Original Research Article

Non-genetic factors in the craniofacial region contribute to the incidence of non-syndromic CLEFS

Syeda Parveen Fatima[1*], Syeda Nasreen Fatima[2], Mohammed Obaidullah[3]

[1]Assistant Professor, Department of Anatomy Dr. V.R.K. Women's Medical College, Teaching Hospital & Research Centre. Hyderabad, Telangana, India
[2]Associate Professor, Department of Anatomy, Deccan College of Medical Sciences, Hyderabad, Telangana, India
[3]Post Graduate Student, Rainbow Children's Hospital, Hyderabad, Telangana, India

Received: 11-11-2021 / Revised: 15-12-2021 / Accepted: 11-01-2022

Abstract

In addition to genetic and environmental influences, clefts have a complex origin. Many research has studies tried out to determine the genetic basis of the aetiology of clefts and the effect of maternal folic acid intake on the incidence of clefts in children and adults. In addition to genetics, there has been little research done on the environmental factors that contribute to clefts. Non-genetic variables related to the development of nonsyndromic clefts are the subject of the current investigation. Mother's folic acid intake during pregnancy, family history, parental age, socioeconomic position (including alcoholism and smoking), and parent's occupational exposure are among the variables examined in the research. 200 participants from the South Indian population were included in the study, 100 of whom had nonsyndromic clefts and 200 who were healthy controls. In a detailed questionnaire administered via direct interview, the information was gathered, and the information was analyzed using GraphPad Prism 9. The odds ratio (OR) for the independent variables was calculated using a logistic regression model, and the significance of the results was determined using a Chi-square test.The study group included 6 craniofacial clefts, 5 facial clefts and 64 cases of cleft lip and palate. Clefts occurred at a rate of 12 per cent in the craniofacial region and 26percent in the lip region. The case group (24.6%) had a lower maternal age than the control group (12%), with a p-value of 0.001. Paternal ages more significant than 40 years were detected in 8.0 per cent of cases and 0.5% of controls. However, parental medicine and smoking were shown to be insignificant in terms of pesticide exposure, whereas parental occupational exposure in terms of pesticide exposure was found to be significant.

There should be no doubt about the importance of maternal folic acid and multivitamin consumption throughout the periconceptional stage for the prevention of mouth clefts. Clefts are more likely to occur in families where there is a history of clefts, and the risk is higher when clefts are present in the parents or siblings. Furthermore, maternal age greater than 35 years is revealed to be more significant than paternal age. The presence of consanguinity was associated with a fourfold increase in clefts. Apart from the family's financial position, the maternal diet is an important component since it is directly tied to folic acid and vitamin supplements.

Keywords: cleft lip, cleft lip palate, status socio-economic-political, cleft lip and palate.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Orofacial clefts are a collection of anatomically unique birth disorders. There is a gap or break in typical mouth characteristics, often the roof of the mouth (the palate), the upper lip, or both. The most frequent anatomical forms of orofacial clefts, as depicted in Figure 1, are cleft lip (CL), cleft palate (CP), and cleft lip and palate (CL&P) (CLP). Orofacial clefts can impact other parts of the face and mouth, although the vast majority of instances involve newborns with one of the three most prevalent types[1]. Normally, the face and mouth develop exceptionally early in pregnancy, reflecting a complicated process of cell growth and migration, followed by the fusing of symmetric structures to form the palate dividing the mouth and nasal cavity, with the outside structures of the face forming before the inner tissues. CL, CLP, and CP are the most prevalent craniofacial birth abnormalities globally, with affected children experiencing eating difficulties early in life and often requiring several corrective surgeries, therapeutic dental operations, and speech therapy throughout childhood[2-4]. Furthermore, even in affluent countries with competent medical treatment, individuals born with an orofacial cleft have a higher incidence of mental health disorders and a higher overall death rate at all stages of life. Infants born with CP or CLP have a high death rate due to difficulty breastfeeding, and untreated CL and CLP cases can endure social discrimination throughout their life in areas where access to medical care is severely limited. As a result, these congenital abnormalities have been subject to significant selective pressure for most of human history[1, 2]. Even though clefts develop early in pregnancy, we base most epidemiologic research on the cleft frequency at delivery. All orofacial clefts' global average birth prevalence is 9.92 per 10,000 (almost one per 1,000). However, there is a significant variance between populations[3].

According to a new study, over 72,000 children and adults in India have unrepaired cleft lip or cleft palate, underlining the unmet need for cleft lip and palate (CL/P) care. According to the statistics, there are 72,637 cases of unrepaired CL/P in India. Individuals with unrepaired CL/P who were older than the corresponding target age category of 1-2 ranged from 37.0% in Goa to 65.8% in Bihar. Newborns in poor and middle-income countries suffer severe impediments to treatment, resulting in long-term disfigurement, social stigma, speech difficulty, and feeding difficulties, leading to Newbornsto malnutrition and mortality. In their report published online by JAMA Facial Plastic Surgery, the researchers stated that safe, timely, and effective surgery could cause successful outcomes. Poorer states, such as Bihar, with fewer healthcare facilities, were found to have very high rates of surgery. Unrepaired CL/P rates ranged from less than 3.5 per 100,000 people in Kerala and Goa to 10.9 per 100,000 people in Bihar[4,5].

*Correspondence
Dr. Syeda Parveen Fatima
Assistant Professor, Department of Anatomy Dr. V.R.K. Women's Medical College, Teaching Hospital & Research Centre. Hyderabad, Telangana, India
E-mail: Marziyyahsohail123@gmail.com

To sincerely know OFC aetiology, one must comprehend facial embryogenesis and morphogenesis. The activation of risk factors causes OFC clefts at various phases of face morphogenesis. Face morphogenesis has five stages. The frontons, maxillary, and mandibular processes comprise mesenchyme and are bordered by epithelium, as does the entire mouth cavity. The desmocranium, chondrocranium, and viscerocranium make form the human skull. All parts play a role in optimal growth[6]. Various factors can disrupt or affect the normal course of facial development during pregnancy. Facial processes grow in their unique way. They form surrounded the frontal process from the medial and lateral nasal processes. The upper lip, alveolus, and main palate are formed by fusing anterior and maxillary processes[7]. Oral clefts, like cleft lip and cleft palate, have many congenital failure episodes. The union of the maxillary and median nasal processes breaks down in the cleft lip. The palate doesn't fuse properly, causing cleft. The secondary palate is formed by moving the maxillary processes posteriorly. Orofacial clefts have a multifactor aetiology and impact on cleft producing factors[7,8]. In addition, a variety of disorders can cause orofacial clefts. Also, genetic abnormalities play a role in cleft formation. Many diseases and gene abnormalities produce facial deformities. It's also worth noting that clefts can be linked to many disorders and abnormalities. The Pierre-Robin is the most frequent. CHARGE syndrome (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness) Trisomy Waardenburg, Hedgehog 13 Patau's syndrome Many studies show that females are more likely to develop breast cancer and primary brain cancer than males. Behavioural difficulties, anxiety, despair, low self-esteem, and other variables affect patients' QOL Clefts can produce dental, facial, or mixed anomalies. A cleft with or without other oriental malformations or disorders is rare[9,10].

Methods and materials

This study comprised 200 patients from the South Indian population, 100 of whom had non-syndromic congenital clefts of the craniofacial region and 100 healthy controls who were matched for gender, age, and geography. The plastic surgery department referred the cleft patients, whereas the paediatrics, obstetrics, and gynaecology departments referred to the controls. The patients were clinically assessed to rule out syndromic clefts, and their medical records were verified. The approval of the Institute's Ethics Committee was acquired.They got informed written consent from the study group and, in the case of minors, from their parents. The study group and their parents were interviewed, and data were collected using a detailed questionnaire that covers socio-demographic variables, with history, family history, consanguinity, periconceptional folic acid and vitamin intake, maternal stress, maternal diet and medication, parental age at the time of conception, parental alcoholism, smoking, and other teratogenic exposure.Statistical analysis Graph Pad 9 was used to analyze the data[11]. To study the role of the factors that cause clefts, a logistic regression model was used to calculate the odds ratio (OR) for the independent variables that cause clefts. The odds ratio (OR) is given with a 95% confidence interval (CI). The analysis used a level of significance of 0.05. P values less than 0.05 were deemed statistically significant. Chi-square analysis was also used to determine the significance.

Result and discussion

It shows that males were more severely affected by the clefts than females. This discrepancy can be attributed to the fact that males were more likely than females to have cleft lip and palate in this study sample. In other clefts, a majority of females was seen. However, there is no statistically significant difference between the two groups.

Table:1- Shows the gender distribution in different clefts

	Cleft	Gender		Total
		Female	Male	
Controls	Nocleft	50(50.0%)	50(50.0%)	100(50 %)
Cases	Craniofacial	4(8.0%)	2 (4.0%)	6(12 %)
	Facial	3(6.0 %)	2 (4%)	7(14 %)
	Cleftlip	6 (12.0 %)	7(14.0 %)	13(26.0%)
	Cleftlippalate	29 (58.0%)	35 (70.0 %)	61(122%)
	Cleftpalate	8 (16.0%)	4 (8.0 %)	12 (24 %)
Total		100	100	200

Table 2: Shows the significance of nongenetic factors incasesandcontrols.

Variable	OR	CI95%	*P*-value
Maternalfolic acidintake	32.80	12.353-81.09	0.001
Parentalpesticidalexposure	0.623	0.156-2.172	0.365
Socio economic status Poor	3.034	0.5005- 14.887	0.001
Average			0.234
Aboveaverage	0.318	0.225-0.876	0.0032
Maternalage	0.980	0.870-1.215	0.364
Maternaleducation	0.815	0.184- 4.112	0.898
LowAverage/medium	0.768	0.188-2.786	0.4996
Consanguinity	4.345	1.675-17.987	0.0261
Locationofresidence	7.9008	2.008-18.009	0.001

The study group included 6 craniofacial clefts, 5 facial clefts, 13 cases of cleft lip (CL), 64 cases of cleft lip palate (CLP), and 12 isolated cleft palate (CP) cases. Clefts occurred at a rate of12 per cent in the craniofacial region, 10 per cent in the facial region, 26per cent in the lip, 64per cent in the lip palate, and 24per cent in the palate. In general, 26per cent of cleft cases (p=0.001) had a family history of clefts, which was not observed in the control group. There was a familial history of clefts in 10% of cleft lip palate cases, 21.0 % of cleft lip cases, and 6.5% of cleft palate cases, but not in craniofacial clefts. (See Table 1)

The case group (24.6%) had a lower maternal age than the control group (12%), with a p-value of 0.001. Paternal ages more significant than 40 years were detected in 8.0 per cent of cases and 0.5 per cent of controls (p=0.004). Parental age greater than 35 years was found to be significantly more prevalent in cleft instances than in the control group.

According to Kuppuswamy's socioeconomic scale, 68.0 per cent of cases were impoverished, but just 3% of the control group were (pvalue=0.001). In 68.0per cent of patients and 18per cent of the control group, low parental education was observed (pvalue=0.001). Interestingly,68% of cases originated in rural regions, compared to 14% in controls[11].

Low folate consumption

During the first trimester can harm organogenesis. Reduced folate intake and maternal hyperhomocysteinemia may cause incorrect methylation and DNA synthesis in the mother, resulting in clefts. So folic acid supplementation can counteract hyperhomocysteinemia's teratogenic impact.Population-based cohort research found a four-fold increased risk of cleft lip in newborns whose mothers did not take folic acid during the first three months of pregnancy compared to those who did. The absence of folic acid in the first three months of pregnancy was linked to cleft lip and palate[10,12]. The first three months are critical for folate consumption because the lip fuses at 48 days and the palate at 60 days. The study found a 5-fold greater risk of clefts in children whose mothers did not consume folic acid during pregnancy.Folate deficiency is caused by disruptions in the folate metabolism pathway, which affects nucleotide synthesis, cell division, tissue growth, and craniofacial development. High homocysteine levels may also disrupt early developmental activities such as neural crest cell motility and migration. Research in Mexico found that maternal malnutrition, particularly low vitamin B12 levels, increased the risk of clefts. The maternal diet is vital in folate supplementation. A diet high in folate can compensate for a lack of folic acid consumption. All of these studies found that consuming folate-rich foods, folic acid pills, and multivitamins lowered the likelihood of clefts[10,13].

The study found that 40per cent of CL, 70 per centof CLP, and 28 per centof CP women did not take folic acid in the first trimester. No moms of children with craniofacial and facial clefts used folate whereas 81% of mothers in the control group did. Our research also indicated thatthe absence of intake increases the risk of clefts.

Parental pesticide exposure

Agricultural activity exposes parents to teratogenic organic solvents and pesticides. Pesticide exposure to parents increases the likelihood of craniofacial clefts, especially CLP. In this study, 52 per cent of parents were exposed to pesticides, but just 4 per cent of controls were. This maternal pesticide exposure was connected with clefts. (p=0.001). Our analysis found a small increase in risk (OR= 0.573, 95% CI) (0.185 to 1.872). CLP (55.8%) had higher parental pesticide exposure than other clefts (p=0.044)[14].

Indirect pesticide exposure occurs owing to residential proximity and frequent field entrance after pesticide treatment. Pesticide residues remain on the soil for some time after spraying. Spending more time in pesticide-exposed areas immediately after the pesticide spraying will have an additional effect. Humans should minimise pesticide exposure throughout reproductive age, especially during the first trimester of pregnancy, a period of organogenesis and teratogen exposure. Face formation occurs during the first 60 days of the embryonic phase[14], and teratogenic exposure may result in cleft lip and palate during this period.

Consanguinity

There is a considerable link between consanguinity and clefts, especially in the second degree. The study group had no first-degree consanguinity. First-degree consanguinity is parent-child or brother-sister. Third-degree consanguinity has a 3-5 per cent abnormality risk, while second-degree consanguinity has a 5-12per cent chance. No cleft group demonstrated consanguinity. The anomaly decreases with consanguinity. This is because the ancestor's genes are less shared[14].

Consanguinity was found in 38 % of patients and only 8 % of controls in our investigation. Consanguinity was discovered to cause clefts. Consanguineous marriages had a four-fold greater risk of clefts. 4.871, 95 per cent CI 1.689-15.540.

Family history

According to Nouri et al, family history of cleft lip and palate is a substantial genetic predisposing factor. A positive family history of clefts was associated with a higher incidence of CL/P than CP. In our study, 10.6% of cleft patients had a family history of clefts, with CLP (7.2%), CL (2.7%) and CP (0.7%) having the highest rates (0.5 per cent)[16]. Also in Gujarat, 14.4% of cleft instances had a favourable family history, with the CLP having the highest rate, followed by the CP[17]. Our investigation included both CL and CLP cases. Cleft risk increases to 3-7 per cent when a parent is affected and to 15-16 per cent when one parent and a sibling are affected. This shows that more familial clefts increase the risk of occurrence. The control group has no family history of the cleft. No cranial or facial cleft family history was discovered.

Birth order

In this study, one in 42per cent, two in 40per cent, three in 7%, four in 4%, five in 2 %, and six in 0.6 per cent were born first. Our research found that as parity increases, the chance of cleft decreases. Most clefts were in birth order 1 or 2. That doesn't indicate clefts are more likely as birth order decreases. The majority of families have one or two children. As a result, this study group does not indicate a link between cleft and birth order. Families with five or more children should be included in the study group.Many studies have linked clefting to abortion rate and parity[18]. The cases' birth order was higher than the controls. Cleft risk increases with a lack of micronutrients and other dietary supplements may occur as parity rises. This shows that the risk of cleft increases with birth rank. But our study group couldn't link risk with increased parity. Previous research found that mothers aged 40 or older had a twofold increased probability of having a child with cleft than mothers aged 25-29. Orofacial clefts are linked to parental age (40+) and maternal age (35+). In an Iranian study, 36% of cleft instances had a mother aged 31-37 years after pregnancy. This shows that no risk of cleft when the mother is 30 or younger. In our survey, most parents were aged 20-35. 87 per cent of fathers in the case group and 90.5 per cent in the control group were aged 20-35. In cases, 11% of fathers were over 35; in controls, 9% were. No fathers under 20 years old were detected in the control group, but 2% of cases. Thus, the control group has a younger age range of 20-35 years. Parents aged 35 or younger were more likely to be in the case group than the control group. The risk of clefting increases from 30 to 50 years old in the Mexican study[10].

In this presentstudy, 70per cent of cases were 20-35-year-olds, while 90per cent of controls were. The remaining 8per cent were under 20. However, in the case group, 30 % were either under 20 or over 35, which was statistically significant (p = 0.001). A Chinese study revealed a similar finding, with cleft risk increasing with maternal age below 20 years[10].

Parental illness and medication

Environmental variables linked to cleft formation include vitamin deficiencies, especially A and B, high cortisone and steroid use, and anticonvulsants (phenytoin). Excess ACTH (adrenocorticotropic hormone) during pregnancy can cause clefts. In our study, the control group did not use medicines during pregnancy, while 5% of moms of cases did for hyperthyroidism, hypothyroidism, epilepsy, and allergy. The one epileptic case used phenobarbitol and was a familial cleft case. Antiepileptic medicines like phenytoin and phenobarbital may disrupt folate metabolism, increasing the likelihood of orofacial clefts[10]. In our investigation, 8 patients had hyperthyroidism or hypothyroidism. Among the 5% who used drugs, 45% developed CLP and the remaining had cleft palate. This study found no link between cleft and maternal medicines. Only six women admitted to being stressed due to serious family troubles. Stress may have raised corticosteroid levels. During pregnancy, the stress in the mother raises the chance of cleftsvia increasing corticosteroid production[19]. During the first 8 weeks of pregnancy, hyperthermia of over 40°C has been linked to facial clefts in the developing foetus. In our study, just 1% of mothers with clefts had fever during pregnancy, but we couldn't tell if it occurred in the first trimester[20].

Smoking, drinking, and occupational exposure

Orofacial clefts are linked to parental occupational exposureto maternal smoking and heavy alcohol consumption[30]. Maternal tobacco smoke exposure increased the risk of clefts. Our research found no evidence that smoking or drunkenness contribute to cleft development. Only 4% of fathers had a history of smoking or drinking. None of the mothers smoked or drank. 3 per cent of cleft parents had been exposed to organic solvents as painters or dyers.Previous research showed that rural areas had 64% to 68% of cleft cases compared to metropolitan areas[20]. Most rural parentsfarmers Socioeconomic level, parental education, and maternal folic acid supplementation were associated with clefts[25]. In the current study, 73.7 per cent of cleft patients were from rural areas, and the majority of the parents were farmers, whereas only 9% of the control group were. This links socioecological status, residence, occupational exposure, and pesticide exposure. Low SES was revealed to be a risk factor for clefts. The SES influences parental diet and lifestyle. The dietary quality of a family's children determines their general health. SES is affected by education, occupation, and income. Orofacial clefts are more susceptible to socioeconomic deprivation. Cleft incidence declines with SES. Several studies have shown a link between low SES and a higher risk of clefts[24,32]. Our study found the same outcome. In our study, SES was lacking in 61% of instances, medium in 28%, and above average in just 11%. In the control group, SES distribution was 4%, 70.5 %, 25.5 % for poor, average, and rich. Low SES was more common in cases but only 4% in controls, indicating it is a risk factor for cleft (p = 0.001). Maternal nutrition and socioeconomic status The cleft may be caused by rural moms with low SES, poor nutrition, or lack of or decreased folic acid supplementation during pregnancy. Our investigation found it to be over 70%. Rural cleft patients had lower socioeconomic status than urban cleft patients[10].

Parental education

A population-based study linked low maternal education to a higher risk of birth abnormalities, including clefts[21]. In our study, 56 percent of cleft patients had extremely poor or no maternal education, compared to 12per cent in the control group. Parental training wascontrol group high In the control group, 84per cent of mothers and 70per cent of fathers had completed high school. The control group had 20% low educated fathers, but the case group had 74 %, which was statistically significant (p = 0.001). This implies the value of education for the future generation. They are aware of the dietary requirements in intrauterine life, which are not known to impoverish and uneducated parents.

Conclusion

Several factors affect OFC predispositions. The aetiology of orofacial deformities is unknown for many of these. Finding the aetiology and incidence of OFC utilising a newborn data set would be beneficial. Inadequate recordkeeping and medical evaluations lead to misinformation and error in OFC care.Raising knowledge of oral cleft risk factors can help prevent them. Prenatal education on mouth cleft risk factors is critical. It may lower OFC and improve local health systems, but lack of knowledge and education may exacerbate OFC.The parent's attitude towards their child's prognosis and treatment is vital. Parents did not consider terminating a pregnancy due to OFC in the child because OFC is not a severe condition. OFC therapy can significantly improve a patient's quality of life if it starts soon after childbirth and lasts almost their entire life.However, the reality for a child with OFC is less rosy. Their care necessitates an Inconveniences Otofibroblastic cystic fibrosis (OFC), a genetic disorder that affects the osteoblast's ability to produce oocytes. Rehab for nasal breathing, articulation, and occlusion is frequently late.Patients must be educated and given low-teratogenic medicine as needed. Unprescribed medicines might cause OFC problems if not taken as advised.There are several studies. Environmental risk factors in various geographic and ethnic groupings require more investigation.The next challenge is funding Regional and multilateral programs.

References

1. Southby L, Harding S, Phillips V, Wren Y, Joinson C. Speech input processing in children born with cleft palate: A systematic literature review with narrative synthesis. International Journal of Language & Communication Disorders. 2021 Jun 14.
2. Masarei AG. An investigation of the effects of pre-surgical orthopaedics on feeding in infants with cleft lip and/or palate. The University of London, University College London (United Kingdom); 2003.https://discovery.ucl.ac.uk/id/eprint/10100468/
3. Beaty TH, Marazita ML, Leslie EJ. Genetic factors influencing risk to orofacial clefts: today's challenges and tomorrow's opportunities. F1000Research. 2016;5: 2800.
4. Stewart BT, Carlson L, Hatcher KW, Sengupta A, Vander Burg R. Estimate of unmet need for cleft lip and/or palate surgery in India. JAMA facial plastic surgery. 2016 Sep 1;18(5):354-61.
5. The Association of Demographic, Socioeconomic, and Geographic Factors with Potentially Preventable Emergency DepartmentUtilization.https://dx.doi.org/10.5811/westjem.2021.5.50233
6. Kawalec A, Nelke K, Pawlak K, Gerber H. Risk factors involved in orofacial cleft predisposition–review. Open Medicine. 2015 Feb 5;10(1):163-175.
7. Everson JL, Fink DM, Chung HM, Sun MR, Lipinski RJ. Identification of sonic hedgehog-regulated genes and biological processes in the cranial neural crest mesenchyme by comparative transcriptomics. BMC genomics. 2018 Dec;19(1):1-1.
8. Berkowitz S, editor. Cleft lip and palate: Diagnosis and management. Springer Science & Business Media; 2006 May 20.
9. Jyonouchi S, McDonald-McGinn DM, Bale S, Zackai EH, Sullivan KE. CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome and chromosome 22q11. 2 deletion syndrome: a comparison of immunologic and nonimmunologic phenotypic features. Paediatrics. 2009 May 1;123(5):e871-7.
10. Jose BA, Mokhasi V, Subramani SA, Shashirekha M, et al. NON-GENETIC FACTORS CONTRIBUTE TO THE INCIDENCE OF NON SYNDROMIC CLEFTS IN THE CRANIOFACIAL REGION. International Journal of Anatomy and Research [Internet]. I MED Research Publications; 2019 Aug 5;7(3.2):6851–8.
11. Kumar K, Kumar S, Mehrotra D, Gupta S, Khandpur S, Mishra RK. A Psychologic Assessment of the Parents of Patients With Cleft Lip and Palate. Journal of Craniofacial Surgery. 2020 Jan 1;31(1):58-61.
12. Munger RG, Kuppuswamy R, Murthy J, Balakrishnan K, Thangavel G, Sambandam S, Kurpad AV, Molloy AM, Ueland PM, Mossey PA. Maternal vitamin B12 status and risk of cleft lip and cleft palate birth defects in Tamil Nadu state, India. The Cleft Palate-Craniofacial Journal. 2021 May;58(5):567-76.
13. Reddy SG, Reddy RR, Bronkhorst EM, Prasad R, Ettema AM, Sailer HF, Bergé SJ. Incidence of cleft lip and palate in the state of Andhra Pradesh, South India. Indian journal of plastic surgery. 2010 Jul;43(02):184-9.
14. Betty AJ, Varsha M, Subramani SA, ShashirekhaM,Jayanthi KS et al. Parental pesticidal exposure andrisk of clefts in the craniofacial region: A case-control study in South India. Int J of applied biologyandpharmaceuticaltechnology.2015;6(2):230-235.
15. Kingston HM.ABCofClinicalGenetics.3rded.Lon-don:BMJ;2002.P.7.
16. Betty AJ, Subramani SA, Varsha M, Mini J. Consanguinity and clefts in the craniofacial region: A ret-rospective case- control study. Journal of cleft lippalate and craniofacial anomalies. 2015;2(2):113-117.
17. Nouri MA,Hamad SA,Rasheed NE. Incidence ofCleft Lip and Palate in Erbil City.2010; 7(1): 106-112.

18. FigueiredoRF,FigueiredoN,FeguriA,BieskiI,MelloR,Espinosa M et al. Therole of the folic acid to thepreventionof orofacialcleft: an epidemiologicalstudy.OralDis.2015;21(2):240-247.
19. ShahrukhHashmiS,GallawayMS,WallerDK,Langlois PH, Hecht JT. National Birth Defects Pre-vention Study. Maternal fever during early preg-nancyandthe risk oforalclefts. BirthDefects ResA Clin Mol Teratol.2010;288(3):186–194.
20. Rahimov F, JuggesurA, MurrayJ.C. Genetics of nonsyndromic orofacialclefts.Cleftpalatecraniofac.J2012;49(1):73-91
21. Xingguang Zhang, Su Li, Siqintuya Wu, Xiaojin Hao,Shuyi Guoetal.Prevalenceof birthdefects andrisk-factor analysis from a population-based survey inInner Mongolia,China.BMC Pediatrics.2012;12:125.

Conflict of Interest: Nil Source of support: Nil