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Associated factors in oral clefts in Sistan and Baluchestan province, Iran: A cross sectional study.

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Abstract

Introduction: Oral Clefts are gaps in upper lip; palate or both that are associated with many factors. The objective of the current study was to evaluate the parental and newborn factors associated with different types of OC in newborns in Zahedan, Iran.

Methods: This cross-sectional study performed on 212 oral cleft patients to determine the associated factors. The probable factors related to the patients such as gender, parity and weight and maternal factors such as smoking, family marriage, family history of clefts, maternal age at birth, folic acid taking and etc. were considered. The study was a part of a thesis for degree of doctor of dental surgery (DDS) numbered 6831. The collected data analyzed by SPSS 16 using P-value less than 0.05 as statistically significant.

Results: Of patients, 50.5% were female. The prevalence's of CHDs in OCs were 26.4% and distributed in CL, CP and CLP of 26.8%, 30.4% and 42.9%, respectively. 31.60%, 36.3%, 44.8%, 20.3% and 47.2% of OCs children had family history of OCs, family marriage, maternal fever, tobacco using and taking folic acid during pregnancy, respectively. Weight was significantly in three types of OCs ($F=9.795$, $p<0.001$). Children with CLP had the highest birth order significantly ($F=18.561$, $p<0.001$). Maternal age at birth was difference in OCs children ($F=33.389$, $p<0.001$). CHD distributed uniformly among all types of OCs with the prevalence of 26.8%, 30.4% and 42.9% in CL, CP and CLP respectively ($p>0.05$). Lack of consuming folic acid ($p=0.002$), positive family history of OCS ($P<0.001$), family marriage ($p=0.034$) were significant.

Conclusion: Concluded that most of the maternal features such as fever, smoking, taking folic acid had positive impacts on having OCs children.

Keywords: Oral clefts, Associated factors, Congenital heart defects.

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Introduction

Oral Cleft (OC) is a gap or/and split that occur in upper lip(CL), the roof of the mouth named palate(CP) or sometimes lip and palate together(CLP) which are the most common head and neck anomalies [1]. OC is a heterogeneous and the most important groups of congenital defects with prevalence of 1:600-1,000 among newborns [2]. OC prevalence is 1.43/1000 in live births across the world and it is highest in Asians, 2/1000 and followed by Caucasians with 1/1000 and the lowest of 0.4/1000 in African populations [1]. The incidence rate of CLP is 0.9 in Sudan [3] when the prevalence has reported of 1.5/1000 in Oman [1]. The prevalence of OC in Iranian population ranged from 0.86 to 3.73/1000 at birth [4]. In the Southern area of Iran it reported 0.80/1000 [5] and in North as 1.05/1000 [6]. In a city of Iran, Hamedan, OC prevalence has been reported as 1.016/1000 [7], in Tehran 2.14/1000 [8] and 1.9/1000 in Mashhad [9]. Wang et al [10] conducted a based population study on OC and resulted that the overall prevalence was 1.76 per 1000. The prevalence of CLP was 1.49 per 1000 and the prevalence of CP was 0.27 per 1000. The ratio of CLP:CP was 5.60:1 in their analysis [10]. Considering etiology, risk factors are essential to define how prevention and treatment should be planned and implemented, as well as to measure the efficacy of such intervention [9].The causes of OCs among

most infants are unknown [10]. Recently, findings from research studies about some factors that increase the chance of having a baby with an OC shows an higher association with maternal Smoking during pregnancy [11], metabolic disorders diagnosed before pregnancy [12] and other factors, including infant sex [6], maternal age at birth [13], maternal influenza [11], birth order [6], family history of OCs [13], taking folic acid [6], family marriage [6] and many other factors. For instance, a meta-analysis considering parental age showed that fathers with 40 years or older have a 58% higher probability of having a child with cleft palate (CP) and mothers over 40 years of age, the probability is 28% higher for CP and 56% higher for CLP(14). Another factor that needs to be introduced is congenital heart defects (CHDs) that are the most common associated anomalies with OC with wide range prevalence [1]. The objective of the present study was to evaluate the maternal and newborn factors association with different types of OC in newborns in Sistan and Baluchestan province of Iran. With new information achieved, hope to increase public awareness of such risks and thereby help to reduce the incidence of OCs types in the area of the study.

Methodology

Study Design and Population

This cross-sectional study performed on 212 patients with oral cleft to determine the ratio of different types and associated factors. The study conducted on OC newborns that referred to pediatrics heart center of Ali Asghar Hospital, Sistan & Baluchestan province, Zahedan that located in south eastern of Iran. Between 1st Jan 2013 and 30th Dec 2016 all OC newborns entered to the study with the target population of Iranian nationality. The foreignness with OCs excluded from the study, specially, Afghan refugee who live in the province.

Methods

By organizing the results according to the OCs children from the hospitals, 212 subjects referred to the Pediatric Heart Center. Before diagnosing the CHDs, patients' mothers asked to answer some questions of age, birth weight, birth order, gender, parental conditions and patients such as smoking tobacco by hookah, family marriage, maternal age at birth, taking folic acid during pregnancy, oral clefts types and family history of clefts.

To diagnose CHDs, patients were under echocardiography using Manual (M) Mode and two-dimensional with Doppler irrespective of whether they are symptomatic or not for the presence of congenital heart diseases.

Ethics Statement

The study conducted after ethical approve by the research committee of School of Medicine, Zahedan University of Medical Sciences as a thesis for the degree of doctor of dental surgery (DDS) numbered 6831. Written informed consent obtained from all parents.

Statistical Analysis

The data analyzed using the statistical package for social science, version 16.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics, Chi-square test was used to compare proportions between two or more groups and analysis of variance were used for comparing means in more than 2 groups. P-value less than 0.05 were considered statistically significant.

Results

Table1 showed that 212 OCs patients analyzed and resulted, 57 (26.9%), 84 (39.6%) and 72 (34%) for CL, CP and CLP, respectively. Of patients 50.5% were female. The prevalence of CHDs in these patients was 26.4% accounted for 56 individuals. These CHD patients distributed in different types of OCs, lip, palate and both as 15 (26.8%), 17 (30.4%) and 24 (42.9%), respectively. From the OCs children 67 (31.60%) had one or more family members with OCs. Family marriage between parents of OCs children was 77 (36.3%). Mothers who had fever during pregnancy were 95 (44.8%) and this percent for mother who smoke tobacco was 43 (20.3%). Mother who took folic acid during pregnancy was 100 (47.2%).

Table 1 showed the results of ANOVA test that OCs children with CL (5.209 ± 4.42) had higher age at the time of survey in months, that was non-significantly compared to the others OCs ($F=0.308$, $p=0.735$).

Weight at survey time was significantly different amongst the three types of OCs ($F=9.795$, $p<0.001$). Birth order considers one of index to evaluate its effect on specific type of OCs. The results showed that children with CLP had the highest birth order significantly ($F=18.561$, $p<0.001$). Maternal age at birth was low in children with CL (23.30 ± 3.99) compared others (27.54 ± 5.83 and 32.47 ± 7.31 for CP and CLP). The difference was significantly ($F=33.389$, $p<0.001$). Table 2 showed the follow-up test of Tukey. In the case of weight at survey time for OCs children, the difference were significant between all paired groups; CL and CP, CL and CLP, CP and CLP with $p=0.004$, $p<0.001$ and $p=0.004$, respectively. Parity of OCs children was different only in the paired groups of CL and CLP, with $p<0.001$. Maternal age at birth was significant in all paired groups; CL and CP, CL and CLP, CP and CLP with $p=0.002$, $p<0.001$ and $p=0.002$, respectively. Table 3 showed frequency of OCs in the categorization of socio-economic-demographic features. The distribution of females was higher in CP but not significantly ($P=0.157$). Positive family history of OCs were significantly in CL children ($P<0.001$). CHD distributed uniformly among all types of OCs with the prevalence of 26.8%, 30.4% and 42.9% in CL, CP and CLP, respectively ($p>0.05$). Of 212 OCs children 95 had mother with fever during pregnancy. The distribution

Table 1. *ANOVA test results of continuous variables among different type of OC*

Variable	Oral cleft	Number	Mean	SD	F	P
Age at survey time in months	CL	58	5.21	4.42	0.308	0.735
	CP	82	4.92	4.33		
	CLP	72	4.62	4.04		
	Total	212	4.90	4.25		
Weight at survey time	CL	58	5.97	1.94	9.795	<0.001
	CP	82	4.87	2.25		
	CLP	72	4.45	1.70		
	Total	212	5.02	2.07		
Parity	CL	58	2.47	1.60	18.561	<0.001
	CP	82	3.09	1.69		
	CLP	72	4.43	2.32		
	Total	212	3.37	2.06		
Maternal age at birth	CL	58	23.98	3.99	33.389	<0.001
	CP	82	27.54	5.83		
	CLP	72	32.47	7.31		
	Total	212	28.24	6.83		

Table 2. *Follow up Tukey test for pairwise comparison of continuous variables among different type of OC*

Variables (i)	OCs (i)	OCs (j)	Mean Difference (i-j)	SD	p value
Age at survey time in months	CL	CP	0.29358	0.73073	0.915
		CLP	0.58871	0.75146	0.714
	CP	CLP	0.29513	0.68786	0.904
Weight at survey time	CL	CP	1.10286*	0.34186	0.004
		CLP	1.52158*	0.35156	<0.001
	CP	CLP	-1.10286*	0.34186	0.004
parity	CL	CP	-0.61985	0.32728	0.143
		CLP	-1.96504*	0.33656	<0.001
	CP	CLP	0.61985	0.32728	0.143
Mother age at birth	CL	CP	-3.55383*	1.02458	0.002
		CLP	-8.48946*	1.05364	<0.001
	CP	CLP	3.55383*	1.02458	0.002

among different types of OC were 55 (57.9%), 19 (20%) and 21 (22.1%) for CLP, CP and CL, respectively. This trends was significant (p<0.001). Forty three mothers was smoking tobacco using hookah during pregnancy. Of 43 mothers, 4 (9.3%), 38 (88.4%) and 1 (2.3%) had children with CL, CP and CLP respectively. This pattern was significant (p<0.001). Another factor that likely affected on type of OC is lake of consuming folic acid during pregnancy. From our study population, 100 from 212 children had mothers with taking folic acid during pregnancy with the distribution of CL, CP and CLP of 38%. 37% and 25% respectively in which was higher for the children with CL. The mentioned distribution was significant (p=0.002). Consanguineous marriage (Family marriage) was more in children with CL (37.7%) and followed by CP and CLP equally (31.2%). This dissimilarity in distribution was significant (p=0.034).

Discussion

The analysis of the present study showed that CP was more frequent than other types. The distribution of females was higher in CP. CHD prevalence in OCs children was little more than quarter. And one third of the study population had one or more family members with OCs. Family marriage between parents of OCs children was one third. Mothers who had fever during pregnancy and took folic acid were half and this percent for mother who smoke tobacco was one fifth approximately. The factors of child's weight at survey time, child parity and mother age at birth were different in OCs. Positive family history of OCs was more in children with CL. The trends of maternal fever were more in CLP. Smoking tobacco using hookah during pregnancy was higher in isolated CP. Non-consuming folic acids by mothers during pregnancy were higher in

Table 3. *Frequency of oral cleft in the categorization of socio-economic-demographic features*

Variables	Options	Statistics	Oral Cleft types			Total	Contingency Coefficient	p value
			CL	CP	CLP			
sex	Male	Number	33	34	38	105	0.131	0.157
		Percent	31.4%	32.4%	36.2%	100.0%		
	Female	Number	25	48	34	107		
		Percent	23.4%	44.9%	31.8%	100.0%		
Positive family history of OCs	No	Number	17	71	57	145	0.462	<0.001
		Percent	11.7%	49.0%	39.3%	100.0%		
	Yes	Number	41	11	15	67		
		Percent	61.2%	16.4%	22.4%	100.0%		
Congenital heart defect	No	Number	43	65	48	156	0.121	0.208
		Percent	27.6%	41.7%	30.8%	100.0%		
	Yes	Number	15	17	24	56		
		Percent	26.8%	30.4%	42.9%	100.0%		
Maternal fever	No	Number	37	63	17	117	0.423	<0.001
		Percent	31.6%	53.8%	14.5%	100.0%		
	Yes	Number	21	19	55	95		
		Percent	22.1%	20.0%	57.9%	100.0%		
Maternal smoking hookah	No	Number	54	44	71	169	0.46	<0.001
		Percent	32.0%	26.0%	42.0%	100.0%		
	Yes	Number	4	38	1	43		
		Percent	9.3%	88.4%	2.3%	100.0%		
Folic acid taking	No	Number	20	45	47	112	0.236	0.002
		Percent	17.9%	40.2%	42.0%	100.0%		
	Yes	Number	38	37	25	100		
		Percent	38.0%	37.0%	25.0%	100.0%		
Consanguineous marriage	Yes	Number	29	24	24	77	0.175	0.034
		Percent	37.7%	31.2%	31.2%	100.0%		
	No	Number	29	58	48	135		
		Percent	21.5%	43.0%	35.6%	100.0%		

CLP children and those who married with relatives had more children with isolated CL [14].

There are unknown pattern of OCs types. Manyama et al. [15] resulted that the most common OCs was isolated CL followed by CLP and isolated CP respectively. Martelli-Junior et al. [16] and Rajabian and Aghaei [5] received to the same conclusion with Manyama et al. [15] that CLP was the most common type. These results were different with the present study findings in this specific outcome. Has been expressed that this variation may reflect a biological phenomenon especially in Africa, Asia and South America [15]. Lei et al. [17] said that the prevalence was higher for CLP. Overall prevalence was 0.1% for CLP and 0.04% for CP over the 8 year study period. From the present study resulted that CP was more frequent than two other OCS consisted with the study that conducted in china by Sun et al. [18] with results of significantly more common in CP but Priyadharshini et al. [19] and Rittler et al. [20] resulted that CLP was more common. They also reported that isolated CP and isolated CL were in the second and third ranking, respectively.

The present study received to the conclusion of more males than females at OCs risk and was consisted with Wang et al. [10] that reported CLP and CL were more common in males than in females, whereas CP was more common in females than in males. Furthermore, Golalipour et al. [6] in Iran, Sadri [21] in Iran and Natsume et al. [22] in Japan resulted that OCs were found to be more common in males than females. Manyama et al. [15] reported that males were slightly more affected than females among all clefts and reported that this variation was not statistically significant. CLP was more frequent in males, but females more often have only CP.

The present study resulted that the prevalence of CHDs in OCs was 26.41% and the distribution of CHDs among OCs were similar; CHDs were more in CLP and followed by CP and then CL. This similarity distribution was consisted with Noori et al. [1] and Barbosa et al. [23] results that showed, CHDs had the highest frequency in CLP and had the lowest in children with CL. Meanwhile Sun et al. [18] showed dissimilar results in china, where CHDs were higher in CP. Priyadharshini et al. [19] study showed that the prevalence of CHDs in Cleft children was 21.9% whereas a study done by Shafi et al. [24] and Murthy and Bhaskar [25] showed the overall prevalence of CHDs in children with OCs changed from 6.7% to 15%.

Wang et al. [10] found that a history of fever or cold during the pregnancy period was associated with approximately a threefold increased risk of OCs, which persisted after controlling for other covariates. Because cold is a common source of fever, and fever and colds often occur concomitantly, they investigated them as one item in the questionnaire, and therefore could not determine from our data whether the increased risk observed was attributable to the fever or to the cold. This difference might arise from socioeconomic [26]. Environmental factors in study made by Molina-Solana et al. [27] indicated that one of the main factors in CLP main factors was fever during pregnancy. The results of the present study showed that the distribution of mothers with fever were different in types of OCs [28,29].

Previous studies have reported the association between OCs and maternal cigarette smoking. A study conducted in Cosovo and reported that maternal smoking had a little impact on having OCs children [3]. Leite et al. [28] in a case-control study, investigated that the possible association between smoking during the first trimester of pregnancy and non-syndromic CLP and CP.

Honein et al. [11] in a study on maternal smoking tobacco found that maternal smoking was associated with CLP and more strongly associated with bilateral cleft, with a weaker association observed for isolated CP.

Gil-da-Silva-Lopes and Monlleo [2] found a positive association between maternal smoking during the first trimester of pregnancy with both cleft lip with or without cleft palate and isolated cleft palate in the United Kingdom. Chung et al. [30] reported the largest study to test the association between maternal cigarette smoking during pregnancy and having a newborn with OCs. Tobacco intake seems to have the most serious influence on OCs according to Lebby et al. [31]. On the other hand, study performed by Leite and Koifman [28] concludes that maternal smoking in first trimester of pregnancy was not statistically significant with OCs. Meyer et al. [32] reported an association between OCs and maternal cigarette smoking during pregnancy, while other study that conducted by Wang et al. [10] in Shenyang, China showed statistically significant association between history of smoking during pregnancy and having OCs children, they observed the chance of 2.37 more than mothers without history of smoking to have children with OCs.

Another important factor is the parental age. The older parents had higher probability to have OCs children. In Cosovo study [3], found that with an increase in the maternal age, there was an increased of OCs in newborns. They concluded that the maternal age has a greater impact compared with that of the fathers. They reported that 1 year increase in the maternal age increased the risk for clefts 1.83 times, while the same increase in the paternal age increases this risk 1.3 times. In reference to the effect of maternal age as a risk factor, Sipek et al. [33] confirmed that women older than 35 were higher at risk for OCs. Whereas, Shaw et al. [34] concluded that the risk for women older than 39 of having children with OCs was 3 times higher compared with women aged 25 to 29. Bille et al. [35] conducted a study of separate analyses of mother's and father's age in Denmark and showed that older parental age was associated with increased risk of OCs. Mothers, who had age greater than 35 years, were more at risk to have OCs children in Gorgan a city of Iran. Golalipour conducted a study in this area and received with a non-association between maternal age and oral cleft [6]. The present study concluded that maternal age was associated with the types of OCs similar with Vallino-Napoli et al. [36], Elahi et al. [37], Jagomagi et al. [38] and Bille et al. [35] studies and dissimilar with Fathololumi et al. [39], Abramowicz et al. [40] and Golalipour et al. [6]. Wang et al. [10] said that with maternal age increasing, the chance of having oral cleft child decrease in which the reported that mothers with age lower than 25 years had the highest risk of having a child with oral cleft, when mothers with age greater than 40 years had the lowest risk. Florida said maternal age was significantly associated with the risk of a child with OC. Bille et al. [35] said some about parent age that older mother's and father's age was associated with increased risk of OCs.

Golalipour et al. [6] said that there was no association between risk of cleft and family marriage. Meanwhile Sadri and Ahmadi [21], Azimi and Karimian [41] and Reddy et al. [42] reported a significant association between OCs and family marriage. The present study is confirmed by Sadri and Ahmadi [21], Azimi and Karimian [41] and Reddy et al. [42] that received to the conclusion of significant association between OCs types and family marriage.

Leite and Koifman [28] reported a significant association between parental consanguinity and only with cleft lip and cleft palate. One risk factor that did show an association with an increased risk of oral clefts was the parity of the mother. Golalipour et al. [6] reported that the Parity higher than 2 was significantly associated with an increased risk of oral clefts. They observed association between parity and an increased risk of oral clefts and reported that it may be due to the physiological condition of the mother, as increased parity may have adverse effects on micronutrients and subsequently increase the risk of oral clefs. Recently, Vieira and Orioli [43] in a meta-analysis found an increasing risk with increasing birth order for cleft lip with or without cleft palate and cleft palate only. In Golalipour et al. [6] study, folic acid consumption was not significantly associated with oral clefts but Van Rooij et al. [44] in the Netherlands reported a significant reduction in the risk of cleft lip and/or palate with the use of folic acid supplements. In this case, Wilcox et al. [45] reported a significant decrease in the risk of cleft lip and palate with the use of folic acid supplements adjusted for the use of multivitamins. Bille et al. [35] found an interaction

between maternal age and oral cleft. This interaction might be the result of social confounding. The constellation of a young mother and an old father, who in their analysis had a relatively low risk of cleft, may be associated with preventive environmental factors such as vitamin intake or high intake of dietary folic acid. Van Rooij et al. [44] in a meta-analysis reported decreased rates of oral clefts with folic acid use.

A study in Cosovo [3] confirmed that positive family cleft history increased the odds of having a child with OCs compared with those cases with a negative family history. Leite et al. [28], in a case-control study, found that the family history of OCs either in the father's or in the mother's relatives was strongly associated with OCs. Zarante et al. [46] found that a positive OCs family history was important risk factor for OCs in children. In Korea [47], positive family history was found in seven percents of cleft cases, with the most common in CL followed by CL P and then CP. Natsume et al. [22] found that families with cleft had more OCs children compared to their counterparts. Togoo et al. [48] said a history of OCs in family members was observed in children with OCs compared with Non-OCs children. Suleiman et al. [3] said, Factors affecting the incidence of OCs were considered to be a positive family history.

Study Limitation

The limitation of this study was the sample size. We also need to maintain an accurate database for cleft registrations; systematic record keeping is essential in this area. The database did not provide information on maternal health or peri-conceptual conditions, which may play a role in development of facial cleft deformities. Additional demographic factors such as socioeconomic status and area of residence (urban or rural), which have been associated with different prevalence rates, were also not recorded.

Conclusion

From the present study concluded that the CHDs prevalence in OCs children was more compared to many regions in Sistan & Baluchestan province, Iran. Most of the maternal features such as fever, smoking, taking folic acid, family marriage, maternal age at birth and parity had correlation with on having OCs children.

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