Birth weight and gestational age of newborns with cleft lip with or without cleft palate and with isolated cleft palate

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The birth weight and gestational age of 1368 newborns with isolated cleft lip with or without cleft palate and 582 with isolated cleft palate were compared to those of matched healthy controls. The results indicate that fetuses with oral clefts are at elevated risk of having low and very low birth weight, but not of having a premature birth. Speculations on a relationship between these findings and the presence of oral clefts are presented.

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INTRODUCTION

Oral clefts (OCs) are among the most extensively studied structural birth defects due to visibility and frequent occurrence (1 child is born with an OC in approximately 750 births).[1,2] It has been recognized, since the pioneer work of Paul Fogh Andersen in 1942, that cleft lip with or without cleft palate (CL/P) and isolated cleft palate (CP) are distinct entities with different etiological backgrounds. Later, a further delineation of these conditions was done by identifying cases with Robin sequence (RS) from those with CP.[1] Finally, a pathogenetic distinction was made between isolated or nonsyndromic OCs and multiple or syndromic OCs.[3,4] Most cases with nonsyndromic CL/P are due to complex interactions between genetic and environmental factors,[5] while a considerable proportion of cases with CP and RS are due to monogenic entities.[6,7]

While much research has been published in the areas of etiology and treatment of patients with oral clefts, few systematic studies were done focused on neonatal characteristics. Therefore, the purpose of this study is to examine whether newborns with OCs are at increased risk of low and very low birth weight and of preterm birth in a large population-based case-control study conducted in Hungary between 1980 and 1996.

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MATERIALS AND METHODS

Cases

Cases were considered eligible for this study if they presented isolated (nonsyndromic) OCs (CL/P or CP). The source of case ascertainment was the nation-wide Hungarian Congenital Abnormality Registry between 1980 and 1996.[8] Notification by physicians of cases with congenital anomalies (CAs) was mandatory during this period. Most reports were from obstetricians, since in Hungary almost all deliveries occur in inpatient obstetric clinics, or from pediatricians, who were working in the neonatal units of inpatient obstetrics clinics and in various inpatient and outpatient pediatrics clinics. During the study period, autopsy was required for all infant deaths, and was a common practice for stillborn fetuses. Pathologists sent a copy of each autopsy report to the Registry when CAs were identified. The recorded total (birth+fetal) prevalence of cases with CAs diagnosed from the second trimester of gestation through one year of age was 35 per 1000 informative offspring (liveborn infants, stillborn and malformed fetuses from electively-terminated pregnancies). About 90% of all major CAs were reported to the Registry during the 17 years of the study period.[8]

Controls

Controls were infants without CAs, matched to each case on sex, week of birth, and district of residence of the parents. The source of control ascertainment was the National Birth Registry of the Central Statistical Office. Close to one control per case was selected. About 3% of the matched controls had some CA and these infants were excluded from the study.

Interview Data

Data on cases and controls were obtained from multiple sources.[9] First, personal and pregnancy outcome

Table 1. Characteristics of parents and offspring in a matched case-control study of birth weight and gestational age and oral clefts.

Variables	CL/P Cases (n = 1,368)	CP Controls (n = 1,374)	Cases (n = 582)	Controls (n = 581)
Mean maternal age in years (SD)[1]	25.7 (5.7)	25.7 (5.9)	26.3 (5.8)	25.9 (5.4)
Mean paternal age in years (SD)	28.9 (6.5)	28.8 (6.4)	29.4 (6.2)	28.8 (5.9)
This is the first live birth *n* %	790 (57.8)	821 (59.8)	310 (53.3)	318 (54.7)
Maternal occupation *n* %				
Professional	106 (7.8)	144 (10.7)	51 (8.9)	69 (12.1)
Managerial	280 (20.7)	350 (26.0)	121 (21.0)	157 (39.7)
Skilled workers	391 (28.9)	444 (32.9)	180 (31.3)	177 (31.1)
Semiskilled workers	248 (18.3)	190 (14.1)	91 (15.8)	88 (15.5)
Unskilled workers	89 (6.6)	75 (5.6)	49 (8.5)	24 (4.22)
Homemaker	127 (9.4)	80 (5.9)	49 (8.5)	28 (4.9)
Others[2]	114 (8.4)	66 (4.9)	34 (5.9)	26 (4.6)
Male newborns *n* %	878 (64.2)	862 (62.7)	240 (41.2)	259 (44.6)
Twin newborns *n* %	18 (1.3)	10 (0.7)	4 (0.7)	4 (0.7)
Mean birth weight age in gms (SD)	3,089 (598)	3,286 (499)	3,080 (579)	3,239 (516)
Mean gestational age in weeks (SD)	39.1 (2.4)	39.4 (2.0)	39.2 (2.4)	39.1 (2.7)
Low birth weight (<2500 gms) *n* %	183 (13.4)	67 (4.9)	76 (13.1)	41 (7.1)
Preterm birth (<37 weeks) *n* %	159 (11.6)	120 (8.7)	65 (11.2)	73 (12.6)

[1]SD: standard deviation; *n*: number; %: percentage.
[2]students, unemployed, others, unknown.

data of cases were available on the basis of the notification form sent to the Registry, while some personal data of controls were collected from the National Birth Registry.

Second, a structured questionnaire was mailed to the parents of cases and controls after birth. At this time, parents were asked to check and complete the available personal and pregnancy outcome data recorded in the questionnaire. The data on pregnancy complications, acute and chronic maternal disorders, drug intake, employment status, occupational exposures, and family history were collected through this questionnaire. Lists of maternal diseases and drugs were mailed to mothers as well, to increase recall before completing the questionnaire. No information was obtained regarding smoking and alcohol use because the pilot study showed that the reliability of these data is very low.[10] Completed questionnaires were returned, on average, at 1.6 and 3.5 postnatal months for cases and controls, respectively.

Third, mothers of cases and controls were requested to mail the prenatal care logbook, the discharge summary of the delivery (which includes birth weight and gestational age), and all other medical records concerning the diseases or CA of the child.

Fourth, regional district nurses visited and interviewed non-responding families of cases. Non-respondent families of controls could not be visited as part of this study, as the local ethics committee precluded the nurses from doing so. Nonetheless, 200 non-responding families of controls were visited and interviewed as part of the pilot study. In total, information was available from 88% of cases (80% from mailed responses, 8% from visits) and 75% of controls. Of 1950 cases with OC in the study, 176 (9%) had no matched control, thus a matched control was selected from the rest of the 38,151 controls on the basis of the matching criteria.

Statistical analyses

Statistical analyses were done with the software Stata®, version 7.0.[11] For continuous data, mean values and standard deviations were calculated. For categorical data, odds ratios (OR) and the 95% confidence intervals (CI) were estimated. Conditional logistic regression analysis was used to adjust for potential confounders such as maternal age, birth order, employment status (as indicator of socioeconomic status), pregnancy complications, and acute and maternal disorders. Post hoc pairwise multiple comparisons were performed using Tukey and Bonferroni procedures.[12]

RESULTS

Cleft lip with/without cleft palate (CL/P)

The dataset included 1368 liveborn infants with isolated CL/P born between 1980 and 1996 and 1374

Table 2. Maternal conditions during pregnancy in the CL/P and CP case mothers and their matched controls.

	CL/P Cases (*n* = 1,368)	CP Controls (*n* = 1,374)	OR	95% CI	Cases (*n* = 581)	Controls (*n* = 582)	OR	95% CI
Pregnancy Complications								
Nausea, vomiting (excessive)	92	130	0.69	0.52-0.91	44	66	0.64	0.43-0.95
Threatened abortion	209	227	0.83	0.67-1.01	79	81	0.97	0.70-1.36
Preeclampsia[1]	82	116	0.69	0.52-0.93	56	43	1.34	0.88-2.02
Threatened preterm birth[2]	146	150	0.97	0.77-1.24	60	51	1.20	0.81-1.77
Placental disorders[3]	10	26	0.38	0.19-0.78	2	7	0.28	0.07-1.19
Polyhydramnios	9	6	1.51	0.56-4.11	1	0	-	-
Gestational diabetes	10	13	0.77	0.34-1.73	3	2	1.51	0.30-7.66
Anemia	190	239	0.77	0.62-0.94	86	111	0.74	0.54-1.00
Acute infectious diseases								
Influenza-common cold	413	253	1.92	1.60-2.29	157	106	1.66	1.26-2.20
Respiratory system	197	150	1.37	1.09-1.72	69	69	1.00	0.70-1.43
Digestive system	20	12	1.68	0.83.3.42	4	3	1.34	0.33-4.43
Urinary tract	113	77	1.52	1.12-2.05	46	40	1.34	0.86-2.07
Genital organs	117	112	1.05	0.80-1.38	33	46	0.70	0.44-1.11
Others	71	51	1.42	0.98-2.05	22	17	1.31	0.69-2.47
Chronic diseases								
Epilepsy	9	3	3.03	0.89-10.33	5	0	-	-
Diabetes mellitus	4	0	-	-	2	0	-	-
Others	224	225	1.00	0.82-1.22	80	85	0.93	0.67-1.30

[1]including hypertension, edema, proteinuria, and preeclampsia.
[2]including cervical incompetence as well.
[3]placenta previa, premature separation of placenta, other placenta disorders

Table 3. Adjusted conditional odds ratios (OR) and 95% confidence intervals (95% CI) for cleft lip with or without palate (total CL/P, n = 1368) and isolated cleft palate (total CP, n = 582) and low birth weight and preterm pregnancy by child's sex and very low birth weight.

Type of Cleft	Variable	Patient's Sex	Number of Patients	Conditional OR (95% CI)
CL/P	Low birth weight[1]	Male	102	2.79 (1.72-4.55)
		Female	81	2.69 (1.48-4.87)
		Both	183	2.78 (1.95-3.97)
	Very Low birth weight[1]	Both	16	5.03 (1.11-22.78)
	Preterm[2]	Male	100	1.42 (1.01-1.99)
		Female	59	1.08 (0.69-1.67)
		Both	159	1.27 (0.98-1.65)
CP	Low birth weight[1]	Male	23	2.65 (1.13-6.25)
		Female	53	2.55 (1.38-4.73)
		Both	76	2.49 (1.55-3.99)
	Very Low birth weight[1]	Both	6	2.25 (0.51-9.82)
	Preterm[2]	Male	65	0.60 (0.31-1.15)
		Female	17	1.02 (0.63-1.68)
		Both	48	0.87 (0.60-1.26)

[1]CL/P: Adjusted for gestational age, socio-economic status, and maternal risk; CP: same as CL/P except for gestational age.
[2]Adjusted for socio-economic status and maternal risk.

matched controls. Table 1 shows the distribution of cases by mean maternal and paternal age, birth order, child's sex, parity, and maternal employment status. As expected, CL/P was more frequent among male babies. There was no statistically significant difference between cases with CL/P and controls regarding mean maternal and paternal age, multiple birth occurrence, or birth order. Mothers of controls were of higher socioeconomic status as determined by employment status, (ie, higher proportion of professionals and managers and lower proportion of unskilled workers and homemakers; OR: 1.70, 95% CI: 1.45-2.00).

Cases with CL/P had a slightly lower birth weight than controls (mean difference: 197 gms, 95% CI: 155-238, $t = 9.35$, $p < 0.001$). For women delivering before 37 weeks, there was no statistically significant

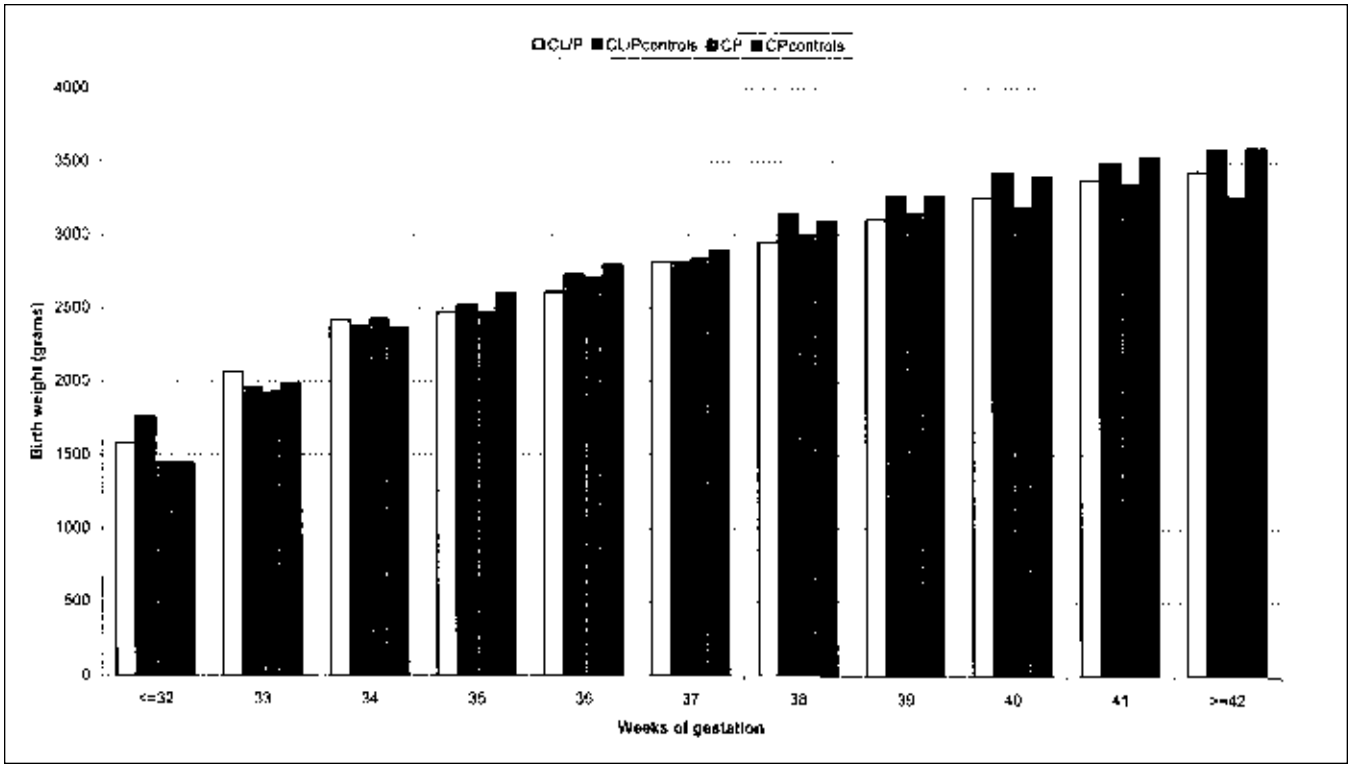

Figure 1. Mean birth weight for oral cleft cases and matched controls by gestational age. CL/P: cleft lip with or without cleft palate, CP: isolated cleft palate.

difference in birth weight between cases and controls ($p = 0.114$) (Figure 1). However, for women delivering at (37 weeks, the birth weights were generally lower among cases than among controls ($\beta < 0$, $p < 0.001$). When gestational age was analyzed as a continuous variable, it was found to be slightly shorter for cases as well (mean difference: 3 days, 95% CI: 2-5, $t = 4.13$, $p < 0.001$) and it was included in the conditional logistic model. Because several maternal ailments during pregnancy were individually significant predictors of CL/P status (Table 2), an index of "maternal risk" was created combining all maternal diseases during the pregnancy. Women with positive "pregnancy risk index" were at increased risk for CL/P (unadjusted conditional $OR_{\text{maternal risk}}$: 1.59, 95% CI: 1.30-1.95); thus, this variable was included in the analysis.

Low birth weight (< 2500 gms) and preterm birth (< 37 weeks) were substantially more common in cases with CL/P than in controls (unadjusted $OR_{\text{low birth weight}}$: 3.15, 95% CI: 2.32-4.28; OR_{preterm}: 1.38, 95% CI: 1.07-1.78; Table 3). When low birth weight was adjusted for gestational age, socio-economic status, and pregnancy risk, the $OR_{\text{low birth weight}}$ declined to 2.79, with 95% CI: 1.72-4.55, while the OR_{preterm} became marginally significant (OR_{preterm}: 1.42, 95% CI: 1.01-1.99). The odds ratio for males was slightly higher than that for females, although their confidence intervals overlapped. The comparison of prevalence of very low birth weight (<1500 gms) in cases ($n = 16$ or 1.2% of the total) and controls ($n = 2$ or 0.2% of the total) resulted in a high point estimate with wide confidence intervals (adjusted $OR_{\text{very low birth weight}}$: 5.03, 95% CI: 1.11-22.78). Fifty percent of case and control newborns with very low birth weight were male.

Preconceptional maternal weight and height were not recorded; however, maternal weight gain during pregnancy was obtained in a pilot study (Czeizel and Nagy, '86). Obvious weight gain (defined as weight gain > 15 kg) was more common among mothers of babies born with CL/P ($n = 115$ or 18.3%) than in control mothers ($n = 107$ or 13.2%; $OR_{\text{maternal weight gain}}$: 1.47, 95% CI: 1.10-1.95).

Cleft palate (CP)

A total of 582 liveborn infants with isolated CP and 581 matched controls were analyzed. Cases and controls did not differ in terms of maternal or paternal age and parity; however, mothers of controls occupied a higher occupational level than those of cases (70.8% vs. 61.2 % were professional and skilled mothers of controls and cases, respectively; OR: 1.53, 95% CI: 1.20-1.97; Table 1).

Overall, cases with CP had slightly lower birth weight than controls (average difference: 159 g, 95% CI: 95-222, $t = 4.94$; $p < 0.001$). Male cases with CP had higher birth weight than their female counterpart (mean birth weight for males: 3187.6 g, mean birth weight for females: 3005 g, $p < 0.001$). Girls with CP had

lower birth weight than girl controls (unadjusted $OR_{birthweight\ CP\ females}$: 2.0, 95% CI: 1.20-3.33); however, male cases and controls did not differ in their birth weight ($p = 0.082$).

As it was described for CL/P, for women delivering before 37 weeks, there was no statistically significant difference in birth weight between cases with CP and the matched controls ($p = 0.988$) (Figure 1). However, for women delivering at ≥37 weeks, the birth weights were generally lower among cases than among controls ($\beta < 0, p < 0.001$). Gestational age, as a continuous variable, did not differ between cases and controls ($p = 0.403$). "Maternal risk" was a significant risk factor for CP (unadjusted conditional $OR_{maternal\ risk}$: 1.56, 95% CI: 1.13-2.13) and it was included in the analysis.

Low birth weight was more common in cases with CP than in controls (unadjusted $OR_{low\ birth\ weight}$: 1.95, 95% CI: 1.31-2.89; Table 3). The prevalence of preterm birth was not different between cases and controls ($p = 0.462$). When low birth weight was adjusted for socio-economic status and pregnancy risk, the $OR_{low\ birth\ weight}$ increased to 2.49, with 95% CI: 1.55-3.99. Six cases and 5 controls had very low birth weight (adjusted $OR_{very\ low\ birth\ weight}$: 2.25, 95% CI: 0.51-9.82). Regarding maternal weight gain, no significant difference was found when mothers of children with CP were compared to those of controls in the pilot study (cases, $n = 28$ or 15.6%; controls, n = 107 or 13.2%; $OR_{maternal\ weight\ gain}$: 1.22, 95% CI: 0.78-1.91).

DISCUSSION

The study presented here provides further evidence that newborns with isolated OCs have lower birth weight, but not shorter gestational age than controls. The HCCSCA dataset has many advantages: (1) it is population-based, (2) it is large, including 1368 cases with isolated CL/P and 582 with isolated CP, (3) response rate was good: 80% in cases and 75% in controls, (4) controls without a CA were individually matched to each case, (5) it is from a homogenous ethnic population in Hungary, (6) cases were carefully studied by a medical geneticist to distinguish nonsyndromic from syndromic OC cases (the latter were excluded from the study), (7) birth weight and gestational age were recorded by medical professionals following a standardized protocol, and (8) potential confounding factors were available for analysis.

Limitations of the dataset need to be mentioned as well. It is possible that a small number of cases with syndromic OCs may have been misclassified as isolated OCs. Given the large size of the dataset, and the careful examination of the participants by a clinical geneticist, we believe that the effect of such misclassification would be very modest, if any. Unfortunately, information was not available on potential confounders such as maternal smoking, alcohol consumption, diet intake, body mass of the mother index, and weight gain during pregnancy. However, it should be noted that these variables have been shown to be associated with variability in birth weight, but not with risk to oral clefting in a significant way.[5,13]

Few anthropometric studies of newborns with oral clefts have been done, and most state that children with oral clefts are smaller and lighter than control subjects.[14,15] In a study using cases and controls from the Swedish Registry of Congenital Malformations and the Medical Birth Registry, Becker *et al*.[16] found that low birth weight was significantly different between controls and 84 cases with CL/P (OR: 2.04, 95% CI: 1.64-2.56) and 45 cases with CP (OR: 1.47, 95% CI: 1.10-1.96). Cases with CL/P were more likely to be preterm as well (OR: 1.49, 95% CI: 1.22-1.83). These results are similar to ours.

Wyszynski and Wu[17] studied 2437 cases with OCs and 4871 non-malformed matched controls from the 1997 US Natality database of the National Center for Health Statistics. The prevalence of preterm births was higher among cases than controls. The highest odds ratios were found when very premature babies (born between 20 and 27 weeks of gestation) were compared, with an OR: 2.1 and 95% CI: 1.1 to 4.1. Low birth weight and very low birth weight were significantly more common among cases than controls, as well ($OR_{low\ birth\ weight}$: 1.59, 95% CI: 1.3-1.9; $OR_{very\ low\ birth\ weight}$: 1.7, 95% CI: 1.0-2.0). The median birth weight for cases and controls was 3,345 and 3,402gm, respectively ($\chi^2 = 27.95$, $p < 0.01$).

In the Hungarian dataset there are only two very premature cases with CL/P, one with CP and one control; therefore, the analysis for this subgroup cannot be replicated. The odds ratios for low birth weight presented here are higher and those for preterm birth are lower than those presented by Wyszynski and Wu. This might be a real finding or due to the differences in the populations under study and methodological issues. Wyszynski and Wu's study included data on cases and controls obtained from birth certificates, which may be less reliable than those collected by the HCCSCA. Also, birth certificates do not discriminate between CL/P and CP. It should be noted, however, that even when the Hungarian CL/P and CP datasets are merged, these differences between studies persist. Finally, Wyszynski and Wu could adjust for the effects of maternal smoking and alcohol use. If these factors are truly influencing birth weight in a meaningful way, differences between the two studies are expected to arise.

Transforming growth factors are extracellular signaling molecules that play widespread roles in regulating development. In particular, the transforming growth factors alpha (TGFα) and beta (TGFβ) are known to contribute to facial development, especially in the area of palate formation.[18-21] However, they are involved in general growth as well. For example, the TGFβ superfamily of polypeptides performs a wide range of

regulatory functions. Members include the TGFβ family ($TGF\beta_1$, $TGF\beta_2$, $TGF\beta_3$, $TGF\beta_4$, and $TGF\beta_5$), and more distantly related members such as the bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and the activin/inhibin family. Thus, it is reasonable to speculate that deficiencies in the normal physiological activity could induce both poor general growth and OCs.[20] This is an area that deserves much more research.

In summary, the study presented here indicates that fetuses with CL/P and with isolated CP are at increased risk of low and very low birth weight but not of preterm birth compared to healthy controls. There are several alternative explanations for these findings: (1) it is possible, although unlikely, that the lower birth weight in OC cases might be related to the absence or incomplete development of facial tissues, (2) unmeasured confounders, such as maternal cigarette smoking, alcohol use, and maternal dietary intake, may have a retarding effect on fetal development, (3) genes thought to be involved in the etiology of some cases of OCs, such as MSX1 (a homeo box gene), transforming growth factor alpha (TGFα), and transforming growth factor beta-3 (TGFβ3) may also have a general effect in the development of the entire body. Normal development may be distorted by mutations in these genes, producing an association between OCs and low birth weight. This is an area of much promise and further studies are needed to determine whether birth weight and OCs are entities with distinct etiology.

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