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The Prevalence and Risk Factors of Cleft Lip and Palate in Northern Region of Saudi Arabia

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Abstract

Background: Knowing the prevalence and avoidable risk factors of Cleft Palate (CP)/lip (CL) in the targeted area is of utmost importance. We aimed to determine the prevalence of and risk factors for CL and/or CP in the northern region of Saudi Arabia.

Methods: A retrospective record-based study was conducted at Sakaka, Dawmat Al-Jandal, Tabrjal, Qurayyat, and Arar. We included all the valid complete live birth records, from the local Maternity and Children Hospitals, in the period covering 2016 to 2020.

Results: Out of 62088 birth records, the study included 99 children that give a rate of 1.6/1000 that is relatively high. 28 (28.3%) of them had CL only, 24 (24.2%) had CP only, and 47 (47.5%) had both CL & CP. It was left-sided among 47 (48%) children, right-sided among 26(26.5%) children, and, bilateral congenital anomaly was recorded for 25 (25.5%) children. There is mild male preponderance (n=56; 56.6%), 20 (20.2%) were first family child and 14 (14.1%) were late (≥ 6th) child. One quarter of the children (n=26; 26.3%) were born with low birth weight (<2.5 Kg) and 7 (7.1%) were born with a birth weight >4 Kg. Three children were preterm and were born at 7th month. The most reported risk factors among the study children were father smoking (50.5%), mother passive smoking during pregnancy (45.5%), lack of folic acid supplementation during pregnancy (36.4%), previous history of abortion (31.3%), multivitamin deficiency during pregnancy (26.3%), gestational diabetes (11.1%) and irregular pregnancy follow-up (25.3%). Family history of congenital anomalies and epilepsy were the least reported factors (8.1% and 2%, respectively). As for parental factors, consanguinity was reported among parents of 60 children (60.6%); 40 (40.4%) couples had 1st degree and 20 (20.2%) couples had 2nd degree consanguinity. All of these risk factors are preventable/modifiable through proper approaches locally and nationally.

Conclusion: The rate of CL/CP in our population is relatively high and it has preventable/modifiable risk factors that necessitate implementation of counteracting specific local and national measures.

Keywords: Cleft palate; Cleft lip; Oro-facial clefts; Risk factors; Prevalence; Saudi Arabia

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Introduction

Cleft Lip (CL), Palate (CP), or both (CL/CP) are the most congenital birth defects and the most widely recognized oro-facial congenital malformation found among live births world-wide. CL and CP are issues of enormous universal extents, influencing more than 10 million individuals around the world [1]. This group of anomalies, comprising cleft of facial structures and/or cleft of oral structures, like the hard palate, is heterogeneous [2]. It was reported that, with increases in world population, and parallel increases in life expectancy, there will be an obvious increase in the numbers of peoples living with oro-facial clefts [3]. Overall, oro-facial clefts happen in all races, both genders, and all socioeconomic groups, and vary internationally. The child and the family often suffer serious psychological problems and socio-economic impact. Each of CL and/or CP cases requires several surgical procedures and complex medical treatments [4,5].

The etiology of the problem remains complex and poorly understood. Hence, there is no one detected specific cause and the problem seems to result from multiple genetic and environmental factors along with a complex gene-environment interactions. Majority of CL and/or CP are non-syndromic (70%) without any additional physical or cognitive deficits [6]. It can also be caused

by chromosomal abnormalities in peoples born with genetic syndromes. The risk factors that increase the likelihood of CL and/or CP include a strong family history of CL and/or CP, exposure to certain environmental substances (e.g., tobacco, alcohol, toxins and plasticizers, prescription and illegal drugs), folate, vitamin A and multi-vitamin deficiencies, parental consanguinity, mother's age at birth time, and pathogens [5,7,8]. Previous studies highlighted the involvement of these life-style, genetic, medical, and malnutrition factors in the increased frequency of inborn birth defects; particularly for CL/CP [9-13]. The signs and symptoms related with the cleft rely upon an assortment of factors; including type, and seriousness, and whether both lip and palate are involved [14,15].

CL and/or CP are 2nd most common birth deformity in the United States; influencing 1/940 births. For CP, approximately 1 in 1,574 infants is born with CP [16]. In Istanbul, Turkey, it was found that, unilateral CL/CP was the most common cleft type, and was seen more on the left side. While males were affected more by CL/CP, isolated CP was seen more in females [17]. In Ontario, Canada, incidence of Oro-Facial Clefts (OFCs) had a decreasing trend from 1994 to 2017. Mortality in children with OFCs was high, mostly in the first 2 years of life, and was usually connected with the presence of other congenital or chromosomal anomalies [18]. CL/CP prevalence was 6.0 per 10,000 live births in Colombia [19]. In Georgia prevalence of CL/CP in 2006 to 2015 was 0.95 ± 0.04/1000 live births, while in 1981 to 1990 it was 1.05, with significant variance across the country regions-a lowest of 0.56 to a highest of 2.28/1000. CL/CP is the most frequently occurring anomaly in Georgia accounting for 39.8% of all congenital malformations, while CL alone ranks the second 36.1%, followed by CP alone (24.1%). There is male preponderance of 60.3% [20].

Such geographical variation, country and region-wise, is also evident in Saudi Arabia. Qassim, Saudi Arabia, showed the highest incidence of clefts (2.19/1000 live births) [21]. A study investigated risk factors and features and prevalence of non-syndromic OFCs in 3 major cities of Saudi Arabia (Riyadh, Jeddah and Madinah) found a general prevalence of 1.17/1000. CL rated 0.47/1000 infants, CP rated 0.28/1000 infants, and CL/CP rated 0.42/1000 infants. CP was uniquely significantly related to first cousin marriages [22]. Records from King Faisal Specialist Hospital and Research Center, Riyadh, revealed 807 cases of CL and/or CP. They comprised 451 boys and 356 girls. Combined CL/CP were more common (n=387) than separate CP (n=294) or CL (n=122). Boy to girl ratios was 1.6:1, 1.2:1, and 0.9:1 for CL/CP, separated CL, and separated CP, respectively [23]. Lower universal prevalence of OFCs in the population of the southern Saudi Najran province was reported (0.65/1000 live newborns). While consanguinity was observed in 81.3% of identified cases, the study did not observe a relationship with paternal smoking during pregnancy [24]. Further lower rate of facial clefts (0.3/1000 live births) was also reported in Riyadh [25].

Lack of a birth-defect registering system and an absence of national surveys on this topic in Saudi Arabia, makes the exact national prevalence of OFCs, pattern, and risks factors largely unknown. We aimed to dig the live birth records and family medical history of the Maternity and Children Hospitals of the northern Saudi region for CL and/or CP birth anomalies, and to correlate its frequency with known risk factors (including paternal, life-style and environmental factors).

Material and Methods

A retrospective hospital record-based study was conducted in the Maternity and Children Hospitals of the northern region of Saudi Arabia; Sakaka, Dawmat Al-Jandal, Tabrjal, Qurayyat, and Arar, during the period from January 1st to 31st June, 2021. We included all of the valid complete records of live births of the years 2016 to 2020. As the region has ~50,000 women at the fertile age, a sufficient sample size turned to be 380 [26]. Incomplete/invalid records were excluded, except in cases that we succeeded to retrieve the data through personal communications with the parents, particularly for records with the target anomaly.

Relevant data was collected using a predesigned data collection proforma. The collected data included the cleft type, mother's age at childbirth time, gender of the newborn, and presence of other anomalies, family house/home location (urban, rural, area environment with hazards, e.g., nearby electromagnetic stations and pesticides/herbicides, lead, and aliphatic acids, and organic solvents exposures), father's and mother's age and occupation at birth time, family (mother and father sides) medical history, mother's obesity during pregnancy, infection (viral and antiretroviral drugs), fevers and environmental exposure during pregnancy (alcohol, smoking and medications, e.g., asthmatic mothers with bronchodilators, corticosteroids, antibiotics, and anticonvulsant drugs), mother's diet habits (fruit and vegetables and multivitamins particularly folic acid, vitamins A and B6, zinc and copper before and during pregnancy), mother's medial history (e.g., diabetes before pregnancy, and antipsychotic drug and antimetabolite administration during pregnancy), ethnic and geographical background of mother and father, infant gender, and presence of other anomalies. The cleft types was classified as 1) CL; right, left, or bilateral), 2) CL and CP; right, left, or bilateral, or, 3) CP; complete or incomplete. This was presented in the light of the total birth rate in the area sub-regions and in the region at large.

Ethical considerations

Approval to conduct the study was obtained from the Research Ethics Committee of Jouf University, Sakaka, Saudi Arabia (Approval No. 19-4-42). Although special groups are involved, the study is record-base and no need for direct interaction with pregnant mother or the newborns. Once records were validated/completed, data were anonymously recorded and were group statistically analyzed.

Data analysis

Data was analyzed using IBM SPSS version 22 (SPSS, Inc. Chicago, IL) implementing two tailed tests and considering P value ≤ 0.05 as statistically significant. Descriptive analysis based on frequency and percent distribution was done for all variables including children and parents' demographic data, co-morbidities, CL/CP data, and risk factors. Cross-tabulation was used to assess distribution of children pattern of the cleft according to children bio-clinical data and risk factors. Significance of relationships in cross-tabulation was tested using exact probability test (due to the small frequencies).

Results

The study included 99 children with the cleft anomaly out of 62,088 live birth records reviewed that gives a rate of 1/627 (or 1.6/1000) live births. 28 (28.3%) of children had CL alone, 24 (24.2%) had CP alone, and 47 (47.5%) had both CL & CP. Side-wise, it was on the left side among 47 (48%) children, on the right side among 26

Table 1: Pattern of Cleft Lip (CL) and Cleft Palate (CP) among the studied northern Saudi children. Data shown are frequency; n and %.

Characteristic		n	%
Type	CP only	24	24.2
	CL only	28	28.3
	Both CL & CP	47	47.5
Side	Right-sided	26	26.5
	Left-sided	47	48
	Bilateral	25	25.5

Table 2: Relevant characteristics of the studied northern Saudi children with cleft lip and/or cleft palate. Data shown are frequency; n and %.

Characteristic		n	%
Child gender	Male	56	56.6
	Female	43	43.4
Child order within the family	First	20	20.2
	2^{nd} - 3^{rd}	33	33.3
	4^{th} - 5^{th}	32	32.3
	≥ 6^{th}	14	14.1
Childbirth weight	<2.5 Kg	26	26.3
	2.5 - 4 Kg	66	66.7
	>4 Kg	7	7.1
Mode of delivery	Normal vaginal delivery	64	64.6
	Caesarean section	35	35.4
Delivery month	7^{th}	3	3
	8^{th}	12	12.1
	9^{th}	70	70.7
	>9^{th}	14	14.1
Child blood group	A^-	4	4
	A^+	24	24.4
	B^-	3	3
	B^+	8	8.1
	AB^-	0	0
	AB^+	6	6.1
	O^-	7	7.1
	O^+	47	47.7

(26.5%) children, and bilateral in 25 (25.5%) children.

Table 2 illustrates the relevant characteristics patients. More than half of the affected children were males (n=56; 56.6%). Regarding child order within families, 20 (20.2%) of the affected children were first family child, while 14 (14.1%) were ≥ 6^{th} child. 26 (26.3%) of the affected children were born with low birth weight (<2.5 Kg), and 7 (7.1%) were born with birth weight >4 Kg. The most reported mode of delivery was vaginal delivery (n=64; 64.6%). Also, majority of the affected children were full-term and were born at 9^{th} month of pregnancy, 3 children were preterm and were born at 7^{th} month. As for children's blood groups, the most reported blood group was O+ (33.3%) followed by A^+ (14.1%), and B^+ (8.1%).

Table 3 shows relevant parents characteristics for the children. At childbirth, 48.5% of their mothers aged 30 years to 39 years, while only 9.1% of children were born for mothers below the age of 20 years and 5.1% were born for mother aged ≥ 40 years. As for father age at pregnancy, 50% were aged 30 to 39 years, while 4% aged less than 20 years, and 21.2% aged ≥ 40. 37.4% of the children

Table 3: Socio-demographics and medical history of parents of the studied northern Saudi children with cleft lip and/or cleft palate. Data shown are frequency; n and %.

Characteristic		n	%
Mother's age at the child birth, years	<20	9	9.1
	20 to 29	37	37.4
	30 to 39	48	48.5
	≥ 40	5	5.1
Father's age at the child conception, years	<20	4	4
	20 to 29	24	24.2
	30 to 39	50	50.5
	>40	21	21.2
Mother employment	Unemployed	62	62.6
	Governmental	32	32.3
	Private	5	5.1
Father employment	Unemployed	8	8.1
	Healthcare sector	13	13.1
	Non-health sector	51	51.5
	Military sector	27	27.3
Mother chronic health problems and type	Yes	17	17.2
	No	82	82.8
	Diabetes mellitus	7	41.2
	Hypothyroidism	5	29.4
	Hypertension	2	11.8
	Others	3	17.6

Table 4: Potential risk factors for cleft lip and/or cleft palate among the studied northern Saudi children with cleft lip and/or cleft palate. Data shown are frequency; n and %.

Risk factor		n	%
Father's tobacco smoker		50	50.5
Mother's passive smoking during pregnancy		45	45.5
Not having folic acid during pregnancy		36	36.4
History of abortion		31	31.3
Multivitamin deficiency during pregnancy		26	26.3
Irregular pregnancy follow-up		25	25.3
Have nutrient supplementary during pregnancy		20	20.2
Had medication treatments during pregnancy		20	20.2
Exposure to infection during pregnancy		20	20.2
Family history of cleft lip and/or palate		16	16.2
X-Ray exposure during pregnancy		15	15.2
Gestational diabetes		11	11.1
The child having other congenital anomalies		10	10.1
Mother smoking during pregnancy		9	9.1
Family history of other congenital anomalies		8	8.1
Mother's Epilepsy		2	2
Parents consanguinity	No	39	39.4
	First degree	40	40.4
	Second degree	20	20.2

Table 5: Distribution of type of Cleft Lip (CL) and/or Cleft Palate (CP) congenital anomaly stratified for the children and parent's characteristics and risk factors among the studied northern Saudi children with CL and/or CP. Data shown are frequency, n and %, and P values of Exact Probability Test.

Characteristic		Type the Cleft						P
		CPalone		CL alone		Both CP/CL		
		n	%	n	%	n	%	
Child gender	Male	11	19.6	17	30.4	28	50	0.474
	Female	13	30.2	11	25.6	19	44.2	
Term pregnancy age, month	7^{th}	0	0	0	0	3	100	0.041
	8^{th}	0	0	4	33.3	8	66.7	
	9^{th}	17	24.3	20	28.6	33	47.1	
	$>9^{th}$	7	50	4	28.6	3	21.4	
Blood group of the child	A^-	0	0	2	50	2	50	0.767
	A^+	7	28.6	5	21.4	12	50	
	B^-	1	33.3	0	0	2	66.7	
	B^+	3	37.5	3	37.5	2	25	
	AB^-	0	0	0	0	0	0	
	AB^+	2	33.3	0	0	4	66.7	
	O^-	1	14.3	1	14.3	5	71.4	
	O^+	10	21.2	17	36.4	20	42.4	
Mother age at birth, years	<20	2	22.2	3	33.3	4	44.4	0.38
	20 to 29	10	27	12	32.4	15	40.5	
	30 to 39	12	25	13	27.1	23	47.9	
	≥ 40	0	0	0	0	5	100	
Father age at conception, years	<20	0	0	0	0	4	100	0.251
	20 to 29	6	25	9	37.5	9	37.5	
	30 to 39	15	30	13	26	22	44	
	≥ 40	3	14.3	6	28.6	12	57.1	
Have folic acid during pregnancy	Yes	18	28.6	17	27	28	44.4	0.411
	No	6	16.7	11	30.6	19	52.8	
Multivitamin deficiency during pregnancy	Yes	8	30.8	8	30.8	10	38.5	0.522
	No	16	21.9	20	27.4	37	50.7	
Gestational diabetes	Yes	1	9.1	1	9.1	9	81.8	0.049
	No	23	26.1	27	30.7	38	43.2	
Passive smoking during pregnancy	Yes	10	22.2	15	33.3	20	44.4	0.594
	No	14	25.9	13	24.1	27	50	
Father is a smoker	Yes	11	22	17	34	22	44	0.442
	No	13	26.5	11	22.4	25	51	
Parents consanguinity	No	9	23.1	16	41	14	35.9	0.035
	1^{st} degree	8	20	6	15	26	65	
	2^{nd} degree	7	35	6	30	7	35	

had a working mother, while 13.1% of the children had healthcare professional fathers. Exact of 17 (17.2%) of the children mothers' had chronic health problem; the most reported of them were DM (41.2%), hypothyroidism (29.4%) and HTN (11.8%).

Regarding the recorded risk factors for CL/CP (Table 4), the most frequent of them were father smoking (50.5%), mother passive smoking during pregnancy (45.5%), lack of folic acid intake during pregnancy (36.4%), previous history of abortion (31.3%), multivitamin deficiency during pregnancy (26.3%), gestational diabetes (11.1%) and irregular pregnancy follow-up (25.3%). Family history of congenital anomalies and epilepsy were the least frequent factors (8.1% and 2%, respectively). As for parents' consanguinity, it was reported among 60 children (60.6%). Consanguinity of first degree was reported for 40 (40.4%) children and of second degree was observed for 20 (20.2%) children.

Table 5 presents the association between the type of congenital

anomaly with children and parents characteristics, and risk factors. Both CL & CP were recorded among all preterm children born at 7th month gestational age (n=3) compared to 47.1% for full-term children with a statistically significant association (P=0.041). Also, 81.8% of children born for mothers with gestational diabetes had both CL and CP compared to 43.2% of mothers without diabetes with a statistically significant association (P=0.049). 65% of children born for parents with first degree consanguinity had both CL & CP compared to 35.9% of non-related parents; a statistically significant association (P=0.035).

Discussion

CL and CP are the most striking human congenital anomalies at a rate of one baby of every 700 to 1000 live birth [27]. CL/CP is the second most occurring birth defects after Down syndrome at 10.48 cases per 10,000 births [28]. Incidence of CL/CP among Chinese and Philippine infants born in the United States is lower than those born in their native country. Low socio-economic status was shown to have increased risk for CL/CP [29].

The current study aimed to assess pattern and factors associated with CL/CP among children of the northern region of Saudi Arabia. The study revealed that most of children had both CL and CP, while one quarter of them had either type. This is consistent with what was reported by Tettamanti et al. [30] showing that the most diagnosed presentation was the unilateral combined cleft lip and palate (46%), followed by cleft palate only (33%). CP has decreased from 32.9% to 20.2%, CL has increased from 17.4% to 34.2%, and the highest rate was for CLP that declined from 49.6% to 45.5% in 2014 and 2017 in Colombia, respectively [19]. As for the side of cleft, left-sided cleft was observed in nearly half of our children, while the other two quarters were either right-sided or bilateral. This is consistent with literatures finding for the variation of the distribution of the congenital anomaly [31-33].

Regarding the gender distribution of our children with CL and/or CP, most of the children were males. Bilateral cleft palate was more common among the male children with mothers complained of gestational diabetes and those who were born to 1st degree consanguineous couple. This is contrasted with CP which occurs more in females (57%) than in males (43%). Stronger male preponderance was evident in a Georgian study [20]. Reportedly, gender differences may be related to differences in timing of embryologic development [34]. As for its relationship with gestational diabetes, this was consistent with previous reports [35-37]. Maternal diabetes is mainly associated with neural tube defects, cardiovascular defects, and OFCs [38-40]. OFCs seem to be highly correlated with pre-pregnancy diabetes mellitus [41,42]. Regarding the child birth weight, the current study revealed that nearly one quarter of the children with combined CL-CP were born underweight, while <10% were born with overweight. In support, some young mothers were diabetic (7 mothers). Considering blood group of the children, blood group O^+ was the dominant subtype (one third of the children) followed by A^+ and B^+. Ghaib et al. [43] stated that AB blood group is the most prevailing subtype associated with CL and/or CP, while group O is the least associated. This may be because of its association with other genetic makeup [43].

As for the risk factors of CL-CP, the current study revealed that father/mother smoking was one of the most reported risk factors accounting for more than half of the children. Reportedly, maternal smoking had a strong association with CL-CP syndrome [44-46]. Folic acid and multivitamin deficiency were the second most reported risk factors for CL-CP in our study. Inadequate pregnancy follow-up was the third ranked risk factor. Other risk factors included exposure to X-rays during pregnancy, and family history of congenital anomalies and epilepsy. These strengthen the evidence in literature regarding reported risk factors of CL-CP that included genetic factors, environmental factors, and maternal-related risk [47,48]. Also, the current study revealed that parent's consanguinity was reported as one of the significant risk factors for CL-CP syndrome. Nearly two thirds of the current study children were born for related parents, especially first-degree couples. The link with parent's consanguinity was previously reported at varying rates that could depend mainly on culture and community traditions regarding interfamilial marriages [49-52].

The strength of this study is that it is one of a kind for the target area that determined the prevalence and nature of the OFCs and highlighted some of its potential risk factor.

The main limitation of the study is the fact that not all birth of the area were included, since some them are excepted to getting born outside the area hospitals, as at large it is a rural area but with high income, particularly with a pregnancy that is expected to be complication. Risk factor such as the effect of radioactive and electromagnetic radiation was not investigated. The area is the border line with Iraq that was bombarded with Depleted Uranium during Gulf War II.

Conclusion

In our study, most of children had both CL and CP, with a mild male preponderance. Most of them were related to mothers complained of gestational diabetes and were born to first degree related couples. Other risk factors included father smoking, mother passive smoking during pregnancy, lack of folic acid intake during pregnancy, previous history of abortion, multivitamin deficiency during pregnancy, and irregular pregnancy follow-up. Rate of CL and/or CP among the reviewed birth records was 1/627 (or 1.6/1000) live births (n=99 out of 62088) which is relatively high. Since all of these risk factors are modifiable/preventable, measures should be planned towards that sake locally and nationally.

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