ORIGINAL RESEARCH

Orofacial Cleft and Its Association with Consanguineous Marriage and Other Risk Factors: A Case-control Study from a Tertiary Care Hospital in Jammu Province

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Abstract

Background: Orofacial cleft is among the most common craniofacial malformations. It presents a complex and multifactorial etiology that involves genetic and environmental factors. One of the etiological factors is consanguinity (marriage between blood relatives). Multiple environmental risk factors, such as advanced maternal age, parity, maternal smoking, radiation, alcohol consumption, diabetes mellitus, and maternal use of drugs (i.e., anticonvulsants), folic acid deficiency, etc., have also been linked to the development of cleft lip and/or palate (CL/P). There is a dearth of literature reporting the occurrence of cleft due to consanguinity and other risk factors.

Aim: The aim of this study is to describe the orofacial cleft demographics and to determine the influence of parental consanguinity and other associated risk factors on the occurrence of orofacial clefts (OFC) at a tertiary healthcare hospital in Jammu Province.

Materials and methods: This was a hospital-based case-control study. In the present study, data collection was specifically done regarding demographic features, history of consanguinity, degree of consanguinity, and other associated maternal risk factors in both the cleft and control groups.

Result: This study elucidates a significant association between parental consanguinity, degree of consanguinity, and other associated risk factors (i.e., maternal age ≥30 years, birth order ≥3, maternal smoking, alcohol consumption, and lack of folic acid consumption) with the occurrence of OFC.

Conclusion: Prevention is better than cure. Awareness programs and appropriate counseling should be conducted to educate the community about the risk factors and the anticipated genetic consequences of consanguinity to prevent the development of cleft anomalies in such populations.

Keywords: Consanguineous marriage, Consanguinity, Cleft lip and palate, Maternal risk factors, Orofacial cleft.

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Introduction

Orofacial clefts (OFC), comprising cleft lip (CL) (i.e., cheiloschisis), cleft palate (CP) (i.e., palatoschisis), and cleft lip and palate (CLCP), are among the most common congenital malformations affecting humans.[1] The burden of OFC is a significant problem worldwide and in India. The estimated global prevalence of cleft lip and/or palate (CL/P) is one out of every 600 newborn babies.[2] A meta-analysis conducted by Allagh et al. in 2015, which included 11 hospital-based studies, revealed that the prevalence of OFC in India ranged from 0.2 to 2.9 per 1,000 total births, with a cumulative rate of 1.3 per 1,000 total births. Mossey and Modell estimated the prevalence to be 28,600 per year across the country.[2,3] It has also been estimated that the prevalence of CL, associated with or without a palate, among males is approximately twice that of females (2:1), while isolated CP is less frequent among males than females (1:2).[4] CL can manifest as either a complete cleft that extends into the nostril or as an incomplete cleft, which may be a small opening or groove in the lip. The CL can be either unilateral or bilateral and may or may not be associated with CP. It is caused by the failure of the maxillary prominence and medial nasal processes to fuse. The CP refers to a split or opening in the roof of the mouth. A CP may involve the hard palate and/or the soft palate. It can be complete or incomplete and occurs due to the failure of the lateral palatine processes, the nasal septum, or the median palatine processes to fuse together.[5] Children affected by CL/P experience a range of functional, aesthetic, and psychological problems, such as feeding challenges at birth, swallowing difficulties, nasal regurgitation, speech difficulties, hearing problems, articulation issues, and challenges with social integration. OFC can be syndromic when associated with other anomalies, or nonsyndromic when present in an isolated form, not associated with syndromes, accounting for 60–70% of cases.[6] The etiology of nonsyndromic clefts is multifactorial.[7] It presents a complex etiology that encompasses both genetic and environmental factors.[8,9] Consanguinity is a cultural custom that may have an epigenetic role in the development of congenital abnormalities, such as CLCP. Consanguineous marriages are a common social norm in various communities across the globe, where marriages occur between closely related blood relatives, thereby heightening the risk of transmission of genetic disorders, particularly autosomal recessive ones.[10] In India, consanguineous marriages are common due to prevailing cultural norms.[11] Therefore, consanguinity, as a cultural element, also contributes to the etiology of CL/P. Multiple environmental risk factors, such as advanced maternal age, parity,

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maternal smoking, radiation, alcohol consumption, maternal use of drugs such as anticonvulsants, maternal diabetes mellitus type II, vitamin deficiencies such as folic acid deficiency, etc., have also been linked to the development of CL/P.[12,13] In India, there is a dearth of documented data or literature supporting the relation between consanguinity and other associated risk factors with OFC.[14] Thus, the objectives of this study were to estimate the proportion of different types of OFCs, describe their demographic profile, and evaluate the relationship between consanguineous marriages and other associated risk factors with the occurrence of CL/P. This will help educate and raise awareness among the public about the involved risk factors and develop strategies for preventing the occurrence of clefts.

Aim

The aim of this study is to describe the orofacial cleft demographics and to determine the influence of parental consanguinity and other associated risk factors on the occurrence of OFC at a tertiary healthcare hospital in Jammu Province.

Materials and Methods

Variables
Sociodemographic
Gender—Male/female
Residence—Urban/rural
Cleft type—CL/CP/CLCP
Sub type—Unilateral/bilateral
Side affected—Left/median/right
Risk factors
Consanguineous marriage
Degree of consanguineous marriage
Maternal age
Order of birth
Radiation exposure
Consumption of alcohol
Maternal diabetes type II
Maternal drug intake of anticonvulsants
Maternal smoking
Secondary exposure to smoke
Consumption of folic acid during pregnancy

Study Design and Settings

This was a hospital-based case-control study. The study population was recruited from the Department of Pedodontics, Indira Gandhi Government Dental College, Jammu. The cases referred from the Department of Pediatrics, Department of Obstetrics and Gynecology, Sri Maharaja Gulab Singh Hospital, Jammu, and the Department of Plastic Surgery, Government Medical College, Jammu, were included.

Cases and Controls

Cases

The cases included children born with CL/P, having an ear, nose, and throat (ENT) report describing the diagnosis and classification, a pediatric report screening for any related syndromes, and accessible information regarding the risk factors of CL/P analyzed in our study.

Controls

The control group included healthy children born full-term without CL/P, gender- and age-matched with the cases.

Sample Size

During the study period, 103 cleft cases (cleft lip/P) were reported. The study included cases associated with nonsyndromic clefts and excluded cases associated with syndromic clefts. The sample size was based on the total number of people who consented to participate in the case group. About 90 cases and 90 controls were included in the study.

Data Collection and Management

The collection of data was done from July 2020 to December 2022. The information was gathered through interviews with the mothers and by evaluating their medical records wherever feasible. At the time of the interview, these cases were either in the hospital, visiting the hospital for follow-up, or were referred for surgical intervention.

Exposures Measured

To collect the data, a form was prepared. The data acquired included demographic details such as gender, residence, cleft type, subtype, and affected side. The risk factors included history of consanguineous marriage, degree of consanguinity, maternal age, parity, consumption of alcohol, smoking, secondary exposure to smoke, use of certain drugs during pregnancy such as anticonvulsants, diabetes mellitus type II, and lack of folic acid consumption.

Ethical Consideration

Informed consent from eligible mothers was obtained after thoroughly explaining the study to them. Approval from the Ethics Committee was also obtained (IEC No.: IECGDC/60/2023).

Statistical Analysis

The information was gathered and recorded into a Microsoft Excel sheet. IBM SPSS v.22 Statistics Software was used for statistical analysis. The odds ratio (OR) was estimated using the Chi-squared test and logistic regression, with a 95% confidence interval (95% CI). The *p*-values <0.05 were considered statistically significant.

Results

Demographic Profile

The demographic features have been depicted in Figure 1. The number of cleft cases seen in males (58.89%) was higher than in females (41.11%). Clefts were reported more frequently in rural settings (56.67%) compared to urban areas (43.33%). CLCP was the most common type (51.11%), followed by CP (34.44%) and CL cases (25.56%). Among CLCP cases, 60.87% had unilateral and 39.13% had bilateral CLCP. Among CL cases, 65.21% had unilateral and 34.78% had bilateral CL. Left-sided CL/CLCP were predominant (60% and 56.75%, respectively) (Fig. 2). Gender distribution according to the type of cleft showed that CL and CLCP were more common in males (56.52% and 69.56%, respectively), while CP was more common in females (61.29%) (Fig. 3).

Association of Cleft and Consanguineous Marriage

A total of 64.44% of parents in the cleft group had consanguineous marriages. When comparing consanguineous and nonconsanguineous marriages in parents of the cleft and control groups, the association between consanguineous marriage and the occurrence of clefts was highly significant ($p < 0.001$). The odds of having children with a cleft were 2.54 times higher in parents who had

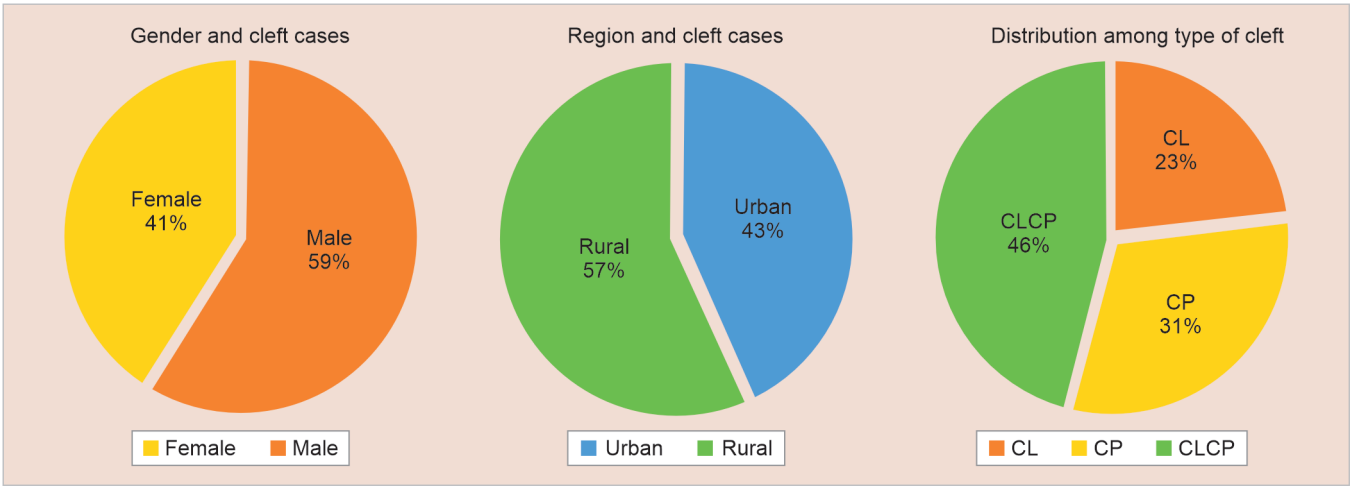
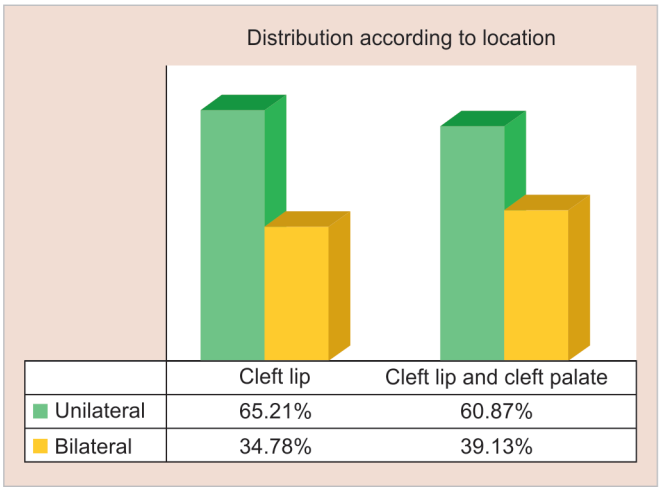
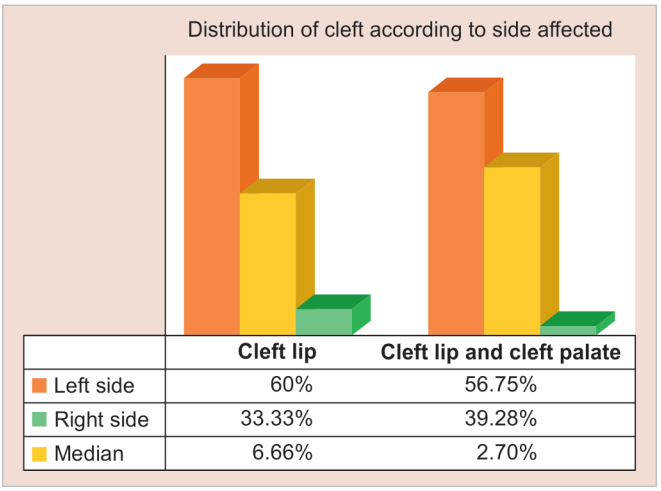


Fig. 1: Demographic profile of cleft cases

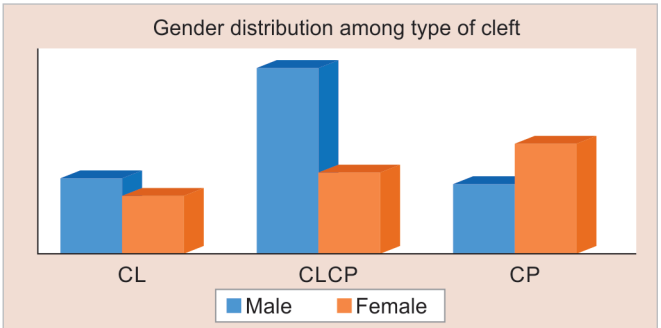


	Cleft lip	Cleft lip and cleft palate
Unilateral	65.21%	60.87%
Bilateral	34.78%	39.13%



	Cleft lip	Cleft lip and cleft palate
Left side	60%	56.75%
Right side	33.33%	39.28%
Median	6.66%	2.70%

Fig. 2: Distribution of cleft according to the location and side affected



Cleft subtype	Male	Female
Cleft lip	13 (56.52%)	10 (43.47%)
Cleft palate	12 (38.71%)	19 (61.29%)
Cleft lip and cleft palate	32 (69.56%)	14 (30.43%)

Fig. 3: Gender distribution among type of cleft

consanguineous marriages. The total number of clefts associated with second-degree consanguineous marriages (72.41%) was significantly higher than with third-degree (15.52%) and fourth-degree consanguineous marriages (12.06%) ($p < 0.005$). In our study, the multiple logistic regression model indicates that second-degree consanguineous marriages increase the incidence of clefts by 1.68 times (Table 1; Fig. 4).

Association of Cleft and Other Associated Risk Factors

A significant association between the occurrence of clefts and maternal age ≥30 years was observed ($p = 0.015$) (OR = 1.63, 95% CI). The odds of having children with a cleft were 1.63 times higher in mothers whose maternal age was >30. A significant association was also observed between the occurrence of clefts and birth order ≥3 ($p = 0.034$) (OR = 1.07, 95% CI). The results of this study found no statistically significant relationship between maternal drug intake of anticonvulsants, radiation exposure, secondary exposure to smoke, maternal diabetes, and CLCP. However, a statistically significant relationship was observed between CLCP and the following risk factors: maternal alcohol consumption ($p = 0.049$) (OR = 1.13, 95% CI), cigarette smoking ($p = 0.048$) (OR = 1.96, 95% CI), and nonconsumption of folic acid during pregnancy ($p = 0.001$) (OR = 1.29, 95% CI) (Table 2).

Discussion

In this study, the gender distribution of the study sample revealed that the clefts were higher among males as compared to females. This distribution corresponded with the results of research

conducted by Jalilevand and Jalaie in 2015 and de Aquino et al. in 2017.[15,16] Although currently there is no widely recognized cause of this gender disparity, the possible explanation could be the difference in the timing of critical stages of craniofacial development between males and females.[17]

Clefts were reported more from rural settings as compared to urban settings, indicating a constellation of exposures that might vary between urban and rural dwelling and lesser awareness about the involved risk factors in the rural population. Similar results were seen in a study by Messer et al. in 2010.[18]

Regarding the distribution of the study sample in accordance with the type of cleft, the most common type of cleft observed was CLCP, followed by isolated CP and isolated CL. Studies conducted by Jagomagi et al. in 2010 and Mbuyi-Musanzayi et al. in 2018 showed a similar distribution of the clefts.[19,20] While another study by Zandi and Heidari in 2011 also revealed CLCP dominance, CL rather than CP was found to be the second most prevalent cleft.[21]

Regarding the subtype and location of the CL, unilateral clefts were more common as compared to bilateral clefts and were more predominant on the left side of the face. A similar association is

Table 1: Association of consanguineous marriage and its degree with occurrence of cleft

Characteristics	*Cases N = 90*	*%*	*Controls N = 90*	*%*	*OR*	*95% CI*	*p-value*
Consanguineous marriage							
No	32	35.56	56	62.22	1	–	–
Yes*	58	64.44	34	37.78	2.54	1.678–2.732	0.001*
Degree							
Fourth degree	7	12.06	6	17.64	1	–	–
Third degree	9	15.52	7	20.58	1.16	1.08–1.32	0.062
Second degree*	42	72.41	21	61.76	1.68	1.54–1.74	0.005*

*Indicates association of consanguinity with occurrence of cleft

Table 2: Association of other maternal risk factors with occurrence of cleft

Characteristics	*Cases N = 90*	*%*	*Controls N = 90*	*%*	*OR*	*95% CI*	*p-value*
Maternal age							
<30	41	45.55	43	47.78	1	–	–
>30*	49	54.44	47	52.22	1.63	0.87–3.44	0.015*
Order of birth							
<3	42	46.67	44	48.89	1	–	–
≥3*	48	53.33	46	51.11	1.07	0.65–2.13	0.034*
Radiation exposure							
No	74	82.22	77	85.56	1	–	–
Yes	13	14.44	16	17.77	1.48	0.79–2.98	0.714
Alcohol consumption							
No	81	90	84	93.3	1	–	–
Yes*	9	10	6	6.66	1.13	0.36–3.16	0.049*
Maternal diabetes							
No	67	74.44	53	58.89	1	–	–
Yes	23	25.55	37	41.11	1.49	1.32–1.96	0.414
Maternal drug intake of anticonvulsants							
No	89	98.89	88	97.78	1	–	–
Yes	1	1.11	2	2.22	1.01	0.54–2.56	0.913
Maternal smoking							
No	79	87.77	82	87.78	1	–	–
Yes*	11	12.22	8	12.22	1.96	0.33–2.86	0.048*
Secondary exposure to smoke							
No	79	87.77	73	81.11	1	–	–
Yes	11	12.22	17	18.89	1.67	0.38–1.74	0.654
Folic acid supplements taken during pregnancy							
Yes	44	48.89	48	53.33	1	–	–
No*	46	51.11	42	46.67	1.29	0.08–1.47	0.001*

*Indicates association of maternal risk factors with occurrence of cleft

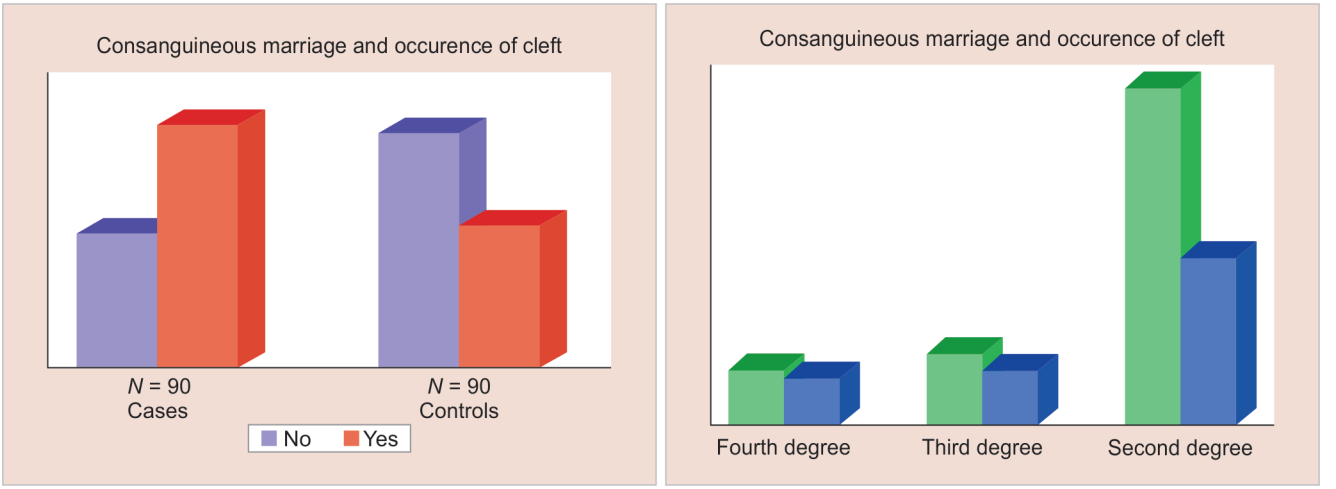


Fig. 4: Association of consanguineous marriage and its degree with occurrence of cleft

seen in a study by Maranhão et al. in 2021.[22] Oral clefts feature nonrandom laterality, wherein left-sided clefts were found to be more prevalent than right-sided clefts, a pattern which might be influenced by genetics or the environment. The greater frequency of unilateral clefts on the left side shows directed asymmetry instead of fluctuating asymmetry.[23]

Regarding gender distribution according to the types of cleft cases, it was observed that CLCP and CL were more common in males and CP in females. Our results were similar to the study by Yassaei et al. in 2010 which reported similar findings.[24] The possible explanation could be that palatine shelves in females close one week later than in males, hence explaining the female preponderance of CP.[25]

Syndromic CL/P are associated with direct Mendelian inheritance, whereas the nonsyndromic form of CL/P appears to be driven by gene-environmental interactions such as consanguineous marriage, maternal age, order of birth, maternal exposure to smoke, alcohol, radiation, diseases, drugs, diet, etc. Thus, the study included the cases of nonsyndromic cleft.[26]

Consanguineous marriage refers to the marriage that occurs among blood relatives. Consanguinity is practiced commonly in Arab countries, India, China, Latin America, Japan, South Europe, and less commonly in the United States, Russia, Australia, parts of Latin America, and Europe.[27] Consanguinity is a broad and intricate issue that involves significant social, demographic, and economic factors, differential reproductive behavior, and early as well as late onset morbidity and mortality. Consanguinity has been associated with a higher risk of congenital abnormalities.[28] Consanguinity and its impact on the occurrence of clefts have also been studied and reported widely.[29] In Arab countries, various observational studies demonstrating an association between consanguinity and the occurrence of clefts have been reported.[30] However, in India, limited literature has been documented, particularly regarding the southern states.[11,29,31]

In India, consanguineous unions are reportedly prevalent. According to the National Family Health Survey (NFHS-5), among North India, Jammu and Kashmir ranks second in the practice of consanguineous marriages, with an approximate percentage of 12%.[32] A number of cases with a history of consanguineous marriage were observed by the primary author during the residency period in the Jammu region, which led to the inception of this study. Additionally, consanguineous marriages have been observed to be higher among the Muslim population of North India and the Hindu population of South India, among the other backward classes, and the less educated people of the middle and higher wealth indices.[11]

The degree of consanguinity is determined by how closely two people are related to one another, which in turn is determined by the shared amount of genes between them. The genetic relationship between parent and child or brother and sister is referred to as first-degree consanguinity. In such situations, the percentage of gene sharing is 1/2, and the likelihood of an anomaly in the progeny is 50%. The relationship between grandparents and grandchildren, half-siblings, uncle and niece, aunt and nephew, and double first cousins is referred to as second-degree consanguinity. The frequency of gene sharing is 1/4, and the probability of anomaly in the progeny is 5–10%. The relationship between great-grandparents and great-grandchildren, half-uncle and niece, and first cousins is referred to as third-degree consanguinity. The frequency of gene sharing is 1/8, and the probability of anomaly in the progeny is 3–5%. Thus, the risk of anomaly decreases as the degree of consanguinity moves further.[33] In light of the above factors, the occurrence of clefts and consanguinity ought to be assessed. This study depicts the association between consanguinity and OFC. It also reflects upon the degree of consanguinity.

In this study, the occurrence of cleft was significantly associated with consanguineous marriages. On comparing the frequency of occurrence of clefts with the consanguinity between the cleft and the control groups, the difference was statistically significant in favor of the cleft group. The likelihood of a child being born with a cleft was 2.54 times greater in parents who had a consanguineous marriage. Studies by Aljohar et al. in 2008 and Ravichandran et al. in 2012 reveal a similar finding.[30,34] The prevalence of consanguinity is lower than that observed by Aljohar et al. and Ravichandran et al., indicating a lower prevalence in comparison to Arab nations.[34] The probability of the offspring inheriting identical copies of detrimental recessive genes increases with the closeness of the biological relationship between the parents. Our study elucidated more cases of clefts associated with second-degree consanguineous marriages than with third- and fourth-degree consanguineous marriages in the cleft group. This is due to the decreased likelihood of inheriting a gene from

a common ancestor. No case of first-degree consanguinity was reported in our study.

Because the consanguineous marriage system is characterized by several variables such as area, religion, and caste, it is significant to the general populace. The results of this study are important in understanding the practice of the existing consanguineous marriage system and are pertinent in regard to the risk factor for CLCP abnormalities. Knowing the prevalence will help develop strategies for preventing and educating the masses about the consequences of consanguinity.

A significant association was seen between maternal age ≥30 years and the occurrence of cleft. The odds of having children with a cleft were 1.63 times greater in mothers whose maternal age was >30. An increased probability of nonsyndromic orofacial cleft in a child was associated with advanced maternal age, according to a meta-analysis by de Queiroz Herkrath et al. Possible explanations for our findings could be due to the cumulative changes in gametes occurring over the course of a lifetime, brought about by environmental exposures or chromosomal alterations.[35] Our study also observed that the occurrence of cleft was significantly associated with a birth order >3. In certain communities, a high rate of consanguinity, in conjunction with large family size, may cause the expression of autosomal recessive disorders, such as CLCP.[36]

According to a study by Domínguez and Núñez in 2014, a history of smoking and alcohol consumption during pregnancy are substantial risk factors, putting the fetus at a high risk of developing multiple congenital abnormalities.[37] A statistically significant association was found between the occurrence of CLCP and maternal alcohol consumption and cigarette smoking in this study. Leite and Koifman in 2009 also suggested that exposure to alcohol and tobacco smoke during pregnancy plays a role in the etiology of nonsyndromic oral clefts.[38] Although the precise mechanism is uncertain, smoking products may directly interact with neonatal tissue, resulting in induced hypoxia due to nicotine-mediated vasoconstriction and defective angiogenesis, which has been reported to impair palatal fusion in animal models.[39] Another theory suggests that smoking may alter DNA methylation in the fetus, influencing the expression of genes responsible for the development of the lip and palate.[40] Omo-Aghoja et al. in 2010 also studied the impact of alcohol consumption on the risk of developing cleft deformities and noted a positive association between alcohol intake and the development of cleft deformities.[41] Kotch and Sulik suggested that prenatal exposure to alcohol caused excessive cell death, resulting in craniofacial abnormalities, and also revealed that the association of OFC with alcohol exposure could be linked to the action of alcohol on cranial neural crest embryonic cells.[42]

Folic acid deficiency has been known to contribute to several chronic and developmental diseases. In our study population, the development of CLCP was significantly associated with the lack of folic acid intake during pregnancy. Several studies have demonstrated that peri-conceptional consumption of folic acid provides a protective effect and can prevent CLCP.[43] India has a primarily vegetarian population with low levels of maternal vitamin B12. According to Goh et al.'s meta-analysis in 2006, folic acid consumption before and during pregnancy was associated with a lower incidence of several birth defects, including CLCP.[44]

While no statistically significant association between maternal drug intake of anticonvulsants, radiation exposure, secondary exposure to smoke, or maternal diabetes and the occurrence of CLCP was observed.

This is, to the best of our knowledge, the first study conducted in Jammu province endeavoring to determine the association between consanguineous marriage and other associated maternal risk factors for the development of CLCP in newborns.

Conclusion

This study elucidates a significant association between parental consanguinity, degree of consanguinity, and other associated risk factors, that is, maternal age ≥30 years, birth order ≥3, lack of folic acid consumption, maternal smoking, and alcohol consumption with the occurrence of OFC.

This research will be conducive to a robust understanding of epidemiology, gene-environment interactions, and prospective preventive strategies. Awareness programs and appropriate counseling should be conducted to inform the community about the risk factors to prevent the occurrence of cleft. Awareness of the problems associated with consanguineous marriage is needed, along with genetic counseling. In communities where consanguineous marriages are customarily performed, instead of discouraging such marriages, raising public awareness about consanguinity and providing access to premarital and preconception genetic counseling is a more sensible course of action that is more likely to be accepted by the community to preserve and improve health. Prenatal counseling of mothers should be conducted to make them aware of maternal risk factors that can increase the likelihood of CLCP.

Limitations

One of the limitations of the study was that it included a hospital-based approach rather than a population-based approach. Another limitation was that the information about folic acid consumption during pregnancy was based on recall. Recall bias may have resulted from the lack of medical records or documentation regarding the duration and frequency of folic acid intake during pregnancy.

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