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Original Research Article

A retrospective survey to study the prevalence of maternal modifiable risk factors leading to cleft lip and/or palate in cases reporting to a tertiary care centre in Navi Mumbai

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Abstract

Introduction: Orofacial clefts (OFC) encompass a variety of disorders impacting the lips and oral cavity. As a multifactorial condition, OFC is influenced by both genetic and environmental risk factors. Children affected by OFC require multidisciplinary care from birth through adulthood.
Aim: This study aims to evaluate ways of preventing the development of OFC's through understanding the maternal modifiable risk factors leading to such congenital defects in offsprings.
Materials and Methods: This cross-sectional questionnaire-based study, was carried out in MGM Dental College & Hospital, Navi Mumbai. A questionnaire was fabricated that included 11 parameters. 127 cases of cleft lip & or palate were interviewed. Data was analysed to evaluate the prevalence of different factors leading to development of cleft lip and palate.
Results: There was a general tendency for females to be more affected, with cleft palate being more commonly observed in females. Unilateral and left sided clefts were more common. 63% cases were socioeconomically below poverty line, consanguineous marriages accounted to 12.6%. 15% of the mothers reported passive smoking through a family member during pregnancy and 44% mothers reported usage of chulha for cooking. 70.8% mothers reported use of multi-vitamins and folic acid supplementation during pregnancy and 52% mothers gave a history of polished rice consumption during pregnancy.
Conclusion: Maternal active smoking, passive smoking, consanguineous marriage, polished rice consumption should be discouraged. Use of clean-burning cookstoves, multi-vitamins and folic acid supplementation, genetic counselling should be encouraged. Patient-centric solutions should be implemented for the prevention and management of such cases.

Keywords: Cleft lip and palate, Passive smoking, Consanguineous marriage, Chulha smoke

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1. Introduction

Clefts of the lip and palate are among the most common congenital birth defects globally. The incidence of CLP in India is found to be around 0.93-1.3.[1] Orofacial clefts (OFC) encompass cleft lip only, cleft lip and palate, and cleft palate alone, representing a range of conditions that affect the lips and oral cavity.[2] Although orofacial clefts are recognized as multifactorial disorders, influenced by a combination of genetic and environmental factors, their exact etiology is still not fully understood.[3]

Clefts can affect appearance, speech, hearing, and cognition, leading to long-term negative consequences for both health and social amalgamation[1] Children born with clefts require comprehensive, multidisciplinary care from infancy to adulthood and face elevated risks of morbidity and mortality throughout their lives compared to those who are unaffected.[4,5] Comprehensive medical and behavioural interventions are essential to address these frequent congenital malformations which place a substantial burden on physical health, psychological and economic aspects.[6]

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The three stages of prevention are primary, secondary, and tertiary which aim to address different phases in managing diseases. Primary prevention intends to stop the onset of disease by addressing and eliminating known risk factors. Secondary prevention comprises the early detection and management of conditions to halt their progression. Tertiary prevention focuses on minimizing the impairments and complications caused by a disease. Primary prevention aims to eliminate known causes and risk factors. Secondary prevention has evolved to include measures such as prenatal diagnosis and counselling, timely hospital presentation at birth, and prompt access to all available care. Various forms of support are available, including psychosocial, nutritional, medical, surgical, and dental assistance, among others. Tertiary prevention encompasses the provision of psychosocial care for patients with orofacial clefts (OFC) and ensuring their effective integration into all aspects of life. This includes secondary surgical interventions such as, speech therapy, orthodontic treatments, and orthognathic surgery, among others. Among these, primary prevention of these conditions is the most prudent. It is the only approach focused on completely eradicating the development of the disease and will be the central focus of this paper.[7]

As a result, preventing it proves to be cost-effective and highly beneficial, particularly in developing nations where access to comprehensive healthcare is restricted. Although the exact causes of orofacial clefts (OFC) are not fully known, research efforts are primarily focussing on their prevention.[7] There are few studies in literature that have studied some risk factors related to cleft lip and palate in different parts of India.[8,9] Our study is based on the population residing in the western part of Maharashtra which is not studied previously. Modifiable risk factors are those that individuals can change through lifestyle adjustments to reduce their susceptibility to diseases. This study aims to evaluate ways of preventing the development of OFC's through understanding the maternal modifiable risk factors that might lead to such congenital defects in offsprings.

2. Materials and Methods

This cross-sectional questionnaire-based study was conducted at Mahatma Gandhi Mission's Dental College & Hospital in Navi Mumbai, Maharashtra, India. A questionnaire was fabricated incorporating the areas of interest in between. This questionnaire was structured, modified and approved after consultation with five subject experts. It included 11 parameters including age of mother and father during conception, family history of cleft lip and palate, socioeconomic status, consanguineous marriages, maternal alcohol ingestion during pregnancy, maternal smoking during pregnancy, maternal exposure to passive smoking during pregnancy from a family member, exposure to chulha smoke, multi-vitamin and folic acid supplementation during pregnancy, polished rice consumption during pregnancy, history of any disease or consumption of medication during pregnancy.

After receiving clearance from the Scientific Advisory Committee and the Institutional Ethics Committee, 127 cases of cleft lip & or palate were interviewed who reported to MGM Dental College & Hospital, Navi Mumbai between 1st September 2023 to 30th May 2024. Age of these patients ranged between seven days to fifteen years and these patients reported to the cleft care unit in the hospital for seeking treatment for various deformities related to cleft lip and palate. The primary investigator interviewed the parents/caregivers of the patients with a set of questions and all the responses were documented. The participation was completely voluntary and all the participants had an option of opting out of the study whenever desired.

The collected data was stored electronically in a Microsoft Office Excel 97-2003 Worksheet. Statistical analysis was performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0, Armonk, NY: IBM Corp.). Descriptive statistics, including mean, standard deviation, frequency, and percentage, were utilized. Pearson's chi-square test and Spearman's rho test were applied to analyze the data and assess the association of various factors with the development of cleft lip and palate. Statistical significance was determined at $p<0.05$.

3. Results

The questionnaire was completed for all 127 participants. All participants provided informed consent. The study population included 53 males (41.7%) and 74 females (58.2%). (**Figure 1**) The gender prevalence is as shown in **Table 1** and there was more female predilection. Significant difference was found between type of cleft and gender of offspring (Chi square test p value is 0.048). Cleft palate was more prevalent in females (n=19). (**Figure 2**)

Out of 127 cases, 16 cases had cleft lip, 24 had cleft palate and 87 had cleft lip and palate. Out of 16 cleft lip cases, 10 had left and 3 had right cleft lip, 3 had bilateral cleft lip. Out of 24 cleft palate cases, 2 had left and 3 had right cleft palate, 19 had median cleft palate. Out of 87 cases of cleft lip and palate, 38 had left and 16 had right sided defect, 33 had bilateral defect. There was a significant difference between location of cleft and type of cleft (Spearman's rho 2-tailed p value is 0.005). Cleft lip and palate was more prevalent (68.5%) than isolated cleft lip and/or palate. 56.7% had unilateral cleft (69.4% Left, 30.6% Right) and 43.3% had bilateral cleft. Thus, unilateral and left sided clefts were more common. (**Figure 3**)

58 fathers and 16 mothers were above 30 years of age during conception but none of them were above 40 years of age. 16 cases reported having immediate family members with similar congenital defect. 63% cases were

socioeconomically below poverty line. Consanguineous marriages accounted to 12.6% of the samples.

None of the mothers reported any consumption of alcohol during pregnancy. None of the mothers reported history of smoking during pregnancy. 15% of the mothers reported passive smoking through a family member during pregnancy. 44% mothers reported usage of chulha for cooking. 70.8% mothers reported use of multi-vitamins and folic acid supplementation during pregnancy but others were not sure. 52% mothers gave a history of polished rice consumption during pregnancy. Only 3 mothers reported use of medication for hyperthyroid, hypotension and viral infection. All others did not report any significant disease or use of medication to treat such diseases.

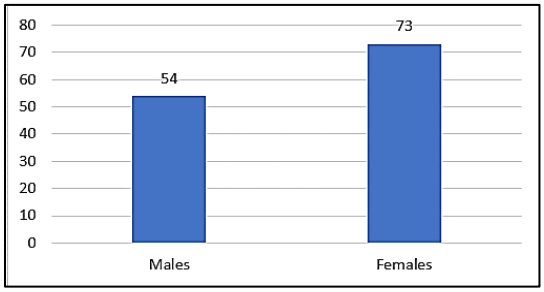

Figure 1: Gender prevalence of the cases of cleft lip & or palate who reported to MGM Dental College & Hospital, Navi Mumbai.

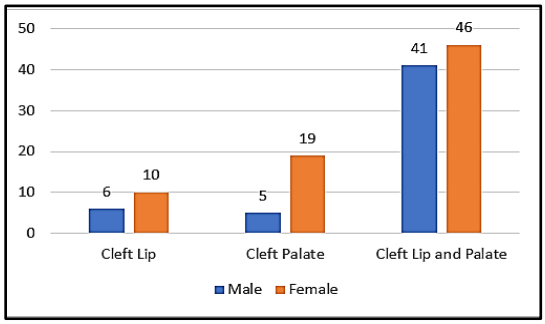

Figure 2: Gender and site prevalence of the cases of cleft lip & or palate who reported to MGM Dental College & Hospital, Navi Mumbai.

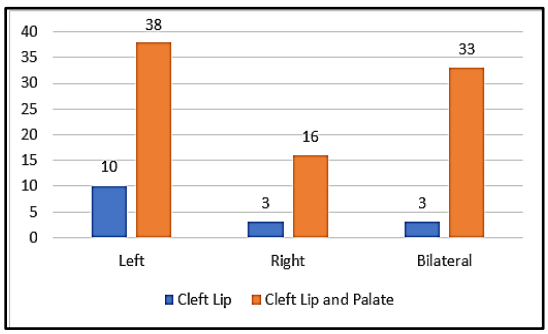

Figure 3: Cleft site distribution of the cases of cleft lip & or palate who reported to MGM Dental College & Hospital, Navi Mumbai

Table 1: Gender prevalence of the cases of cleft lip & or palate who reported to MGM Dental College & Hospital, Navi Mumbai.

	Male	Female	Total
Cleft lip	6	10	16
Cleft palate	5	19	24
Cleft lip & palate	41	46	87

4. Discussion

In previous reports on classification system of clefts by Natsume[10] and Aragaki[11], cleft lip and palate was the most prevalent type, subsequently followed by cleft lip and then cleft palate. Nagase Y[12] and Otsuki et al.[13] found that cleft lip and palate was the most prevalent condition, accounting for 40.8%, followed by isolated cleft palate. In a similar study done in Mangalore region (India), cleft lip (CL) along with cleft palate (CP) was found to be the highest (64.6%), followed by isolated CL (28.5%), followed by isolated CP (5.1%).[14] The results of these studies were consistent with our findings.

The gender differences observed in our study align with previous reports, indicating that cleft palate occurs more frequently in females, with a greater female predilection observed across all types of clefts. Similar findings have been documented in other countries.[2,15,16] Hirayama[17] suggested that gender may be linked to the development of this condition, with variations in developmental stages, hormonal influences, or other contributing factors playing a role. In terms of the factors contributing to gender-related variations in cleft patterns, the association with female sex hormones and the development of the palatine processes has been proposed by Miura et al.[18] Subsequently, the bilateral palatine processes begin their initial movement earlier in males and later in females during palatal development, which may influence the severity of the cleft. However, Nambiar et al observed that there was a slight predilection for males over females among cleft cases in Mangalore region (India).[14]

In our study, cleft lip and palate, as well as cleft lip, were found to occur more frequently on the left side, which aligns with previous reports by Nagase Y.[12] According to Hirayama[17], one possible explanation for the greater occurrence on the left side is that the development of the facial artery may progress more slowly on the left side compared to the right, although this explanation has not been definitively established. Additionally, the most commonly observed cleft pattern was a left-sided complete cleft lip and palate, which could be relevant for future studies exploring genetic factors.

Since our results align with those reported in previous studies, they can be regarded as reflective of the distributions observed in the general population. Although no definitive conclusions can be drawn from the current data alone, future studies that confirm similar phenomena could provide valuable new insights. The observed cleft patterns and sex-

based differences indicate the potential for previously undiscovered knowledge that conventional classification methods may not have revealed. Moreover, this approach to analysing cleft patterns could be effectively employed in preventive medicine through understanding underlying pathologies and improving genetic counselling. By exploring potential relationships between cleft patterns and various factors, including environmental and genetic influences, it may improve our understanding of the risk factors linked to cleft lip and palate. Orofacial clefts have a multifactorial etiology.[19] An interplay between genetic and environmental factors have been implicated, though their influence is often location-specific in various regions around the world. The worldwide prevalence of orofacial clefts was estimated at 59.68 per 100,000 individuals. The highest prevalence per 100,000 was observed in South Asia (107.55), followed by the Middle East/North Africa (90.10), Sub-Saharan Africa (52.15), East Asia and the Pacific (45.47), Europe and Central Asia (32.40), Latin America and the Caribbean (29.62), and North America (13.98).[20] Notably, this understanding directs our focus in pursuit of prevention. Significant attention has been directed toward the genetic causes of syndromic clefts, which are more thoroughly studied and comprehended than non-syndromic (NS) types. Epidemiological and experimental evidence suggest that environmental risk factors may significantly contribute to the development of non-syndromic cleft lip and palate. Over the years, various factors have been identified, each with differing levels of certainty. This includes maternal exposure to tobacco smoke, alcohol, viral infections, medications, other teratogens and inadequate nutrition, encountered in both workplace and home environments during early pregnancy. Furthermore, the influence of pregnancy planning has also been examined along with various other factors.[21,22]

This study was conducted to investigate the role of modifiable causative factors contributing to cleft lip and/or palate in patients referred to a tertiary care centre in Navi Mumbai.

Maternal tobacco usage during pregnancy has been repeatedly linked to a heightened risk of cleft lip (with or without cleft palate) and isolated cleft palate, with the population-attributable risk estimated to be as high as 20%.[23,24] The literature consistently supports a connection between maternal smoking and an increased risk of clefts in offspring. Notably, a meta-analysis of 23 case-control studies and 6 cohort studies revealed that mothers who smoked had a 37% higher likelihood of having a child with cleft lip (with or without cleft palate) compared to non-smokers.[24,25,26] Orofacial clefts develop prior to the 9th week of pregnancy as palate develops embryo logically during that time, so first trimester maternal smoke exposures are the most crucial.[2] In our study, we observed that none of the mothers reported history of smoking during pregnancy. The reason might be because in low-resource populations, smoking is often economically inaccessible to women and culturally stigmatized.[27]

Several studies in the literature support the interrelationship between maternal passive smoking and an increased risk of clefts in offspring. In our study, 15% of mothers reported exposure to passive smoke from a family member during pregnancy. Similarly, Kummet et al. found a positive link between first-trimester passive smoking and oral clefts, a finding that was consistent across various populations.[27] Sabbagh et al. reported a 1.5-fold increase in the risk of non-syndromic orofacial clefts associated with maternal passive smoking, emphasizing the substantial impact of second hand smoke exposure during pregnancy on the likelihood of these birth defects.[28] The most notable positive association is a report indicating nearly a two-fold increased risk of cleft lip, with or without cleft palate, in infants in China whose mothers were exposed to passive smoke during pregnancy.[29] In our study, 44% mothers reported usage of chulha for cooking. The study conducted by Auslander et al. in 2020 examined the link between indoor cooking over an open flame and non-syndromic clefts based on data from multiple low-resource countries. The findings indicated that mothers who reported exposure to indoor cooking smoke were approximately 50% higher likelihood of having a child with a cleft.[30] Likewise, a previous case-control study by Liu et al. in China found a link between indoor air pollution and an increased risk of cleft lip and palate, especially in homes without adequate ventilation. The study attributed this association to the utilization of coal-burning heating systems, which release harmful pollutants into the indoor environment, elevating the likelihood of birth defects.[31] In a study conducted by Kharbanda et al. across Delhi and National Capital Region (NCR), recorded that 14.6% cases had a familial association of cleft and 54.26% gave a positive history of exposure to smoke during 1st trimester of pregnancy. This sample included mothers exposed to smoke from cigarette smoking, passive smoking and/or use of chulha during the 1st trimester of the affected pregnancy.[8] Thus, maternal exposure to cooking smoke is linked to a higher risk of cleft lip and palate in offspring, likely caused by the inhalation of hazardous pollutants released during cooking, especially in areas with poor ventilation.

Current literature has detailed the mechanism connecting smoke exposure to cleft formation during embryonic development. Maternal exposure to passive smoke is hypothesized to interact with genetic factors, potentially elevating the risk of birth defects. One proposed mechanism involves the interaction between passive smoking and the infant's MIR140 gene (microRNA-140), which may heighten the risk of cleft lip and palate. Passive smoke may reduce microRNA-140 levels during critical stages of palatal development, thereby increasing the likelihood of these congenital anomalies.[29] An interaction between the zinc finger protein 533 gene (ZNF533) and maternal exposure to

passive smoking during the first trimester has been observed in the Chinese case-parent trios, where it was linked to an elevated risk of cleft lip (either with or without a cleft palate). This suggests that maternal smoking may influence genetic susceptibility to these conditions.[32] Passive smoke from tobacco and fuel combustion contains recognized teratogens, such as polycyclic aromatic hydrocarbons, carbon monoxide and heavy metals. Shum et al. showed that maternal exposure to the polycyclic aromatic hydrocarbon benzo [a] pyrene during the periconceptional period results in cleft formation in genetically unresponsive inbred mice, which are metabolically deficient.[33] Maternal exposure to low levels of carbon monoxide has been shown to cause tissue hypoxia in rat fetuses.[34] This reduces the cellular metabolism of benzo[a]pyrene[35], indicating a possible role of carbon monoxide in cleft development. The combustion of tobacco and biomass fuels emits heavy metals, such as cadmium, which has been shown to play a role in cleft development in rats.[36,37] At the population level, Langlois et al. showed that maternal occupational exposure to higher levels of polycyclic aromatic hydrocarbons in certain work environments is linked to an increased risk of cleft lip and/or cleft palate in the progeny.[38] Therefore, maternal exposure to smoke from cooking and passive smoking is linked to an increased risk of clefts, and efforts should be made to educate the public to avoid such exposures.

Maternal alcohol consumption is a known cause of foetal alcohol syndrome; however, its role in isolated orofacial clefts (OFCs) is less clear, with some studies suggesting a positive association[39,40,41] but negative in others.[42,43] The social and dietary factors related to alcohol consumption are varied and intricate, potentially influenced or confounded by elements such as nutrition, smoking, and stress,[44] or drug use.[23] In our study, none of the mothers reported any consumption of alcohol during pregnancy.

In our study 58 fathers and 16 mothers were above 30 years of age during conception but none of them were above 40 years of age. However, advanced maternal and paternal ages are also regarded as risk factors for orofacial clefts (OFC), as they can lead to gene mutations and chromosomal abnormalities.[45] Consanguineous marriages accounted to 12.6 % of total cases. The systematic review of the literature and meta-analysis by Sabbagh et al. in 2014,[3] demonstrated that consanguinity is an established risk factor for OFC (P=0.0003). These findings align with the genetic cause of OFCs being inherited through a homozygous recessive mode in consanguineous unions, which raises the likelihood of allelic homozygosity at the same genetic loci. In our study, we observed a 12.6 % of couples who gave a positive history of consanguineous marriages and 16 cases reported having immediate family members with similar congenital defect. Thus, consanguinity is a risk factor for OFC and hence consanguineous marriages should be avoided to prevent occurrence of facial clefts.

Observational studies indicate that maternal nutrition may influence OFCs. Evaluating dietary intake or biochemical indicators of maternal nutritional status can be challenging and often impractical in many impoverished populations, where the rates of orofacial clefts (OFCs) are highest. However, a meta-analysis has indicated that maternal intake of multivitamin supplements during the early weeks of pregnancy is associated with a lower risk of OFCs,[46] This is supported by evidence showing a 25% decrease in the prevalence of orofacial clefts (OFCs) at birth associated with multivitamin use. Specifically, folate deficiency has been demonstrated to cause clefts in animal studies.[47] Furthermore, folate antagonists have been linked to an elevated risk of orofacial clefts (OFCs) in humans.[48] The influence of dietary or supplemental folic acid intake on human cleft disorders remains unclear. However, biomarkers reflecting inadequate vitamin B6 status have been linked to an elevated risk of orofacial clefts in both the Netherlands[49] and the Philippines.[50] Deficiencies in vitamin B1 and B6 are prevalent among populations in Asia that consume high amounts of polished rice. Individuals with vitamin B6 deficiency seem to exhibit higher prevalence of cleft lip, cleft lip with palate, and isolated cleft palate.[50] In our study, 52% of mothers reported consuming polished rice during pregnancy. Zinc is crucial for foetal development, and its deficiency has been associated with isolated cleft palate and additional abnormalities in animals.[51] Additional nutrients that may contribute to the development of OFCs include riboflavin[52] and vitamin A.[53,54] A multifactorial comparison of environmental risk factors associated with this deformity was performed by Kalaskar et al in Nagpur region (India) and demonstrated a positive association between cleft lip and palate and the environmental risk factors of nutritional deficiency, anaemia, and self-administered medications.[9] In our study 63% cases were socioeconomically below poverty line. Although there is a clear correlation between education and income, insufficient paternal education may have prevented the expectant mother from receiving adequate nutrition, potentially contributing to the development of congenital deformities.[55] In a hospital-based study in Delhi and National Capital Region (NCR) concluded that family history of cleft lip/palate, exclusive vegetarianism, and delayed first conception were found to be strongly associated with higher risk of OFCs.[56] Previous studies have acknowledged that poor financial and educational achievement can have long-term negative effects on employment outcomes, social interactions, mental health, and physical health, which may also influence the incidence of orofacial clefts.[57]

Occupational exposure of expectant mothers to organic solvents[58] and agricultural chemicals[59,60] have been linked incoherently with cleft lip and palate anomalies in off springs. Anticonvulsant medications, primarily diazepam, phenytoin, and phenobarbital,[61-63] have been shown to increase the risk of these anomalies. Additionally, positive correlations with maternal corticosteroid use during pregnancy have also been

observed.[64] Other studies have identified additional maternal factors linked to an increased risk of oral clefts such as a history of fever or cold, the use of antipyretic and analgesic medications, and poor ventilation during cooking or heating.[65] In our study, only 3 mothers reported use of medication for hyperthyroid, hypotension and viral infection. Others did not report/recall any significant disease or use of medication to treat such diseases, however, improving and standardizing the measurement of maternal exposure in future studies is essential.

The findings of this study will aid in the development of comprehensive treatment systems tailored to each cleft pattern. We aim to expand our research to gain a more thorough understanding of the pathogenesis of this condition. It is essential to consider risk factors specific to low-resource settings, as individuals in these environments encounter significant barriers to accessing care and are therefore more vulnerable to adverse health outcomes. Understanding these factors can help enlighten public health interventions and education efforts aimed at preventing disease in populations with limited access to care, where children are particularly susceptible to enduring lifelong adversities. Modifiable and patient-centred solutions such as providing clean-burning cookstoves, avoiding consanguineous marriages, and preventing maternal exposure to cooking smoke and passive smoking will be crucial in reducing the global prevalence of cleft conditions and enhance the quality of life for people affected by these conditions.

5. Conclusion

Cleft lip and palate anomalies are more prevalent than isolated cleft lip or cleft palate. Unilateral and left-sided clefts occur more frequently than bilateral clefts, and cleft palate is more prevalent in females than in males.

Maternal active smoking or exposure to passive smoke of any kind should be strictly prevented. Use of clean-burning cookstove should be provided to every household. Consanguineous marriages should be discouraged. Use of multi-vitamins and folic acid supplementation during pregnancy should be made compulsory. Polished rice consumption during pregnancy should be avoided. Individuals having immediate family members with similar congenital defect should be genetically counselled. Socioeconomically below poverty line families should be educated regarding these risk factors.

Implementing patient-centric solutions can significantly impact the prevention and management of cleft cases, thereby improving overall health and quality of life globally.

6. Source of Funding

None.

7. Conflict of Interest

None.

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