3.1±1.0, 3.5±1.2 and 5.2±2.0 months for cases with OFC, patient and population controls, respectively. Second, mothers were requested to send their prenatal care logbooks because obstetricians providing prenatal care are obliged to record all prescribed drugs, pregnancy complications, and diseases in the logbook. Employment status of mothers was recorded in the prenatal care logbook as well. Logbook was available in 94.0% of cases with OFC, 88.4% of patient controls and 91.8% of population controls. Third, regional district nurses visited and interviewed all non-responding families of cases with OFC and patient controls, but only 200 non-responding population control families were visited (18). Altogether, information were available for 97.1% of cases with OFC (85.1% from reply, 12.0% from visit), for 96.1% of patient controls (84.4% from reply, 11.7% from visit) and 83.1% of population controls (82.6% from reply, 0.5% from visit), except mothers with wrong or unknown addresses.

The first classification system of employment status was established in Great Britain, originally devised by Stevenson in 1911 (19). Partly based on this system the Hungarian classification of employment status contains seven major classes. The seventh class included students, unemployed and prematuraly retired persons:

I. Professionals with high-level education (more than 12 classes)
II. Managerial-administrative occupations with high or medium-level education (in general 12 classes)
III. Skilled workers (10–12 classes)
IV. Semi-skilled workers (about 8 classes)
V. Unskilled workers (less than 8 classes)
VI. Housewives
VII. Others.

We investigated the distribution of parents of cases, population and patient controls by occupational categories (agricultural, different industries, trade, health system, military, etc.) as well, but these data are not covered in this paper.

The statistical analysis was based on the SAS version 8.02 statistical software package (SAS Institute Ins., Cary, North Caroline, USA). First, we described the distribution of offsprings by cleft type, control groups and sex. χ^2 tests were used to test for association of the four main study groups with sex. Second, the major features of mothers (maternal age, birth order and marital status) were described. We applied a logistic regression model to compare the maternal variables in the two OFC groups with the population and patient controls. Maternal employment status was included in the logistic regression model in order to control the potential confounding of this variable. The distribution of employment status of mothers was compared among different types of OFC, in addition to cases with OFC and population and patient controls. Adjusted odds ratios (OR) with 95% confidence interval (95% CI) were calculated in a multiple logistic regression model. Finally, folic acid and multivitamin use amid the mothers was compared among the four study groups: two types of OFC, population controls and patient controls. For the calculation of adjusted OR with 95% CI multiple logistic regression model was used. A statistical test for heterogeneity of the odds ratios across the maternal employment status classes was performed when OFC groups were compared with population and patient controls.

RESULTS

The data set of cases with isolated OFC in the HCAR, 1980–1996 is shown in Table 1. Of 1,374 cases with CL±CP, 566 (41.2%) had CL, while 808 (58.8%) were affected with CL+CP. Of these 1,374 cases, only 6 cases with CL + CP occurred in stillborn fetuses. 601 cases with PCP and without RS were found. The characteristic male excess of CL±CP and female excess of PCP cases were confirmed by this data.

Table 2 demonstrates maternal variables such as maternal age, birth order and marital status within the studied groups. The maternal age and birth order was higher in cases with CL±CP and PCP than in population and patient control groups. The proportion of unmarried mothers was higher in the group of CL±CP and PCP than in the group of population controls.

The seven employment status classes of mothers in the study groups are shown in Table 3. The proportion of professionals and managerials among mothers of cases with both types of OFC was

Table 1. *Sex of offspring (newborn infants and fetuses)*

Sex	Cases						Cases with PCP		Population controls		Patient controls	
	with CL		with CL+CP		with CL±CP							
	N	%	N	%	N	%	N	%	N	%	N	%
Male	355	62.7	527	65.2	882	64.2	249	41.4	24,799	65.0	13,852	66.4
Female	211	37.3	281	34.8	492	35.8	352	58.6	13,352	35.0	7,016	33.6
Total	566	100.0	808*	100.0	1,374	100.0	601	100.0	38,151	100.0	20,868**	100.0

*6 were diagnosed in stillborn fet

Table 2. *Maternal age and birth order*

Maternal variables	CL±CP (N=1,374)		PCP (N=601)		Population controls (N=38,151)		CL±CP vs. population controls		PCP vs. population controls		Patient controls (N=20,868)		CL±CP vs. patient controls		PCP vs. patient controls	
	N	%	N	%	N	%	OR*	95%CI	OR*	95%CI	N	%	OR*	95%CI	OR*	95%CI
Maternal age (yr)																
–24	646	47.0	257	42.8	17,994	47.2	reference		reference		10,042	48.1	reference		reference	
25–29	420	30.6	197	32.8	12,885	33.8	1.03	0.90–1.17	1.18	0.98–1.43	6,537	31.3	1.02	0.89–1.16	1.17	0.97–1.41
30–	308	22.4	147	24.5	7,272	19.1	1.32	1.14–1.51	1.54	1.25–1.89	4,289	20.6	1.14	0.99–1.32	1.34	1.08–1.65
Birth order																
1	792	57.6	325	54.1	22,750	59.6	reference		reference		12,797	61.3	reference		reference	
2	382	27.8	186	30.9	11,281	29.6	1.00	0.88–1.13	1.16	0.97–1.40	5,317	25.5	1.17	1.03–1.33	1.37	1.13–1.64
3 or more	200	14.6	90	15.0	4,120	10.8	1.25	1.06–1.47	1.37	1.07–1.75	2,754	13.2	1.18	0.99–1.39	1.30	1.02–1.67
Unmarried	87	6.3	35	5.8	1,471	3.9	1.49	1.19–1.87	1.41	0.99–1.99	1,147	5.5	1.16	0.93–1.46	1.11	0.78–1.58

*OR adjusted for maternal employment status in a multiple logistic regression model

Table 3. *Maternal employment status*

Maternal employment status	CL±CP (N = 1,374)		PCP (N = 601)		Population controls (N = 38,151)		CL±CP vs. population controls		PCP vs. population controls		Patient controls (N = 20,868)		CL±CP vs. patient controls		PCP vs. patient controls	
	N	%	N	%	N	%	OR*	95%CI	OR*	95%CI	N	%	OR*	95%CI	OR*	95%CI
Professional	106	7.7	54	9.0	4,353	11.4	0.52	0.42–0.65	0.60	0.44–0.82	1,741	8.3	0.90	0.72–1.11	1.02	0.75–1.39
Managerial	281	20.5	125	20.8	10,134	26.6	0.74	0.64–0.84	0.73	0.60–0.89	4,562	21.9	0.91	0.79–1.05	0.90	0.73–1.10
Skilled worker	394	28.7	185	30.8	11,690	30.6	0.99	0.88–1.12	1.09	0.91–1.30	5,750	27.6	1.07	0.95–1.21	1.17	0.98–1.40
Semiskilled worker	249	18.1	93	15.5	5,783	15.2	1.28	1.11–1.48	1.06	0.84–1.34	3,527	16.9	1.10	0.95–1.27	0.90	0.72–1.13
Unskilled worker	89	6.5	50	8.3	1,859	4.9	1.31	1.05–1.64	1.74	1.29–2.35	1,364	6.5	0.98	0.78–1.23	1.29	0.95–1.74
Housewife	127	9.2	50	8.3	2,038	5.3	1.72	1.41–2.08	1.54	1.14–2.09	1,951	9.4	0.97	0.80–1.18	0.86	0.63–1.16
Others	128	9.3	44	7.3	2,294	6.0	1.40	1.13–1.73	1.26	0.89–1.78	1,973	9.5	1.00	0.81–1.23	0.88	0.63–1.24

*OR adjusted for maternal age, birth order, use of pregnancy supplements during the entire pregnancy (folic acid/multivitamin) and paternal employment status

lower, and the proportion of unskilled workers and housewives was higher in cases with two types of OFC than in the population controls. Semiskilled workers and others were also found in a higher rate in the groups of cases with CL±CP than in the population control group. However, the comparison of CL±CP and PCP cases with patient controls by maternal employment status did not show a significant difference.

In the next step, folic acid use was compared between CL±CP and PCP and two control groups (Table 4). The folic acid use demonstrated the highest level in the population control group and the lowest level in the PCP group. There was no difference between OFC groups and patient controls. We were interested particularly in the proportion of folic acid supplementation during pregnancy by maternal employment status. Professionals showed a significantly lower level of folic acid use in both groups of CL±CP and PCP cases than in the population control group. The lower use of folic acid by mothers in the professional category was also confirmed by the comparison of CL±CP cases with the

Table 4. *Folic acid use during pregnancy according to maternal employment status in the four main study groups*

Maternal employment status	CL±CP (N=1,374)		PCP (N=601)		Population controls (N=38,151)		CL±CP vs. population controls		PCP vs. population controls		Patient controls (N=20,868)		CL±CP vs. patient controls		PCP vs. patient controls	
	N	%	N	%	N	%	OR*	95%CI	OR*	95%CI	N	%	OR*	95%CI	OR*	95%CI
Professional	41	38.7	23	42.6	2,490	57.2	0.47	0.32–0.70	0.56	0.32–0.96	877	50.4	0.62	0.42–0.93	0.73	0.42–1.26
Managerial	150	53.4	68	54.4	5,881	58.0	0.83	0.66–1.06	0.87	0.61–1.24	2,403	52.7	1.03	0.81–1.31	1.07	0.75–1.53
Skilled worker	209	53.1	72	38.9	6,292	53.8	0.97	0.80–1.19	0.55	0.41–0.74	2,897	50.4	1.12	0.91–1.37	0.63	0.47–0.85
Semiskilled worker	139	55.8	54	58.1	3,120	54.0	1.09	0.84–1.41	1.20	0.79–1.82	1,795	50.9	1.23	0.95–1.59	1.35	0.89–2.04
Unskilled worker	37	41.6	29	58.0	906	48.7	0.75	0.49–1.16	1.46	0.83–2.58	657	48.2	0.77	0.50–1.19	1.50	0.85–2.66
Housewife	48	37.8	19	38.0	917	45.0	0.75	0.52–1.09	0.76	0.42–1.35	845	43.3	0.81	0.56–1.17	0.82	0.46–1.46
Others	55	43.0	21	47.7	1,169	51.0	0.74	0.51–1.05	0.90	0.50–1.64	840	42.6	1.02	0.71–1.46	1.25	0.69–2.27
Total	679	49.4	286	47.6	20,775	54.5	0.81	0.73–0.91	0.76	0.65–0.90	10,314	49.4	1.00	0.90–1.11	0.93	0.79–1.10
Test of heterogeneity							p = 0.02		p = 0.01				p = 0.07		p = 0.02	

*OR adjusted for maternal age and birth order

Table 5. *Multivitamin use during pregnancy according to maternal employment status in the four main study groups*

Maternal employment status	CL±CP (N = 1,374)		PCP (N =601)		Population controls (N = 38,151)		CL±CP vs. population controls		PCP vs. population controls		Patient controls (N = 20,868)		CL±CP vs. patient controls		PCP vs. patient controls	
	N	%	N	%	N	%	OR*	95%CI	OR*	95%CI	N	%	OR*	95%CI	OR*	95%CI
Professional	12	11.3	3	5.6	472	10.8	1.04	0.56–1.91	0.47	0.15–1.52	190	10.9	1.05	0.56–1.94	0.48	0.15–1.55
Managerial	18	6.4	5	4.0	617	6.1	1.06	0.65–1.71	0.64	0.26–1.56	222	4.9	1.35	0.82–2.22	0.82	0.33–2.03
Skilled worker	34	8.6	1	0.5	755	6.5	1.38	0.96–1.97	0.08	0.01–0.56	359	6.2	1.43	0.99–2.06	0.08	0.01–0.58
Semiskilled worker	16	6.4	6	6.5	270	4.7	1.41	0.84–2.37	1.41	0.61–3.25	165	4.7	1.41	0.83–2.39	1.39	0.60–3.24
Unskilled worker	3	3.4	1	2.0	66	3.6	0.95	0.29–3.08	0.56	0.08–4.09	44	3.2	1.06	0.32–3.47	0.63	0.09–4.66
Housewife	2	1.6	2	4.0	75	3.7	0.42	0.10–1.72	1.06	0.25–4.45	85	4.4	0.36	0.09–1.48	0.93	0.22–3.91
Others	8	6.3	2	4.6	271	11.8	0.51	0.25–1.05	0.36	0.09–1.49	160	8.1	0.76	0.37–1.59	0.55	0.13–2.29
Total	98	6.8	20	3.3	2,526	6.6	1.01	0.82–1.25	0.48	0.31–0.75	1,225	5.9	1.16	0.93–1.44	0.55	0.35–1.17
Test of heterogeneity							p = 0.19		p = 0.17				p = 0.44		p = 0.25	

*OR adjusted for maternal age and birth order

patient controls. The skilled-worker mothers of PCP cases had also a lower folic acid use compared with both population and patient control groups. The results of the heterogeneity test indicate that the odds ratios were significantly different among the maternal employment status classes.

The use of multivitamins was relatively rare (Table 5). There was no real difference among the study groups. However, skilled--worker mothers of PCP cases used less frequently multivitamins than mothers of population and patient controls. However, even a lower use of multivitamins was characteristic for the total group of PCP cases compared with the total group of population controls. The odds ratios were not statistically heterogeneous if the two OFC groups were compared with population and patient control groups.

DISCUSSION AND CONCLUSIONS

The mothers of isolated CL±CP and PCP cases showed a slightly lower employment status as indicator of SES than mothers of population controls. However, there was no difference in the maternal employment status between the mothers of these two types of OFC cases and patient controls. Thus the lower SES does not seem to be a specific feature for the mothers of OFC cases among CA groups. A lower use of folic acid was detected in the group of CL±CP and PCP cases compared with the population controls. The lower folic acid supplementation was most characteristic for mothers of CL±CP and PCP cases in professional category.

The strengths of HCCSCA are: (i) it is a population-based (ii) large data set including 1,975 isolated OFC cases (iii) in an ethnically homogeneous European population, (iv) the matching of cases and their population controls, (v) the use of patient controls, (vi) the knowledge of confounding factors, (vii) the good validity of medically recorded OFC diagnosis and (viii) the double checked maternal employment status (based on maternal information and prenatal logbook). However, this data set has also limitations. (i) Though the employment status is the most sensitive indicator of SES in Hungary information on other indicators of SES (e.g. income and housing quality) are not available. (ii) There is an asymmetry in the data collection between OFC cases and population controls because all non-respondent OFC cases and only

200 non-responded population controls were visited by regional nurses. However, there was no difference in the distribution of employment status between responding and non-responding population control families (18).

Our findings are consistent with the previously published data (10, 11, 12, 13, 15). These studies used different criterions and indicators of SES for the evaluation of socioeconomic status with respect to the origin of isolated OFC therefore it is not possible to make a valid comparison. Due to the lack of common criterion for the description of SES including employment status it would be needed to achieve an international consensus in this field.

Our previous study (20) showed that the high dose of folic acid can reduce the birth prevalence of OFC and in the present study we found a low use of folic acid even in the category of professionals. Educational campaigns and public health information should highlight the important role of folic acid supplementation in the prevention of OFC.

There is a well-known worldwide variation in the prevalence of cases with CL±CP and PCP at birth (21), and this variation could be partly explained by the different SES of different populations. On the other hand, a better understanding of the factors associated with low SES in the origin of OFC may contribute to the clarification of aetiology of isolated CL±CP and PCP in general.

REFERENCES

1. Czeizel AE, Hirschberg I: Orofacial clefts in Hungary. Folia Phoniatr Logop. 1997;49:111–6.
2. Mossey PA, Little J: Epidemiology of oral clefts: an international perspective. In: Wyszynski DF, editor. Cleft lip and palate: from origin to treatment. New York: Oxford University Press; 2002. p. 127–58.
3. Fogh-Andersen P: Inheritance of Cleft Lip and Cleft Palate. Copenhagen: Arnold Busck, Nordisk Forlag; 1942.
4. Czeizel AE, Hirschberg I, Tary E: Etiological studies in the Robin sequence. Gyermekgyógyászat. 1986;37:157–71. (In Hungarian with English abstract.)
5. Czeizel AE, Tusnády G: An epidemiological study of cleft lip with or without cleft palate and posterior cleft palate in Hungary. Hum Hered. 1971;21:17–38.
6. Czeizel AE, Telegdi L, Tusnády G: Multiple Congenital Abnormalities. Budapest: Akadémiai Kiadó; 1988.
7. Cohen MM: Syndromes with orofacial clefting. In: Wyszynski DF, editor: Cleft lip and palate: from origin to treatment. New York: Oxford University Press; 2002. p. 53–65.
8. Wyszynski DF, Beaty TH: The role of potential teratogens in the origin of human non-syndromic oral clefts. Teratology. 1996;53:309–17.
9. Marazita ML: Segregation analysis. In: Wyszynski DF, editor: Cleft lip and palate: from origin to treatment. New York: Oxford University Press; 2002. p. 222–33.
10. Sivaloganathan V: Cleft lips in Malaysians. Plast Reconstr Surg. 1972;49:176–9.
11. Lasa C, Manalo P: Update on the occurrence rate of cleft lip and palate. Philippine J Surg Specialities. 1989;44:109–11.
12. Chuangsuwanich A, Aojanepong C, Muangsombut S, Tongpiew P: Epidemiology of cleft lip and palate in Thailand. Ann Plast Surg. 1998;41:7–10.
13. Womersley J, Stone DH: Epidemiology of facial clefts. Arch Dis Child. 1987;62:717–20.
14. Vrijheid M, Dolk H, Stone D, Abramsky L, Alberman E, Scott JES: Socioeconomic inequalities in risk of congenital anomaly. Arch Dis Child. 2000;82:349–52.
15. Clark JD, Mossey PA, Sharp L, Little J: Socioeconomic status and orofacial clefts in Scotland, 1989 to 1998. Cleft Palate Craniofac J. 2003;40:481–5.
16. Czeizel AE, Rockenbauer M, Siffel Cs, Varga E: Description and mission evaluation of the Hungarian Case-Control Surveillance of Congenital Abnormalities. Teratology. 2001;63:176–85.
17. Czeizel AE: First 25 years of the Hungarian Congenital Abnormality Registry. Teratology. 1997;55:299–305.
18. Czeizel AE, Petik D, Vargha P: Validation studies of drug exposures in pregnant women. Pharmacoepid Drug Safety. 2003;12:409–16.
19. Elwood JM, Little J, Elwood JH: Epidemiology and Control of Neural Tube Defects. Oxford: Oxford University Press; 1992.
20. Czeizel AE, Timar L, Sarkozi A: Dose-dependent effect of folic acid on the prevention of orofacial clefts. Pediatrics. 1999;104:e66.
21. International Clearinghouse for Birth Defects Monitoring Systems; EUROCAT; WHO. World Atlas of Birth Defects. Geneva: WHO; 1998.

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