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Original Research Article

A case control study on the risk factors of non-syndromic orofacial clefts

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ABSTRACT

Background: Orofacial clefts (OFCs) are the most common craniofacial malformation of the new born in the world. In India OFCs are the 3rd most common congenital anomaly following anencephaly and club foot. Objectives were to study the association of family history, medications during pregnancy, passive smoking with non-syndromic OFC, and to determine the pattern of OFCs in the study population.
Methods: This is a hospital-based, matched case-control study conducted in a tertiary care centre, Thrissur, Kerala. We interviewed 30 mothers of children affected by non-syndromic OFCs. Mothers were asked about their sociodemographic details and other suspected risk factors using a semi structured questionnaire.
Results: In our study unilateral left sided cleft lip was found to be more prevalent 62%. Those who had a family history of OFCs was found to have a significantly higher risk of OFC (OR 26.333). Medications for diabetes mellitus, hypertension, thyroid dysfunction, bronchial asthma, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) during first trimester of pregnancy posed a higher risk for OFCs (OR 7.222). Maternal age at pregnancy greater than or equal to 30 was also found to be a significant risk factor.
Conclusions: In our study we found out that family history is a risk factor for OFCs. We conclude that exposure of the mother to passive smoking should be avoided during pregnancy and family members should be made aware of the health hazards of passive smoking. Medications should only be taken after consulting a doctor preferably an obstetrician. Self-medication during pregnancy should be strictly avoided.

Keywords: Orofacial clefts, Birth defect, Risk factors, Cleft palate/lip

INTRODUCTION

Orofacial clefts (OFCs) are among the most common congenital birth defects.[1] Approximately 2,50,000 babies are born with these defects each year worldwide out of which approximately 28,600 babies are born in India, that is, 78 infants per day in the country. The prevalence varies by ethnicity, sex, and socioeconomic status.[2] OFCs, which include three distinct subgroups, cleft lip only (CLO), cleft lip and palate (CLP), and cleft palate only (CPO), result from fusion failures in weeks 5 (fusion of lip) and 9 (fusion of palate) from the date of conception.[3]

They are categorized as syndromic if they are accompanied with additional structural or developmental abnormalities (like as in Pierre Robin syndrome, Van der Wonde syndrome, Velocardio facial syndrome and median facial dysplasia) and non-syndromic if they occur in isolation without other apparent abnormalities.[4] The

etiology of OFC is polygenic and multi-factorial. Both genetic and environmental factors have been identified though the precise cause in many cases is unclear. The environmental factors include maternal illness, infections, drugs, radiation, alcohol, and contamination of food and water with pesticides, nitrates, and mercury.[5-6]

The presence of cleft lip can be diagnosed during the 5th month anomaly scan whereas cleft palate is usually diagnosed as a post term observation by the mother. Affected children have a range of functional as well as aesthetic problems. These include feeding difficulties at birth due to problems with oral seal, swallowing and nasal regurgitation, hearing difficulties due to abnormalities in the palatal musculature, and speech difficulties due to nasal escape and articulation problems.[7] OFCs are the most common craniofacial malformation of the new born in the world.[8]

OFCs may impose a large burden on the health quality of life and socioeconomic wellbeing of affected families and individuals. Therefore understanding the risk factors and providing awareness on how to prevent exposure to these risk factors is important factors such as exposure to pesticides, infections, obesity, dietary factors, folate intake, and passive smoking are preventable.

METHODS

Study design

This is a hospital-based, matched case-control study (1:2 ratio; matching done for age and gender of the child).

Study setting

Study was conducted in Jubilee Mission Medical College and Research Institute, Kerala for a period of 6 weeks June 2019 to July 2019, Thrissur- Kerala.

Study subjects

Case

Mothers of children affected with non-syndromic OFC, less than 20 years old.

Control

Mothers of children without OFC, less than 20 years old.

Inclusion criteria

Mothers of children affected with and without non syndromic OFC were included in the study.

Exclusion criteria

Mothers of children who had anomalies other than non-syndromic OFC were excluded from the study.

Study procedure

This is a hospital based matched case control study were we interviewed 30 mothers of children affected by non-syndromic OFCs who were admitted in the surgery ward and smile train (a programme run by nongovernmental organization that provide free treatment for OFCs) OPD of the institution. The mothers were selected based on a consecutive sampling method and were asked about their sociodemographic details and other suspected risk factors using a predesigned semi-structured questionnaire, prior to use, the content validity was ensured by reviewing with qualified experts from other specialties and to ensure the reliability of the tool internal consistency was checked by using Cronbach's alpha coefficient. Upon analysis Cronbach's alpha value was found to be 0.75 and reliable for data collection. After matching for the age and gender of the child we selected 2 controls for every case, and interviewed those mothers of children without any form of OFCs who were admitted to the gynaecology and pediatric wards and OPD. The mothers were selected after excluding children affected by other congenital anomalies. The interview of both the case and control were done on the same day.

Statistical methods

Numerical variables were expressed as mean and standard deviation. Categorical variables were expressed as frequency and percentage. Mann Whitney U test was applied for comparing mean age between groups. Chi-square/continuity correction/Fisher's exact test were applied to test the association of study variables with groups.

RESULTS

Out of the study subjects 62.5% of case and 63.75 % of control mothers had children less than 5 years old, among the children, 45% were males and 55 were females and among controls, 55% is males and 45% is females. In our study, Malappuram had the highest number of cases of OFC– 14 (35%), followed by Thrissur– 6 (15%), 4 case each from Ernakulam and Palakkad (10% each), 2 case each from Wayanad, Pathanamthitta and Trivandrum (5% each), 1 case each from Kottayam, Idukki, Kannoor, Kollam, Kasargod (2.5% each) and one case from Maharashtra (2.5%). Among the cases of OFCs, cleft lip palate had the maximum occurrence of 63.3%, followed by cleft lip with 20%, and cleft palate with 16.7%. Among the cases of cleft lip and cleft lip palate, unilateral left sided cleft were found to be more prevalent with 60%, followed by bilateral cleft with 28% and least prevalence was unilateral right sided cleft with 12%. The subjects with age of mother during pregnancy more than or equal to 30 have higher risk for having babies with OFC as compared to those less than 30 with odds ratio 6 (2.28-15.769) and the association was found to be statistically significant. The proportion of subjects with the family history of OFC is significantly higher than as

compared to controls (odds ratio 26.333**)**. In our study we found out that those who had history of passive smoking has 5.154 times the risk of having OFC as compared to those without passive smoking.

Table 1: Sociodemographic profile of the study population.

Variables	Case n (%)	Control n (%)
Age of the child		
<5	25 (62.5)	51 (63.75)
5-10	7 (17.5)	16 (20)
>10	8 (20)	13 (16.25)
Gender of the child		
Male	18 (45)	44 (55)
Female	22 (55)	36 (45)
Education of mother		
High school	5 (12.5)	2 (2.5)
Higher secondary	16 (40)	19 (23.75)
Graduate	14 (35)	49 (61.25)
Professional	5 (12.5)	10 (12.5)
Total	40	80

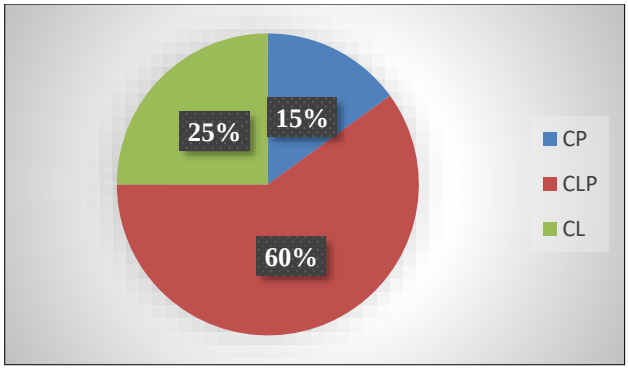

Figure 1: Pattern of different types of OFCs.

In our study those mothers who had taken self-medication during pregnancy is significantly higher than as compared to controls of having OFC with an odds ratio odds of 7.222. The risk factors for which we found association were maternal age at pregnancy, family history, passive smoking, self-medication, religion and miscellaneous medicines. But on applying multi-variant regression, religion and miscellaneous medicine did not have any independent association with the outcome.

Table 2: Maternal risk factors associated with OFCs.

Age of mother at pregnancy	Groups				OR (95% CI)	P value
	Case		Control			
	n=40	%	n=80	%		
<30	24	60	72	90	6.0 (2.28-15.769)	<0.001*
≥30	16	40	8	10		

*Significant at 5% level

Table 3: Association of family history with OFCs.

Family history	Groups				OR (95% CI)	P value
	Case		Control			
	n=40	%	n=80	%		
Yes	10	25	1	1.25	26.333 (3.231-214.647)	<0.001*
No	30	75	79	98.75		

*Significant at 5% level

Table 4: Association of passive smoking with OFCs.

Passive smoking	Groups				OR (95% CI)	P value
	Case		Control			
	n=40	%	n=80	%		
Yes	20	50	13	16.25	5.154 (2.184-12.161)	<0.001*
No	20	50	67	83.75		

*Significant at 5% level

Table 5: Association of self-medications during pregnancy with OFCs.

Medication	Groups				OR (95% CI)	P value
	Case		Control			
	n=40	%	n=80	%		
Yes	25	62.5	15	18.75	7.222 (3.082-16.922)	<0.001*
No	15	37.5	65	81.25		

*Significant at 5% level

Table 6: Multivariant regression analysis.

Variables	P value	OR	95% C.I. for OR	
			Upper	Lower
Age at pregnancy	0.001	6.234	1.543	25.196
Family history	0.001	26.318	2.386	290.354
Passive smoking	0.001	3.109	0.883	10.940
Medication	0.001	8.116	2.659	24.769
Constant	<0.001			

DISCUSSION

In our study 40 cases and 80 controls were taken and the study subjects were mothers of children affected by non-syndromic OFCs. In our study on the risk factors of non-syndromic OFCs, family history had the highest association and could independently influence the outcome, it had an odds ratio of 21.45, this finding was consistent with the study conducted by Leite, department of collective health, Brazil.[8] They found out that the history of OFC either in the father's (CL/P: OR=16 [5.64-69.23], CP: OR=6.64 [1.48-33.75]) or in the mothers family (CL/P: OR=5 [2.31-10.99], CP: OR=12.44 [1.33-294.87]) was strongly associated with both types of clefts, but parental consanguinity was associated only with CL/P (OR=3.8 [1.27-12.18]). In our study mothers who took medications during pregnancy including bronchodilators, medications for thyroid dysfunction, diabetes and hypertension, analgesics and non-steroidal anti-inflammatory drugs (NSAIDS) showed higher risk in giving birth to children with OFCs. It had an odds ratio of 6.476. In a similar study conducted by Kawalec et al in 2015 suggests that medicaments especially bronchodilators, anticonvulsive, amoxicillin, corticosteroids increased the risk for developing OFC.[9]

In a study done by Villeruša, a they found out that the prevalence of OFCs increased depending on maternal age.[10] Our study also had similar finding were the maternal age at pregnancy of 30 or above act as an independently associated risk factor of OFC. In a study done by jubilee centre for medical research about geographic information system (GIS) they found out that maximum number of cases of OFCs were reported from Malappuram and it is consistent with our finding were 36% of children affected by OFCs hailed from Malappuram district.

In a case control study conducted by Leite et al they found out that maternal passive smoking during pregnancy was associated with CL/P with an odds ratio of 1.39.[8] In our study those who had a history of maternal passive smoking had an odds ratio of 5.667. The most common pattern of cleft in our study was cleft lip with palate. This is in conjunction with a study conducted by Kharbanda et al in AIIMS and Safarjung Hospitals.[11]

In another study done by Sutapa et al on the risk factors of OFC in India they pointed towards a positive association between mothers on vegetarian diet and children with OFC [OD 4.47(1.83-10.98)].[12] Their data also revealed a possibility increased intake of pesticidal residues among vegetarian than the general population.

Limitations

Our study was limited to non-syndromic OFCs and does not cover the risk factors associated with syndromic OFCs; recall bias regarding the intake of miscellaneous medicines during first trimester of pregnancy; our study did not include functional difficulties and their consequent complications faced by children having OFCs; and incidence- prevalence bias is a possibility.

CONCLUSION

In our study unilateral left sided cleft lip was found to be more prevalent with 62%. Subjects with family history of OFCs were found to have a significantly higher risk. Medications for diabetes mellitus, hypertension, thyroid dysfunction, bronchial asthma, analgesics and NSAIDs during first trimester of pregnancy posed a higher risk and also mothers who were passive smokers and those who reported reduced folate consumption in pregnancy posed a higher risk but was statistically insignificant. Folic acid did not act as a protective factor. Even though not statistically significant, intake of miscellaneous medications (Ayurveda, Homeopathy, Pachamarunnu and camphor) during pregnancy was also found to be an associated risk factor.

Recommendations

Exposure of the mother to passive smoking should be avoided during pregnancy, especially during the first trimester. Mothers should be made aware of the health hazards of passive smoking. Medications (antiepileptic drugs, bronchodilators) should only be taken after consulting a doctor preferably an obstetrician. Self-medication during pregnancy should be strictly avoided. Consanguineous marriage should not be endorsed. As the maternal age of 30 or above is an associated risk factor, mothers should be made aware of the probable adverse conditions associated with it. Awareness on feeding a child with OFC will help to reduce complications (respiratory and nasal diseases, possibility of death due to aspiration).

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