ORIGINAL ARTICLE

Environmental factors related to the occurrence of oral clefts in a Brazilian subpopulation

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ABSTRACT

Background: A cross-sectional study was conducted at the Craniofacial Rehabilitation Center in the General Hospital of the University of Cuiabá, Cuiabá city, Mato Grosso, Brazil. **Materials and Methods:** Poisson regression model was used to analyze the relationship between antenatal factors and the occurrence of oral clefts in 116 patients. **Results:** Oral clefts were more common in males (64.66%) and White race (46.02%). The mean age of the children was 21.91 months. The most common type of cleft was cleft lip and palate (CLP, 55.17%). Maternal and paternal smoking in the first trimester of pregnancy and parity were significantly associated with the occurrence of CLP. Parent's age, educational level, and occupation did not interfere in the occurrence of oral clefts. There was also no significant association between maternal illness, medication use, alcohol consumption, and maternal exposure to chemicals in the first trimester of pregnancy and the occurrence of clefts in this population. **Conclusion:** The analysis of the environmental factors present during the pregnancy of children with oral clefts revealed a significant association between parity (second onward), maternal smoking, and paternal smoking and the occurrence of CL and/or palate in this population.

Key words: Cleft lip, cleft palate, epidemiology, public health, risk factors

INTRODUCTION

Isolated or nonsyndromic oral clefts, including cleft lip (CL), CL and/or palate (CL and/or P), and isolated cleft palate (CP), are one of the most common congenital malformations in humans.[1] They have geographic and racial variations[2] and seem to occur as a result of a complex interaction between genetic variations and environmental factors.[1-20]

Since environmental factors play a role of major importance in the etiology of oral clefts, the purpose of this study was to investigate its relation with the occurrence of nonsyndromic oral cleft patients in a Brazilian subpopulation.

MATERIALS AND METHODS

A cross-sectional study was conducted at the Craniofacial Rehabilitation Center in the General Hospital of the University of Cuiabá (HGU/UNIC), Cuiabá city, Mato Grosso, Brazil.

From the total of 776 oral cleft patients treated at the HGU/UNIC from 2004 to 2012, 200 patients were selected for this study by fulfilling the inclusion criteria that were: Being isolated or nonsyndromic oral cleft patients and younger than 6 years old. Patients were contacted by telephone and letter and attended to HGU/UNIC 116 volunteers.

The research project was approved by the Ethics Committee in Research of the University of Cuiabá (protocol of approval number: 2012-003) before its beginning. The aim of the study was carefully explained to the patients' parents, and their formal consent was obtained. Procedures followed

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were in accordance with the Helsinki declaration of 1975 as revised in 2000. Confidentiality of subjects was ensured by desisting from mentioning participants' names, initials, or hospital numbers.

A questionnaire was developed and administered by two interviewers supervised by the principal investigator aiming to collect the following information: Sociodemographic profile of the patients and their parents; oral cleft type, age of the parents during pregnancy; number of pregnancies and prenatal events such as maternal health problems, drug use, alcohol use, maternal smoking, and paternal drug use, contact with chemicals and exposure to ionizing radiation.

Descriptive and inferential statistics were used for data analysis. In the descriptive part, absolute and relative frequencies were presented. In the inferential part, measures of association were determined between the dependent variables and the independent or explanatory variables using Chi-square, Fisher's exact test, and likelihood ratio test with a significance level of 0.05. The prevalence ratio was also obtained with its respective confidence intervals of 95% and the association between variables. The variables with $P < 0.20$ were considered for the construction of a multivariate Poisson regression model, with confidence intervals of 95% and P value of selected variables by backward method. The variables with a significance level lower than 0.05 remained in the final model. Statistical analyses were performed with SPSS Version 15.0 (SPSS Inc., Chicago, IL, USA), Minitab Version 15.0 (Minitab Inc., State College, PA, USA), and STATA Version 10.0 (StataCorp LP, College Station, TX, USA).

RESULTS

The cleft lip and palate (CLP) was the most common feature with 64 cases (55.17%), followed by CL with 30 (25.86%) and CP with 22 (18.97%) cases.

Distribution of patients according to sex and age is presented in Table 1. Patients were distributed according to their parent-reported race/color of the skin as White (n = 52, 46.02%), Black (n = 22, 19.47%), Brown (n = 39, 34.51), and Native American (n = 3, 2.60%). According to the order of birth, 46 patients (39.66%) were the fruit of the first pregnancy, 37 (31.90%) the second pregnancy, and 33 (28.45%) the third or other pregnancy.

The parental age during pregnancy is presented in Table 2 and parental schooling divided into illiterate, elementary school, middle school, and higher education is presented in Table 3.

Maternal occupation was divided into housekeeping, service, commerce, student, education, and other. Paternal occupation was divided into service, rural, commerce, industry, education, student, and other. Parental occupation is presented in Table 4.

Table 1: Descriptive statistics of the patient's age

Age (months)	*n*	Mean	Standard deviation	CV	Minimum	Median	Maximum
Total population	116	21.91	18.10	82.63	1.00	16.50	68.00
Male	75	21.76	18.18	83.54	1.00	16.00	68.00
Female	41	22.17	18.17	81.97	1.00	18.00	60.00

Table 2: Distribution of patients according to parental age during pregnancy

	n	%
Maternal age at pregnancy (years)		
≤ 19	37	31.90
20-34	70	60.34
≥35	9	7.76
Total	116	100.00
Paternal age at pregnancy (years)		
≤19	9	7.76
20-39	96	82.76
≥40	11	9.48
Total	116	100.00

Table 3: Distribution of patients according to parental schooling

	n	%
Maternal schooling		
Elementary school	38	32.76
Middle school	65	56.03
Higher education	13	11.21
Total	116	100.00
Paternal schooling		
Illiterate	2	1.72
Elementary school	50	43.10
Middle school	50	43.10
Higher education	14	12.07
Total	116	100.00

Table 4: Distribution of patients according to parental occupation

	n	%
Maternal occuption		
Housekeeping	59	50.86
Servisse	22	18.97
Commerce	12	10.34
Student	10	8.62
Education	6	5.17
Other	7	6.03
Total	116	100.00
Paternal education		
Service	55	47.41
Rural	19	16.38
Commerce	9	7.76
Industry	7	6.03
Education	2	1.72
Student	1	0.86
Other	23	19.83
Total	116	100.00

Regarding changes in maternal health during the first trimester of pregnancy, it was found that 42 (36.21%) mothers of the 116 had infection, 14 (12.07%) had hypertension, and 4 (3.45%) had diabetes.

Concerning the use of medication during the first trimester of pregnancy, 39 mothers (33.62%) reported having used painkillers; 39 (33.62%) administered antibiotics; 4 (3.45%) used benzodiazepines; 3 (2.59%) used anticonvulsants; 3 (2.59%) used anti-inflammatory, and 6 (5.17%) said that they had used homemade medicines. One mother (0.86%) used corticosteroids during pregnancy. From the total mothers, 56 (48.28%) used folic acid and 64 (55.17%) used vitamins during pregnancy.

When asked about alcohol consumption during pregnancy, 22 mothers (17.24%) reported having done so. As for smoking, 9 mothers (7.76%) had this habit during pregnancy. It was also questioned about paternal smoking which was reported in 27 cases (23.28%). Illegal drug use was reported by 2 mothers (1.72%).

The contact of mothers with chemicals during pregnancy was also investigated and 32 (27.59%) said that they had had contact with these products. The chemicals most frequently reported were cleaning products (n = 13, 11.30%), pesticides (n = 9, 7.83%), cosmetics (n = 7, 6.09%), and other (n = 3, 2.61%). Eight mothers (6.96%) were exposed to ionizing radiation during pregnancy.

CL and CLP were considered a single group for the inferential analysis (CL and/or P). Chi-square test, Fisher's exact test, and likelihood ratio test were applied to verify the relationship between the studied environmental factors and the occurrence of CL and/or P or CP.

For the seven independent variables whose association value (P) with CL and/or P was <0.20 (race/color of skin, paternal age, maternal infection, maternal smoking, paternal smoking, contact with chemicals during pregnancy, and parity order), the prevalence ratio was obtained [Table 5].

The prevalence ratio was adjusted with the robust Poisson regression model with confidence interval of 95%. The results showed that maternal smoking (P < 0.001), paternal smoking (P = 0.042), and parity (second or over) (P = 0.042) were associated with the occurrence of CL and/or P. The race/color of the skin variable, although not statistically significant at the 0.05 level, remained in the model as an adjustment variable [Table 6].

Table 5: Prevalence ratio for variables with *P* value below 0.20

Variables	Category	Type of cleft				PR	95% CI	*P*
		CL ± P		CP				
		n	%	*n*	%			
Maternal smoking	No	84	78.51	23	21.49	1.00	-	-
	Yes	9	100	0	0	1.27	[1.15;1.41]	0.041LR
Paternal age	20-39	75	78.12	21	21.88	1.00	-	-
	≥40	9	82.82	2	17.18	1.05	[0.78;1.41]	1.000FE
	≤19	9	100	0	0	1.28	[1.15;1.42]	0.040LR
Infeccion	No	62	83.78	12	16.22	1.00	-	-
	Yes	31	73.81	11	26.19	0.88	[0.72;1.08]	0.195CS
Contact with chemicals	No	70	83.33	14	16.67	1.00	-	-
	Yes	23	71.88	9	28.12	0.86	[0.68;1.09]	0.167CS
Paternal smoking	No	69	77.53	20	22.47	1.00	-	-
	Yes	24	88.89	3	11.11	1.15	[0.96;1.37]	0.195CS
Race/color of skin	White	39	75.00	13	25.00	1.00	-	-
	Not White	54	84.38	10	15.62	1.12	[0.93;1.36]	0.197CS
Order of pregnancy	1st	40	86.96	6	13.04	1.00	-	-
	≥2nd	53	75.71	17	24.29	0.87	[0.73;1.04]	0.137CS

PR – Prevalence ratio; CI 95% – Confidence interval of 95%; *P* – Level of significance considering Chi-Square (CS), Likelihood Ratio (LR) and Fischer's Exact (FE) tests

Table 6: Prevalence ratio adjusted by Robust Poisson regression (PR_a) with their respective confidence intervals (CI) of 95% and *P* value of the variables selected by backward method

Variable	Category	PR_a	95% CI	*P*
Maternal smoking	No	1.00	-	-
	Yes	1.33	1.16-1.52	<0.001*
Paternal smoking	No	1.00	-	-
	Yes	1.21	1.01-1.45	0.042*
Order of pregnancy	1st	1.00	-	-
	≥2nd	1.21	1.01-1.45	0.042*
Race/color of skin	White	1.00	-	-
	Not White	1.17	0.97-1.41	0.096

PR_a – Prevalence Ratio adjusted in Poisson regression model with variable selection. *Significant at 5%. CI – Confidence Interval

DISCUSSION

Mato Grosso is the third largest state of Brazil located in the central-west region with the population of 3,035,122 inhabitants. Since the late 20th century, it is the national champion of grain, cattle, and wood production. The Craniofacial Rehabilitation Center in HGU/UNIC was implanted in 2004 in Cuiabá, capital of Mato Grosso, as the first specialized center for the care of oral cleft patients in the state.[21,22]

The population of this study comprised 64.66% of male patients. Although the study does not reflect the totality of Mato Grosso's oral cleft patients, this result is similar to previous studies that indicate greater incidence of clefts in men.[1,6,9,23-26]

Among the study population, 46.02% were White, 34.51% Brown, 19.47% Black, and 2.60% Native American. Previous studies conducted in different localities also found oral cleft predilection for Caucasians and lower frequency in Afro-descendent population.[9,23,24,27]

For the inferential analysis, CL and CLP were considered as one group (CL and/or P) as they are etiologically,

embryologically, and epidemiologically different from CP.[3,24,25,28]

Among the variables related to the parents of children with clefts, we evaluated the age of the parents at the beginning of pregnancy. Maternal and paternal ages have been investigated as possible risk factors for the occurrence of CLP.[1,9,25,29,30] Herkrath *et al*.[3] conducted a meta-analysis analyzing parental age as a risk factor for CLP. They demonstrated that parents aged 40 or older had an increased risk of generating a child with CP and mothers aged 35–39 years were more likely to produce a child with CP. Mothers aged 40 or older had an increased risk of generating a child with CL and/or P. They also reported that no evidence was found associating younger parents with increased risk to the occurrence of clefts. In our study, 60.34% of mothers were aged between 20 and 34 years and 82.76% of the parents were aged between 20 and 39 years at the start of pregnancy, contrasting the results that suggest an association between advanced age of the parents and the occurrence of oral clefts.[3,25,29-31] This study found no association between maternal and paternal age and the occurrence of CL and/or P or CP.

It was observed that 39.66% of the cleft patients were the result of the first pregnancy and 60.35% of the second pregnancy onward. It was suggested that the greater the number of pregnancies, greater the risk of a woman having a child with cleft perhaps because an excessive number of abortions could lead to damage or dysfunction in the female reproductive tract.[25] Messer *et al*.[30] demonstrated that a higher proportion of cleft cases was generated by women who had three or more previous pregnancies in Texas between 1999 and 2003. A case–control study in China with 713 cases of nonsyndromic oral clefts showed that the highest proportion of cases originated from the second pregnancy onward,[25] similar to the result of this study, found significant association in the occurrence of CL and/or P in children born in the second or posterior pregnancies in the adjusted Poisson regression model ($P = 0.042$).

Regarding parental education, it was observed that mothers had more years of study than fathers since 56.03% of them had middle school education against 43.10% of men. It is noteworthy that only 11.21% of mothers and 12.07% of fathers had higher education. It has been shown in previous studies that parents of oral cleft children tend to have lower educational level.[1,13,27]

The parental occupation variable was analyzed in this study because there could be a parental occupational exposure to different agents during pregnancy, favoring the development of congenital anomalies such as oral clefts.[18,32-34] However, such association was not established in this study.

The association of oral clefts and the use of certain drugs during pregnancy have been suggested over the past decades.[35-42] Medications such as anticonvulsants,[37,41] benzodiazepines,[35,36] and corticosteroids[38-40,42] have been investigated. However, the association of these drugs with the occurrence of oral clefts is still inconclusive since many of these studies limited by a lack of statistical power[15] showed weak evidence of association[43] or even absence of association.[15,44] In the present study, mothers reported the use of analgesics (33.62%), antibiotics (33.62%), benzodiazepines (3.45%), anticonvulsants (2.59%), and anti-inflammatories (2.59%). The use of home remedies was also questioned and although Omo-Aghoja *et al*.[31] have found an increased relative risk to CP and unilateral CLP with the use of herbal medicines, this study found only 5.17% reported using home remedies during pregnancy.

On the other hand, the use of folic acid and vitamin supplements during pregnancy has been inversely related to the occurrence of oral clefts,[2,25,45] but this relation still has consistency limitations[45,46] and the mechanism of how this protective effect occurs is still unknown.[46] In this study, it was observed that 55.17% of mothers administered vitamin supplements during pregnancy and 48.28% administered folic acid. This is an important finding because it contradicts an important public health strategy since the preventive administration of folic acid is also associated with a lower incidence of neural tube defects and congenital cardiac anomalies.[13] It was recently shown that the quality of maternal diet could also be associated with a reduction in the risk of neural tube defects and oral clefts even more consistently than maternal administration of isolated nutrients.[47]

A positive association between alcohol consumption during pregnancy and occurrence of oral clefts has been shown in several studies,[8,10,11,31] but not in all.[9,25] This inconsistency in the results may be due to the need of excessive consumption of alcohol for the expression of the anomaly, which is uncommon in pregnancy,[11] thus having a small number of exposed women. In this study, 17.24% of the mothers reported any alcohol consumption in the first trimester of pregnancy, and there was no association with the occurrence of oral clefts.

We also assessed maternal smoking during the first trimester of pregnancy and paternal smoking. The association between maternal smoking and oral clefts has been investigated in many studies that have suggested a modest association.[1,6-9,14,48] In this study, we found a significant association between maternal smoking and occurrence of CL and/or P in the adjusted Poisson regression model ($P < 0.001$) as in several studies.[1,6,8,9,48] Likewise, paternal smoking in this study has also been associated with the occurrence of CLP ($P = 0.042$), confirming the results found by Jia *et al*.[25] and Zhang *et al*.[1]

Considering maternal contact with chemical agents in the first trimester of pregnancy, we found that 27.59% of the mothers came into contact with these products being 11.30% with cleaning agents, 7.83% with pesticides, and 6.09% with cosmetics. Garlantézec *et al*.[18] showed that maternal exposure to solvents is associated with the occurrence of oral clefts, these solvents being present in cleaning agents and cosmetics and other products. As for pesticides, for decades, their relationship with birth defects including CLP has been investigated. Despite scientific evidence suggesting this association, it is not conclusive.[14,19,34,49] Recent studies in the State of Mato Grosso showed the relationship between the use of pesticides and the occurrence of congenital malformations;[50,51] the association, however, was not observed in this study.

CONCLUSION

The analysis of the environmental factors present during the pregnancy of children with oral clefts revealed a significant association between parity (second onward), maternal smoking, and paternal smoking and the occurrence of CL and/or P in this population.

The present data may subside oral clefts prevention and counseling programs.

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Conflicts of interest
There are no conflicts of interest.

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