

OROFACIAL CLEFTS AND CARDIOVASCULAR RISK AND DISEASES: THE CAUSAL RELATIONSHIP AND ASSOCIATIONS

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ABSTRACT

There is a complex interplay between orofacial clefts (OFCs) or cleft of the lip and palate and cardiovascular risk factors and cardiac diseases. The presence of maternal cardiovascular risk factors serves as a potent predisposing factor to the development of OFCs during foetal development in addition to the fact that various congenital anomalies are associated with OFCs either in syndromic or non-syndromic relationship. This article narratively explores this complex interplay, which is not uncommon.

Keywords: Cleft lip and palate, Cardiovascular diseases, Obesity, Hypertension, Natal, Prenatal

INTRODUCTION

Cardiovascular diseases (CVDs) are on the rise globally and cause one-third of deaths worldwide, with 80% of such mortality in developing countries.¹ The burden of CVD is primarily driven by dyslipidemia, hypertension, obesity, diabetes, physical inactivity, poor diet, and smoking.¹ The CVDs burden is anticipated to burgeon in the coming years.²

Orofacial clefts (OFCs) or cleft lip and palate defects are the commonest congenital malformation of the head & neck and one of the most frequent congenital disabilities globally.^{3,4} The disorder is of enormous medical, surgical, or cosmetic importance in addition to the colossal health care cost. They can occur as syndromic or non-syndromic forms with the latter being the more common.^{3,4}

The estimated prevalence of OFCs in Nigeria is about 0.5:1000 live births.⁵⁻⁷ It occurs in about 1 in 700 live births globally while it accounted for 3,800 deaths globally in 2017 or 3.8 per 100,000 person death from the Global Burden of Disease (GBD) 2017 estimates.^{8,9} Furthermore, the highest prevalence at birth of OFCs is among the native American and Asian (1 in 500 live births), while the lowest prevalence is among the populations of African descent, with approximately 1 in 2,500 live births.¹⁰

The usual male: female ratio was 2:1 in the various OFC variants such as cleft lip and/or cleft lip and palate.⁹ The Nigerian craniofacial anomalies study,

Nigeria CRAN, showed a male: female ratio of 1.19:1 of all OFCs.⁷

Furthermore, cardiovascular anomalies are commonly associated with OFCs and these associated cardiovascular defects may require lifelong follow up after corrective surgery for OFCs.¹¹ Cardiovascular diseases or cardiovascular risk factors and oro-facial defects interplay may be a casual relation or a mere association.

Pre-conceptional, as well as conceptional maternal cardiovascular risk factors (CRFs) may predispose to the development of cleft palate in the offspring. Such increased causality or the CRFs interlink with OFCs may be the strong link to the possibility of reversal of the epidemiological burden for OFCs or just the continuous presence of cases as CVDs/CRFs are on the increase. The key CRFs linked to OFCs includes alcohol use, obesity and smoking with obesity and smoking each having 6% population attributable risk factors.¹¹ Cardiovascular conditions in the form of congenital heart diseases usually present alongside this condition in newborns.

Cleft lip and/or cleft palate may arise in isolation or association with a syndrome and CRFs, and Congenital heart diseases (CHDs) are associated with both syndromic and non-syndromic OFCs although commoner in the former.^{4,12}

Primordial: Predisposing Cardiovascular Risk Factors

The development of OFCs in offspring is associated with the presence of pre-conceptional maternal cardiovascular risk factors particularly obesity, dietary patterns, maternal hypertension, maternal diabetes mellitus and smoking (passive and non-passive) (See Table 1).^{10,11,13}

A systematic review and meta-analysis of a collection of data spanning forty-three years from North America, Europe and Australia revealed a significant association between maternal obesity, as measured by the Body Mass Index (BMI), and having a pregnancy complicated by cleft palate.¹⁴ Maternal obesity was noted to lead to the development of foetal cleft palate (OR, 1.23; 95% CI, 1.03-1.47; P=.02) or cleft lip and

Table 1: Table highlighting studies demonstrating the link of cardiovascular risk factors and OFCs

Study	Authors	Year of publication	Type of study	Country /countries	Sample size	Key cardio-vascular risk factors
Association Between Maternal Diabetes Mellitus and Newborn Oral Cleft	Spilson <i>et al.</i> ¹⁶	2001	Case control	United States of America	6621 (2,207 cases, 4,414 controls)	Maternal pre-gestational diabetes mellitus
Diabetes mellitus and birth defects	Correa <i>et al.</i> ¹⁷	2008	Case-control	United States of America	17,925 (13,030 cases, 4,895 controls)	Maternal pre-gestational diabetes mellitus
Native American Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil	Leite <i>et al.</i> ⁴⁰	2009	Case-control	Brazil	822 (274 cases, 548 controls)	Maternal cigarette smoking, Maternal Alcohol Abuse
Risk factors for oral clefts: a population-based case-control study in Shenyang, China	Wang <i>et al.</i> ⁴¹	2009	Case-control	China	586 cases 1172 control mothers	Maternal diet
Maternal Factors and Disparities Associated with Oral Clefts	Lebby <i>et al.</i> ³⁰	2010	Cohort	United States of America	3,23(Case 1654 Control 1654)	Maternal cigarette smoking, Pregnancy-associated hypertension
Increased risk of orofacial clefts associated with maternal obesity: a case-control study and Monte Carlo-based bias analysis	Stott-Miller <i>et al.</i> ⁴²	2010	Case-control	United States of America	20,223 (2,153 cases, 18,070 controls)	Maternal pre-pregnancy obesity
Maternal malnutrition, environmental exposure during pregnancy and the risk of nonsyndromic orofacial clefts	Jia <i>et al.</i> ⁴³	2011	Case-Control	China	934 (537 cases, 221 controls)	Maternal (passive) smoking
Orofacial Clefts and Risk Factors in Tehran, Iran: A Case-Control Study	Taghavi <i>et al.</i> ⁴⁴	2012	Case-control	Saudi-Arabia	600 (300 cases, 300 controls)	Maternal cigarette passive smoking
Maternal Snuff Use and Smoking and the Risk of Oral Cleft	Gunnerbeck <i>et al.</i> ⁴⁵	2014	Registry survey	Sweden	975,866(1761 cases of oral clefts)	Maternal snuff use, Maternal cigarette smoking
Malformations - A Population-Based Cohort Study						
Association between maternal smoking, gender, and cleft lip and palate	Martelli <i>et al.</i> ⁴⁶	2015	Case-control	Brazil	1519 (843 cases, 676 controls)	Maternal smoking
Maternal Risk Factors Associated with the Development of Cleft Lip and Cleft Palate in Mexico: A Case-Control Study	Angulo-Castro <i>et al.</i> ⁴⁷	2017	Case-control	Mexico	48 (24 cases, 24 controls)	Maternal cigarette smoking, Maternal Alcohol Abuse
Maternal underweight and obesity and risk of orofacial clefts in a large international consortium of population-based studies Hebah	Kutbi <i>et al.</i> ¹³	2017	Population-based	Northern Europe, United States of America	15,535 (4943 cases and 10,592 controls)	Maternal pre-pregnancy obesity

palate (OR, 1.20; 95% CI, 1.03-1.40;P=.02)¹⁴ Other studies also established the predisposition of maternal diabetes mellitus to OFCs. A large study over a ten-year period, among Swedish women, found a similar result even after adjustment for year of birth, parity, maternal age, and maternal smoking.¹⁵ In this case, however, the presence of another major co-existing anomaly alongside cleft palate showed a stronger association with obesity.¹⁵ Although the reason for this association is unknown, it has been attributed to undetected type 2 diabetes.¹⁵ (Table 1).^{16,17}

Maternal western dietary pattern during the preconception period has also been shown to be a risk factor. A case-control study among a female Dutch population showed that diets rich in meat, pizza, potatoes, legumes, French fries, and low in fruits were shown to correlate with cleft palate in the offspring when compared with diets associated with high intake of fish, vegetables, garlic and nuts.¹⁸ This is unconnected with low maternal serum levels of vitamin B12 and folic acid associated such diet.¹⁸

^{12,19,20}, which reduces homocysteine level, although data on the use of folic acid as supplement in prevention of OFC is sparse.¹² However, some studies have revealed no association, while others have been inconclusive.^{12, 21-23}. Further studies are required to associate hyperhomocysteinemia with coexistence of cardiac diseases and OFC.

Pregestational diabetes mellitus is also a well-known risk factor for cleft palate in the offspring.^{24, 25} In a United States Natality database, a population-based case-control study showed that diabetic mothers were almost 1.4 times more likely to develop cleft palate than non-diabetic mothers.^{15,16,26}

Passive and active cigarette smoking in pregnancy has been associated with the development of cleft palate. The records of 3,891,494 live births from the 1996 U.S. Natality database showed this clear predisposition to OFCs using cases-controls design of maternal smoking even after adjustment of confounding

Table 2: OFCs Syndromes and some congenital cardiac anomalies

Syndromes	Aetiology	Associated cardiovascular disorder	Present congenital heart diseases associations
Loeys–Dietz syndrome ^{39, 48}	Genetic- autosomal dominant. Mutation in TGFBR1, TGFBR2, SMAD3, TGFB2, and TGFB3	Aortic aneurysm, Aortic dissection, aortic root dilation, arterial tortuosity, mitral valve prolapse	patent ductus arteriosus and atrial septal defect
Malpuech facial clefting syndrome ⁴⁹	Genetic autosomal recessive COLLEC11 and MASP1 genes mutation		patent ductus arteriosus and atrial & ventricular septal defect
Treacher Collins syndrome or mandibulofacial dysostosis or Franceschetti-Zwahlen-Klein syndrome ^{50, 51}	Genetic- autosomal dominant. TCOF1, POLR1C, or POLR1D mutation		Sinus of Valsalva aneurysm
Oculoauriculovertebral spectrum (Goldenhar syndrome) ⁵²	Autosomal dominant, sporadic		Ventricular septal defect, atrial septal defect, pulmonary stenosis, tetralogy of Fallot atrial/ventricular septal defect
Oculofaciocardiodental syndrome ⁵³	X-linked dominant		
CHARGE syndrome ⁵⁴	Mutation of CHD7 gene		Tetralogy of Fallot, double outlet right ventricle with atrioventricular canal, patent ductus arteriosus, ventricular septal defect and atrial septal defect with or without cleft mitral valve

Hyperhomocysteinemia, which is associated with low levels of folic acid, is a known risk factor for heart disease.¹⁸ Similarly, studies have demonstrated an association between hyperhomocysteinemia and cleft palate¹⁸, while many studies have demonstrated the beneficial effect of maternal folic acid supplementation

variables.²⁷ There was a demonstrable dose-response smoking risk for OFCs in first trimester especially with combined defect of both lips and palate rather than solitary defects.²⁷⁻²⁹ The link with alcohol intake, particularly in the first trimester, may not be unconnected with retinoic acid production.^{28,29} Unlike

the smoking exposure, the association of alcohol intake with OFC is not dose responsive.²⁸

Generally, various cardiovascular risk factors are inter-related. Western dietary patterns could predispose to obesity, and obesity may be an early pointer to diabetes mellitus. Therefore, there may be an underlying, undiagnosed impaired glucose tolerance in these populations that were studied, which most studies did not take into account. While some studies identified the role of maternal alcohol intake during pregnancy on OFCs, many are frosted by small sample sizes. Also implicated are hypertension and the usage of antihypertensive drugs^{10,30}

Finally, cardiovascular diseases appear to be more common in the cleft palate than cleft lip,^{23,27} but more studies are required to confirm these.

Associations of Orofacial Defects and Cardiovascular Diseases

Congenital heart disease is the most frequent associated anomaly in patients with cleft palate as shown in various studies^{3,6,31}, with atrial septal defect^{31,32} often being cited. Others include patent ductus arteriosus,

der Woude syndrome.⁴ Some genetic mutations like that in *TGFBR1* or *TGFBR2* genes have also been reported to cause combined cleft palate and cardiovascular disease (Table 3).³⁶

Orofacial Defects, Paediatric Cardiologist, and the Adult Cardiologist

Even though an affected child may benefit from repair of the defect within a year of birth, such care may not be available in a resource-poor environment like Nigeria especially in situation of non-assess to free treatment intervention such as SMILE programme.^{37,38} Furthermore, it may come with a severe attendant implication which is beyond the primary care specialist that may have initially intervened. Those issues associated with OFCs may not be the initial interest of the parents and caregivers, rather the orofacial defect that pose a severe cosmetic problem. Some of the cardiovascular diseases may linger into adulthood with attendant mortality and morbidity which undermine the quality of life. For example, in Loeyes-Dietz Syndrome, the OFC may be repaired while leaving a risk of widespread and aggressive arterial aneurysms later in childhood or adulthood.³⁹

Table 3: Orofacial clefts and chromosomal anomalies

Chromosomal anomaly	Aetiology	Present congenital heart diseases associations
Velocardiofacial syndrome ⁵⁵ /DiGeorge syndrome ⁵⁶ or Chromosome 22q11.2 deletion syndrome ⁵⁶	Genetic-autosomal dominant. Deletion in Chromosome 22q11	Interrupted aortic arch type B, truncus arteriosus, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, pulmonary atresia with a ventricular septal defect
Edward syndrome ⁵⁷	Sporadic, Trisomy 18	Ventricular septal defect, Patent ductus arteriosus, transposition of great arteries, pulmonary atresia
Patau syndrome ⁵⁸	Sporadic, Trisomy 13	Ventricular septal defect, atrial septal defect, Patent ductus arteriosus

pulmonary stenosis, tetralogy of Fallot and ventricular septal defect.³³ There is a wide variation of the incidence and prevalence of congenital heart disease among neonates with cleft palate.^{7,34} The risk of having a congenital heart disease have been reported to be 23 times that of the general population.³³

Cardiovascular disease and cleft palate can be present in conditions that can affect multiple organ systems, for example, in chromosomal defects like Edward syndrome (Trisomy 18) and Patau syndrome (Trisomy 13) particularly in the non-isolated cleft palate (Table 3).²⁵ They can both be significant components in sequences and syndromes, notably Velocardiofacial syndrome,^{4,35} DiGeorge syndrome,³⁵ and rarely, Van

Therefore, the excellent prognosis is underpinned not only by the initial management but also care and regular follow-up by an experienced interdisciplinary team from infancy until adulthood.

CONCLUSION

Cardiovascular diseases and cleft palate interrelate in various ways; although the mechanisms are unclear, more studies are required to reveal more associations. There is currently enough evidence that maternal cardiovascular risk factors are potent risk factors for foetal OFCs development in addition to the fact that many congenital heart diseases are associated with OFCs.

REFERENCES

1. **Deaton C**, Froelicher ES, Wu LH, *et al*. The global burden of cardiovascular disease. *Eur J Cardiovasc Nurs*. 2011; 10: S5-S13.
2. **Levenson JW**, Skerrett PJ, Gaziano JM. Reducing the Global Burden of Cardiovascular Disease: The Role of Risk Factors. *Prev. Cardiol*. 2002; 5:188-199.
3. **Kim S**, Kim WJ, Oh C, *et al*. Cleft lip and palate incidence among the live births in the Republic of Korea. *J KOREAN MED SCI*. 2002;17:49.
4. **Venkatesh R**. Syndromes and anomalies associated with cleft. *Indian J Plast Surg*. 2009; 42 Suppl:S51-S5.
5. **Adetayo O**, Ford R, Martin M. Africa has unique and urgent barriers to cleft care: lessons from practitioners at the Pan-African Congress on Cleft Lip and Palate. *Pan Afr. Med*. 2012;12.
6. **Ibrahim A**, Mshelbwala P, Obiadazie A, *et al*. A descriptive study of clefts of the primary and secondary palate seen in a tertiary institution in Nigeria. *Niger J Surg Res*. 2015; 15:12.
7. **Butali A**, Adeyemo W, Mossey P, *et al*. Prevalence of orofacial clefts in Nigeria. *The Cleft Palate-CLEFT PALATE-CRAN J*. 2014; 51:320-325.
8. **Roth GA**, Abate D, Abate KH, *et al*. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980 - 2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018; 392:1736-1788.
9. **Hlongwa P**, Levin J, Rispel LC. Epidemiology and clinical profile of individuals with cleft lip and palate utilising specialised academic treatment centres in South Africa. *PLoS One*. 2019; 14:e0215931-e.
10. **Silva HPVd**, Arruda TTS, Souza KSCd, *et al*. Risk factors and comorbidities in Brazilian patients with orofacial clefts. *Brazilian oral research*. 2018; 32.
11. **Simeone RM**, Feldkamp ML, Reefhuis J, *et al*. CDC Grand Rounds: understanding the causes of major birth defects - steps to prevention. *MMWR*. 2015; 64:1104-1107.
12. **Wong WY**, Eskes TK, Kuijpers Jagtman AM, *et al*. Nonsyndromic orofacial clefts: association with maternal hyperhomocysteinemia. *Teratology*. 1999; 60:253-257.
13. **Kutbi H**, Wehby GL, Moreno Uribe LM, *et al*. Maternal underweight and obesity and risk of orofacial clefts in a large international consortium of population-based studies. *Int J Epidemiol*. 2016; 46:190-199.
14. **Stothard KJ**, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. *JAMA*. 2009; 301:636-650.
15. **Cedergren M**, Kallen B. Maternal obesity and the risk for orofacial clefts in the offspring. *CLEFT PALATE-CRAN J* : official publication of the American Cleft Palate-Craniofacial Association. 2005; 42:367-371.
16. **Spilson SV**, Kim HJE, Chung KC. Association between maternal diabetes mellitus and newborn oral cleft. *ANN PLAS SURG*. 2001; 47:477-481.
17. **Correa A**, Gilboa SM, Besser LM, *et al*. Diabetes mellitus and birth defects. *Am J Obstet Gynecol*. 2008; 199:237. e1-e2379.
18. **Vujkovic M**, Ocke MC, van der Spek PJ, *et al*. Maternal Western dietary patterns and the risk of developing a cleft lip with or without a cleft palate. *Obstetrics gynecology*. 2007; 110:378-384.
19. **Wilcox AJ**, Lie RT, Solvoll K, *et al*. Folic acid supplements and risk of facial clefts: national population based case-control study. *BMJ*. 2007; 334:464.
20. **Badovinac RL**, Werler MM, Williams PL, *et al*. Folic acid-containing supplement consumption during pregnancy and risk for oral clefts: A meta-analysis. *Birth Defects Research Part A: Clin Mol Teratol*. 2007; 79:8-15.
21. **Wong WY**, Eskes TK, Kuijpers Jagtman AM, *et al*. Nonsyndromic orofacial clefts: association with maternal hyperhomocysteinemia. *Teratology*. 1999; 60:253-257.
22. **Zhu H**, Curry S, Wen S, *et al*. Are the betaine homocysteine methyltransferase (BHMT and BHMT2) genes risk factors for spina bifida and orofacial clefts? *Am. J. Med. Genet. Part A*. 2005; 135:274-277.
23. **De Regil LM**, Fernández Gaxiola AC, Dowswell T, *et al*. Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochrane Database Syst. Rev*. 2010.
24. **Correa A**, Gilboa S, Besser L, *et al*. Diabetes mellitus and birth defects. *Obstet. Anesth. Dig*. 2009; 29:40-41.
25. **Mastroiacovo P**, Corchia C, Botto LD, *et al*. Epidemiology and genetics of microtia-anotia: a registry based study on over one million births. *Am. J. Med. Genet*. 1995; 32:453-457.
26. **Janssen PA**, Rothman I, Schwartz SM. Congenital malformations in newborns of women with established and gestational diabetes in Washington State, 1984-91. 1996; 10:52-63.
27. **Chung KC**, Kowalski CP, Kim HM, *et al*. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. *Plast Reconstr Surg*. 2000; 105:485-491.
28. **Lieff S**, Olshan AF, Werler M, *et al*. Maternal cigarette smoking during pregnancy and risk of oral clefts in newborns. *Am. J. Epidemiol*. 1999; 150:683-694.

29. **Lorente C**, Cordier S, Goujard J, *et al.* Tobacco and alcohol use during pregnancy and risk of oral clefts. Occupational Exposure and Congenital Malformation Working Group. Am J Public Health. 2000; 90:415-419.
30. **Lebby KD**, Tan F, Brown CP. Maternal factors and disparities associated with oral clefts. Ethn Dis. 2010; 20:S1-149.
31. **Abdollahi Fakhim S**, Shahidi N, *et al.* Prevalence of Associated Anomalies in Cleft Lip and/or Palate Patients. Iran J Otorhinolaryngol. 2016; 28: 135-139.
32. **Akhiwu BI**, Efunkoya AA, Akhiwu HO, *et al.* Congenital Heart Disease in Cleft Lip and Palate Patients: How Common Is the Association? J. Adv. Oral Res. 2017; 8:53-56.
33. **Shafi T**, Khan MR, Atiq M. Congenital heart disease and associated malformations in children with cleft lip and palate in Pakistan. Br. J. Plast. Surg. 2003; 56:106-109.
34. **Otaigbe B**, Akadiri O, Eigbobbo J. Clinical and echocardiographic findings in an African pediatric population of cleft lip/palate patients: A preliminary report. Nig J Cardiol. 2013; 10:6-8.
35. **Setó-Salvia N**, Stanier P. Genetics of cleft lip and/or cleft palate: association with other common anomalies. EUR J HUM GENET. 2014; 57:381-393.
36. **Loeys BL**, Chen J, Neptune ER, *et al.* A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat. Genet. 2005;37:275.
37. **Hubli EH**, Noordhoff MS. Smile Train: Changing the World One Smile at a Time. ANN PLAS SURG. 2013;71:4-5.
38. **Bello SA**, Balogun SA, Oketade I, *et al.* Cleft & facial deformity foundation (CFDF) outreach model: 6 year experience of an indigenous Nigerian mission in the surgical correction of facial clefts. Pan Afr. Med. 2018; 29:1-13.
39. **MacCarrick G**, Black Iii JH, Bowdin S, *et al.* Loeys–Dietz syndrome: a primer for diagnosis and management. Genet Med. 2014;16:576.
40. **Leite ICG**, Koifman S. Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro. Braz. oral res. 2009; 23:31-37.
41. **Wang W**, Guan P, Xu W, *et al.* Risk factors for oral clefts: a population-based case-control study in Shenyang, China. Paediatr. Perinat. Epidemiol. 2009; 23:310-320.
42. **Stott-Miller M**, Heike CL, Kratz M, *et al.* Increased risk of orofacial clefts associated with maternal obesity: case–control study and Monte Carlo-based bias analysis. Paediatr. Perinat. Epidemiol. 2010; 24:502-512.
43. **Jia ZL**, Shi B, Chen CH, *et al.* Maternal malnutrition, environmental exposure during pregnancy and the risk of non-syndromic orofacial clefts. Oral Dis. 2011; 17:584-589.
44. **Taghavi N**, Mollaian M, Alizadeh P, *et al.* Orofacial clefts and risk factors in tehran, Iran: a case control study. Iran Red Crescent Med J. 2012;14:25-30.
45. **Gunnerbeck A**, Edstedt Bonamy AK, Wikström AK, *et al.* Maternal Snuff Use and Smoking and the Risk of Oral Cleft Malformations – A Population-Based Cohort Study. PLoS One. 2014; 9:e84715.
46. **Martelli DRB**, Coletta RD, Oliveira EA, *et al.* Association between maternal smoking, gender, and cleft lip and palate. Braz J Otorhinolaryngol. 2015; 81:514-519.
47. **Angulo-Castro E**, Acosta-Alfaro LF, Guadron-Llanos AM, *et al.* Maternal Risk Factors Associated with the Development of Cleft Lips and Cleft Palate in Mexico: A Case-Control Study. Iran J Otorhinolaryngol. 2017; 29:189-195.
48. **Van Laer L**, Dietz H, Loeys B. Loeys-Dietz Syndrome. In: Halper J, editor. Progress in Heritable Soft Connective Tissue Diseases. Dordrecht: Springer Netherlands; 2014. 95-105.
49. **Kerstjens Frederikse WS**, Brunner, HG, Van Dael CML & Van Essen AJ. (2005). Malpuech syndrome: Three patients and a review. Am. J. Med. Genet. Part A, 134(4), 450-453.
50. **Trainor PA**, Dixon J, Dixon MJ. Treacher Collins syndrome: etiology, pathogenesis and prevention. EUR J HUM GENET. 2009;17:275-283.
51. **Posnick JC**, Ruiz RL. Treacher Collins Syndrome: Current Evaluation, Treatment, and Future Directions. CLEFT PALATE-CRAN J. 2000; 37:1-22.
52. **Pinheiro ALB**, Araújo LC, Oliveira SB, Sampaio MCC, *et al.* Goldenhar's syndrome: case report. Braz. Dent. J. 2003; 14:67-70.
53. **Surapornsawasd T**, Ogawa T, Tsuji M, *et al.* Oculofaciocardiodental syndrome: novel BCOR mutations and expression in dental cells. J. Hum. Genet. 2014; 59:314-320. Ann. Ib. Postgrad. Med. Vol. 18 2020 Cleft Supplement S34
54. **Blake KD**, Prasad C. CHARGE syndrome. Orphanet J. Rare Dis. 2006; 1:34.

55. **Scambler PJ**, Kelly D, Lindsay E, *et al.* Velo-cardio-facial syndrome associated with chromosome 22 deletions encompassing the DiGeorge locus. *The Lancet*. 1992; 339:1138-1139.
56. **McDonald-McGinn DM**, Sullivan KE. Chromosome 22q11.2 Deletion Syndrome (DiGeorge Syndrome/Velocardiofacial Syndrome). *Medicine*. 2011; 90:1-18.
57. **Pont SJ**, Robbins JM, Bird TM, *et al.* Congenital malformations among liveborn infants with trisomies 18 and 13. *Am J Med Genet Part A*. 2006; 140A:1749-1756.
58. **Petry P**, Polli JB, Mattos VF, *et al.* Clinical features and prognosis of a sample of patients with trisomy 13 (Patau syndrome) from Brazil. *Am J Med Genet Part A*. 2013; 161:1278-1283