

Incidence of Cleft Lip and Palate in Al-Ramadi City (Descriptive Epidemiological Study)

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ABSTRACT

Background Birth defects are one of the causes of pediatric disability and mortality in all around the world. Data on birth defects from population-based studies originating from developing countries are lacking. Cleft lip (CL), cleft lip and palate (CLP), and isolated cleft palate (CP), collectively termed oral clefts, occur in all races, both sexes, and all socioeconomic groups and vary internationally ⁽¹⁾. The main aim of this research is to establish the frequency of cleft lip and/or palate in the population of the Al-Ramadi City, and to characterize the demographic features of affected individuals and find possible risk factors.

Materials and methods We conducted a survey of the Educational Maternal and Pediatric Hospital in Al-Ramadi city. The sample population comprised all 5100 babies born at Al-Ramadi City during the 5 months period 1 January 2013 to 31 May 2013. Statistical tests used Pearson's chi-square test, Student's t-test and Spearman's correlation coefficient test according to the type of parameter tested.

Results: During the study period 15 babies were born with oro-facial cleft. The overall incidence of cleft lip and palate was 2.94 per 1000. Cleft palate was significantly more frequent in male than female babies ($P = 0.81$).

Conclusions: A high incidence of facial clefts in this city was seen. This change may be attributed to the wars that occur in Iraq in the last years so increased pollutions and decreased prenatal care in the Iraqi population as part of social and health-related behavior changes.

Keywords: Cleft lip, cleft palate, congenital anomalies, epidemiology, Iraq health. (J Bagh Coll Dentistry 2016; 28(2):139-144).

INTRODUCTION

Definition and Terminology

Larry ⁽²⁾ defined a cleft as a congenital abnormal space or gap in the upper lip, alveolus or palate. Cleft also can be defined as a crack, split, or an opening made by a cleavage or something cut into two. It defines cleft palate as a congenital malformation in the roof of the mouth because the two sides of the palate did not join before birth ⁽³⁾.

Cleft lip is a disorder originated as a failure of fusion of the frontal process with the maxillary process, at about the 7th weeks of development, while cleft palate is due to failure of fusion of secondary palate that mean non union of palatal process of both left & right side of maxillary process ⁽⁴⁾. Danila et al. ⁽⁵⁾ states that "CLP is a complex multi-factorial disorder, is one of the most common congenital malformations with a prevalence of 0.16 to 2.35 per 1000 births in Caucasian population".

Embryology

Human face develops as early as the 14th day of intrauterine life. It formed from processes surrounding the primitive mouth which are frontal process forming the forehead and the nose, the mandibular process forms the lower lip, lower jaw and lower cheek.

The maxillary processes form the upper lip, jaw and cheek. From the maxillary process two palatal shelves formed posterior to the incisive foramina. These shelves first oriented vertically then become horizontally to join in the midline forming the secondary palate.

The primary palate (anterior to the incisive foramina) formed from the nasal prominence (which is formed from the maxillary process), also the nasal prominence form the philtrum of the upper lip and the middle part of the nose. All these events occur between the 4th and 8th week of intrauterine life. Any interruption of any of these events may cause clefts ⁽¹¹⁻¹⁴⁾.

Incidence

Incidence denotes the number of cases entering a population, i.e. new cases in some time period ⁽⁶⁾. CLP considered approximately the fourth most common craniofacial birth defect ⁽⁷⁾. According to Peggy et al. ⁽⁸⁾, CLP affect 1:600 births in USA. While Cawson ⁽⁹⁾ found the incidence of CL in USA is 1: 1000. The incidence of CLP is: in Denmark 1:500, USA 1:1200, France 1:800 and in Iraq 1:1000 ⁽⁴⁾. According to LOH ⁽¹⁰⁾, the prevalence of syndromic or non-syndromic CLP is 1.30 in Chinese. Many studies were conducted to show the influence of the genetic factors i.e. familial background, as well as different environmental factors (e.g. nutrition, drugs, psychological conditions of the mother, types of cleft, parental age and seasonal effect) on the incidence of cleft lip and/or palate.

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Table 1: Incidence of oro-facial clefts according to some studies

Authors /year	place	rates
Ching and Chung,1974	Hawaii	2.45
Tregbulem, 1982	Nigeria	0.369
Morrison,1985	South Africa	0.33
Natsume et al,1987	Japan	2.06
Ernest,1988	Hungary	1.55
Kumar et al , 1991	Saudi Arabia	0.3
Stoll et al, 1992	China	1.11
Molina et al, 1993	Mexico	1.32
Amidei et al, 1994	Colorado city-USA	0.81
Rosche et al, 1998	Magdeurg-Germany	1.85
Yi-NN et al, 1999	Singapore	2.07
Hewson and McNamara, 2000	Ireland	1.14
Rajabian and Sherkat,2000	Iran	1.03
AL-Sadoon et al,2002	Iraq-Basra	0.79
Salvi et al,2003	Switzerland	1.5
AL-Omari and AL-Omari,2004	Jordan	1.39
Suleiman et al,2005	Sudan	0.9
Rajabian and Aghaei,2005	Iran	0.8
Eldad et al,2012	Israel	1.067
Present study ,2013	Iraq	2.94

Etiology

Genetic Factors

There is a family history in 40% of cleft lip and palate and 20% of cleft palate cases, so there is a genetic predisposition that may possibly be triggered by environmental factors⁽⁹⁾. Twins and infants whose parents were first cousins had a stronger risk of CLO than CLP⁽¹⁵⁾. The genetic factors include two categories: first is the Single Mutant Gene: 80% of those syndromes are the result of a single mutant gene, others said it is about 60%^(16,17). Single mutant gene might be autosomal dominant, autosomal recessive and X-linked⁽¹⁸⁾. Second is the Chromosomal Aberrations: The best example of the syndromes that are associated with these chromosomal aberrations are rare syndromes includes E-trisomy, D-trisomy and the XXXXY syndromes in which cleft palate and/or cleft lip are present in high frequency⁽¹⁹⁾.

Environmental Factors

Mean the exogenous factors from the surrounding environment that can cause a defect or disease. Embryonic development is an interaction of genetic and environmental factors⁽²⁰⁾. Environmental factors may include: Drugs⁽²¹⁾, Nutritional deficiency⁽²²⁾. Pathologic Status of The Mother if she had Diabetes, Hyper- and Hypotension, infection with rubella (German Measles)^(20,23), increased mother's weight⁽²⁴⁾, exposure to radiation⁽²⁵⁾. Psychological and emotional stress⁽²⁶⁾, cigarette smoking and

alcohol drinking⁽²³⁾, occupation of the parents⁽²⁷⁾ which give a clue about the parents' education and socioeconomic status.

Problems Associated with Cleft Lip and Palate Feeding Problem

Most babies with a cleft palate cannot generate enough sucking pressure for breast-feeding. To take advantage of the health benefits of breast milk, many mothers elect to feed their baby breast milk in a bottle with a cleft palate nipple⁽²⁸⁾. Presence of cleft lip and palate can compromise maternal nursing which will compromise baby oral health and the surgical/rehabilitation process. Nearly 98.25% of mothers used bottle feeding with milk and other sucrose liquids at one to ten times frequency⁽²⁹⁾.

Baby body weight

Feeding difficulties resulting from the labio-palatine malformation itself or from the inability to take nutrients during the first months of life, as well as infectious processes in the upper airways or middle ear, are factors causing growth deficiency in children with these malformations⁽³⁰⁾.

Psychological and Social Problems

Children with orofacial clefts are probably at risk to develop problems in their social-emotional functioning as a result of their condition, they do not experience major psychosocial problems, but some specific problems may arise such as dissatisfaction with facial appearance, depression, and anxiety⁽³¹⁾.

Audiological Aspect

In CP baby, eustachian tube will be closed ,so when this function is disrupted the middle ear will be a closed space so serous fluids will accumulate and result in otitis media (or called sapparative otitis media),which resulted in chronic otitis media and this is a threat to the hearing⁽³²⁾.

Speech Problems

Many speech problems are associated with CLP .retardation of consonant sounds is common, so much language activity is omitted. Hypernasality is usual in those patients and remain even after surgical palate repair .in soft palate clefts the velopharyngeal mechanism can not function because of the discontinuity of the musculatures attachment thus can not elevate to make contact with the pharyngeal wall, so escape of air to nasal cavity is called hypernasality which is difficult to understand⁽²⁾.

Dental Problems

Complete bilateral cleft lip and palate (BCLP), the prevalence of missing tooth reaches 100%⁽³³⁾. Observes extremely high incidence of enamel hypoplasia in the incisors of both dentitions in patients with clefts⁽³⁴⁾. Dahllof et al⁽³⁵⁾ have found a high incidence of enamel hypermineralisation in cleft lip and palate patients.

Ranta⁽³⁶⁾ said that there may be a delay in the dental development on the cleft side leading to delayed eruption times. The lateral incisor on the affected side may be located in either portion of the alveolar bone adjacent to the cleft. The tooth or teeth will often be displaced palatally and rotated⁽³⁷⁾. As a child with a cleft grows, sometimes the upper jaw does not grow as much as the lower jaw. If this occurs, the resulting differences in the upper and lower dental arches can present problems in appearance, speech, or chewing⁽³⁸⁾.

Respiratory Problem

Various respiratory problems have been reported to be associated with cleft palate patients, due to the fact that cleft palate patients suffer from feeding difficulties accompanied with regurgitation of milk and saliva into the nasopharynx leading to repeated chest infection⁽³⁹⁾.

Associated Anomalies

O'zcelik et al.⁽⁴⁰⁾ reported that T-Wood syndrome as one of the congenital anomalies that is associated with CLP. NDCS⁽³²⁾ reported that CLP is known to occur in more than 400 syndromes; e.g.: Peirr Robin syndrome, 22q11.2 Deletion syndrome, Van Der Woude syndrome, Stickler syndrome, Charge syndrome, Godenhar syndrome, Downs' syndrome, Treacher Cholin syndrome, spina bifida, limb defects and congenital heart diseases. in Down's syndrome cleft lip or palate is present in approximately 1:200, and in the same trisomy 13 (Patau's syndrome) cleft lip or palate is present in up to 70% of cases; this syndrome is the most commonly seen in children with CLP, it affect one child in 8000-30000 births.

MATERIALS AND METHODES

5100 newly born babies were viewed in the Educational Maternal and Pediatric Hospital in Al-Ramadi city for oro-facial clefts for five months between the period (January 2013 to May 2013).all babies were from Al-Ramadi city and are Iraqi in origin.

All clefted viewed babies were included including dead and a life babies. Examination tools are used in addition to a camera to take photos for the babies. The examination was done with the aid of a pediatric surgeon. This examination include extra-oral examination for head, hands, feet and intraoral examination for tongue, lips, palate, cheek and any neonatal teeth.

All information recorded in a specific case sheet designed for this study. Classification of clefts depends on Millard classification 1976. Statistical analysis was performed with Microsoft Office Excel 2007R and SPSS version 14 software. Statistical tests used Pearson's chi-square test, Student's t-test and Spearman's correlation coefficient test according to the type of parameter tested.

RESULTS

1. Clefts seems to affect males more than females with a ratio M:F =1.5:1, and the first order affected more (40%) most of the affected babies were of average weight (46.67%).
2. Congenital anomalies was present in (66.67%) of cleft patients.
3. Highest percentage of patients with cleft were born to the younger parents (30 years and below), and (86.66%) of mothers' were house wives. Consanguinity between the parents was (46.67%).
4. Mothers did not reported smoking or alcohol drinking.
5. The prevalence of normal delivery was (73.34%). previous abortion present in (46.67%), history of threatened abortion was present in (13.34%) of the clefted children s' mothers.
6. (33.34%) of cleft mothers had pregnancy disease.
7. (46.67%) of the affected children mothers had poor food intake during their pregnancy.

DISCUSSION

Incidence of cleft lip and/or palate

According to the results in this study the incidence of cleft lip and /or palate in Al-Ramadi City is nearly (2.9 per 1000) which is nearly close to Indians is about 3.6 per 1000⁽⁴¹⁾; in Japan which is 2.06 per 1000⁽⁵²⁾; in Stockholm-Sweden with a prevalence nearly 2.0⁽⁴³⁾; in Lods-Poland with a prevalence of 2.0⁽⁴⁴⁾; in Singapore with a prevalence of 2.07 per thousand⁽⁴⁵⁾.

However, a great variation was found among the other studies: in Nigeria 0.369⁽⁴⁶⁾; Australia 1.21⁽⁶⁾; Japan 1.46⁽⁴²⁾; Saudi Arabia 0.3⁽⁴⁷⁾; Germany 1.85⁽⁴⁸⁾; in Iran 1.03⁽⁴⁹⁾.

Cleft lip

This study found that cleft lip was found in (13.34%) of the cleft samples. it forms the least common type of clefts. this finding came to be nearly close to Ja'afar⁽⁵⁰⁾ (11.5%). There are some variations that still exist when compared with other studies like: Addekeye and Lavery⁽⁵¹⁾ (59.4%); Natsume and Kawai⁽⁵²⁾ (41.3%). These differences might be due to different ethnic group, sample size, and sample selection.

Cleft palate

CP group formed the majority of the sample among other groups (60%), which was nearly close to Al-Zubaidee et al (53) (50%). Great variation was found among other studies: Al-Janabi⁽⁵⁴⁾ (34.1%) and Ja'afar⁽⁵⁰⁾ (23.5%).

Cleft Lip and Palate

Cleft lip and palate was (26.66%) this percentage considered low because of the cleft sample size. other studies reported higher percentage of CLP like Siegel⁽⁵⁵⁾ (62.5%) and Padilla and Gonzalez⁽⁵⁶⁾ (49.4%). These differences might be due to different ethnic group, sample size, and sample selection.

Associated Congenital Anomalies

This study found that 66.67% of cleft patients had associated congenital anomalies, which was nearly close to that reported by Robert et al.⁽⁵⁷⁾ (63.4%) and Siegel⁽⁵⁵⁾ (77.5%), and much higher than Conway and Wagner⁽⁵⁸⁾ (17.5%) and Al-Janabi⁽⁵⁴⁾ (17.7%), this might be due to the sample selection which was carried out.

Gender

This study found that males were affected with CLP more than females in a ratio of M:F=1.15:1.

Baby body weight

Baby body weight were divided into three groups under weight (<2500g), average weight (2500g-3750g) and over weight (>3750g)⁽⁶⁰⁾. The highest percentage of cleft babies was average weight (46.67%). The impairment in weight and length was more apparent in cleft lip and palate and isolated cleft palate children and may be attributed to feeding difficulties compared to the isolated cleft lip group so growth impairment was reported by weight and length deficiency of the cleft baby⁽⁶¹⁾.

Mother's Age

In this study the younger mothers (up to 30 years) were the predominant age group in cleft samples (80%).

Slavkin⁽⁶²⁾ reported that the mothers at both ends of the age spectrum were associated with high range of cleft babies.

Mother's Occupation

This study found that the majority of the mothers were housewives (86.66% for cleft samples). This may give us a clue about the educational level which has a great influence on the proper maternal health care which has to be achieved, especially those concerned with careful administration of drugs, proper nutrition and accurate behavior.

Type of Delivery

The prevalence of normal deliveries was (73.34%) for cleft samples. For caesarean delivery there was (26.67%). Delivery by operation may give us a clue that the mother had difficulty during pregnancy that may affect the child and may lead to a malformation.

Previous Abortion

Of the cleft patients (46.67%) had previous abortion. Previous history of abortion may give a clue that the mother is susceptible to abortion during pregnancy and the pregnancy is difficult and the mother take drugs like abortion preventatives which might lead to malformations.

Relativity

46.67% of cleft samples parents were relatives. Ingalls et al.⁽⁶³⁾ stated that "cleft lip and cleft palate occurred with a higher frequency among relatives of patients than expected in the general population".

Environment during Pregnancy

Smoking

This study showed no significant association between maternal smoking and clefts since all the mothers were non-smokers. WHO⁽⁶⁴⁾ reported that maternal cigarette smoking during pregnancy has been associated with a moderate increase in the risk of orofacial clefts.

Alcohol Drinking

In this study, none of the mothers were alcohol drinkers. Romitti et al.⁽⁶⁵⁾ found maternal cigarette smoking and alcohol consumption are considered as risk factors for cleft lip and/or palate.

Threaten Abortion

Of the cleft group mothers, (13.34%) gave a history of threatened abortion during the first trimester of pregnancy; bleeding and exhaustion were the main causes. Saxen⁽⁶⁶⁾ mentioned that threaten abortion could be one of the factors that cause cleft lip and/or palate.

Diseases during Pregnancy

Of the cleft mothers (33.34%) had one or more diseases during pregnancy. This may include urinary tract infections, hypertension, diabetes, asthma, epilepsy, typhoid fevere, pregnancy sickness (hypotension, hypoglycemia, morning nausea, stomach acidity, anaemia ...etc). A disease or infection can cause a congenital malformation either by disturbing the normal metabolic processes of the mother or by the effect of drugs administrated to control the pathologic condition⁽²⁰⁾.

Drug Intake

According to this study, the pregnant women took more than one type of drugs during pregnancy like multivitamins, antibiotics, antiepileptic drugs, insulin, sedatives ...etc. All cleft mothers took drugs during the 1st trimester of pregnancy. Multivitamins was the most taken drugs by the pregnant women .Nelson and Forfar⁽⁶⁷⁾ reported that the embryonic development could be affected by various types of drugs e.g. aspirin, antacids, antibiotics.

Nutritional Status

Poor food intake during the pregnancy was reported in (46.67%) of the cleft group mothers. the nutritional deficiency of the mother can increase or decrease the teratogenic effect of exogenous agents and the caloric deficiencies can produce clefts as well as improper intake of certain essential ingredients in food can have an independent potential in disturbing the normal development of the embryo⁽²⁰⁾.

REFERENCES

- Aljohar A, Ravichandran K, Subhani S. Pattern of cleft lip and palate in hospital-based population in Saudi Arabia: Retrospective study. *Cleft Palate–Craniofac J* 2008; 45(6): 592-6.
- Peterson L. Textbook of contemporary oral and maxillofacial surgery .4th ed .Mosby Co.; 2003.
- Illustrated Oxford Dictionary. 4th ed. Oxford Co.; 2003.
- Al-Mulla A. Orthodontics....the challenge. Iraq, 2009.
- Daniela FB, Sunaga DY, Kobayashi GS, Aguena M, Masotti C. Human stem cell cultures from cleft lip and palate patients. 2010; 7: 446-57.
- Ernest BH. Incidence and prevalence as measure of the frequency of congenital malformation and genetic outcomes. Application to oral clefts. *Cleft Palate J* 1988; 2(25): 97-102.
- Graber TM, Robert LV. Orthodontics current principles and technique. 3rd ed. St. Louis: Mosby Co.; 2000.
- Peggy C, David L, Marilyn C, Richard J. text book of cleft palate foundation. 2nd ed. USA: Chapelhill; 2000.
- Cawson O. Essentials of oral pathology and oral medicine. 7th ed. Churchill Livingstone; 2006.
- Loh J, Ascoli N. Cross cultural attitudes and perceptions towards cleft lip and palate deformities. *World Cultural Psychiatry Res J* 2011; 127-34.
- Scott JH, Symons NBB. Introduction to dental anatomy. 9th ed. London: Edinburgh & London E. & S. Livingstone Ltd.; 1982.
- Sperber GH. Crainofacial embryology. 4th ed. Bristol: John Wright; 1984.
- Avery JK. Essentials of oral histology and embryology clinical approach. 1st ed. St. Louis: Mosby; 1992.
- Proffit WR, Fields HW, Sarver DM. Contemporary Orthodontics. 4th ed. St. Louis: Mosby Co.; 2007.
- Emily W, Allen J, Lie RT, Abyholm F. Cleft lip and palate versus cleft lip only: are they distinct defects. *Am J Epidemiol* 2013; 162: 448-53.
- Fraser FC. The genetics of cleft lip and cleft palate. *Am J Human Genetic* 1976; 22: 336-52.
- Habib Z. Genetic counselling and genetics of cleft lip and cleft palate. *Obst Gyeco Survey J* 1978; 33(7): 441-7
- Turvey TA, Vig KWL, Fonseca RJ. Facial clefts and Craniosynostosis, principles and management, Philadelphia: W. B. Saunders Co.; 1996.
- Poole E. Genetic of cleft lip cleft palate. *J Dental Clin North Am* 1975; 19(1): 171-80.
- Nanda R. Teratogenic effects of environmental agents on embryonic development. *Dent Clin North Am* 1975; 19(1): 95-101.
- Rivo E. The clinical use of abortion preventatives. *Pacific Med Surg* 2013; 73: 413.
- Martin J. British National Formulary. Royal Pharmaceutical Society of Great Britian. 1st ed. 2010.
- WHO. Global strategies to reduce the health-care burden of craniofacial anomalies. Report of WHO meetings on International Collaborative Research on Craniofacial Anomalies, Geneva, Switzerland, 5-8 November 2000. pp. 55-9.
- Marie C, Bengt K. Maternal obesity and the risk for orofacial clefts in the offspring. *Cleft palate-craniofac J* 2005; 42: 367-71.
- Maneksha M. Etiology in color atlas of cleft lip surgery. Wolfe Year Book, 1986.
- Abdul-Rahim KK. Cleft lip and cleft palate genetic aspect. *Iraqi Dental J* 1987; 206-19.
- Schnitzer PG, Olshan AF, Savitz DA, Erickson JD. Validity of mother's report of father's occupation in a study of paternal occupation and congenital malformations. *Am J Epidemiol* 1995; 141: 872-7.
- Richard JR. Guide to understanding cleft lip and palate. *Children Craniofacial Assoc J* 2009; 1-5.
- Cinthia M. Birth defects. Cleft lip and palate foundation of smiles 2012: 1-3.
- Luiz C, Montagnoli A, Barbieri H, Lazarini M, Luiz DS .Growth impairment of children with different types of lip and palate clefts in the first 2 years of life. *Jornal de Pediatria* 2005; 81(6): 461-5.
- Anne M, Pieter J, Gunvor S, Ewald M, William C. Reference photographs for nasolabial appearance

- rating in a unilateral CLP. *Craniofacial Surgery J* 2009; 20(Supp. 2): 1683-6.
32. National deaf children's society. Cleft palate and deafness. Cleft lip and palate association website. 2012; 1-20.
 33. Theodosia N. Tooth agenesis patterns in bilateral cleft lip and palate. *Eur J Oral Sci* 2010; 118: 47-52
 34. Dixon DA. Defects of structures and formation of teeth in persons with cleft palate and the effect of reparative surgery on the dental tissues. *Oral Surg* 1968; 25: 435-46.
 35. Dahlllof G, Joandi RU, Idebrg M, Modeer J. Caries, gingivitis and dental abnormalities in preschool children with cleft lip and/or palate. *Cleft Palate J* 1989; 26(3): 146-57.
 36. Ranta R. A review of tooth formation in children with cleft lip/palate. *Am J Orthod Dentofac Orthop* 1986; 90: 11-18.
 37. Jones ML, Oliver RG. *W & H Orthodontic Notes*. 6th ed. Oxford: Wright; 2000.
 38. Thomas A. Orofacial clefts in Czechoslovakia. Incidence, genetics and prevention of cleft lip and palate over a 19-year period. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery* 2012; 21(1): 19-25.
 39. Houston WJB, Stephens CD, Tulley WJ. *A textbook of orthodontics*. 2nd ed. Bristol: Wright; 1992.
 40. zselik Pamplona M, Ysunza A, Guerrero M, Mayer I, Garcia-Velasco M. Surgical correction of velopharyngeal insufficiency with and without compensatory articulation. *International J Pediatric Otorhinolaryngol* 2008; 34: 53-59.
 41. Gorlin RJ, Cervenká J, Pruzansky S. Facial clefting and its syndroms. *Plast Reconstr Surg* 1971; 8: 88-103.
 42. Natsume N, Suzuki T, Kawai T. The prevalence of cleft lip and palate in the Japanese, their birth prevalence in 40304 infants born during 1982. *Oral Surg Oral Med Oral Path* 1987; 63(4): 421-3.
 43. Hagberg C, Larson O, Milard J. Incidence of cleft lip and palate and risks of additional malformations. *Cleft Palate Craniofac J* 1998; 35(1): 46-50.
 44. Antoszewski, Kruk. Longitudinal study of the dental arch diamentions in hard and soft palate clefts. *J Pedod* 1997; 12: 35-47.
 45. Yi-NN. Review of the role of potential teratogens in the origin of human nonsyndromic orofacial clefts. *Teratol* 1999; 53: 309-317.
 46. Tregbulem K. growth characteristics of the premaxilla and orthodontic treatment principles in bilateral cleft lip and palate. *Cleft Palate J* 1982; 20: 289-302 .
 47. Kumar P, Hussanian J, Cardoso E, Hawary MD, Hassanian J. . Facial Clefts in Saudi Arabia. *Plast Reconstr Surg* 1991; 28(4): 373-377.
 48. Roshe SD. The case for early bone grafting in cleft lip and palate. *Plast Reconstr Surg J* 1998; 87: 644-54.
 49. Rajabian MH, Sherkat M. An epidemiologic study of oral clefts in Iran analysis of 1669 cases. *Cleft Palate Craniofac J* 2000; 37(2):191-6.
 50. Ja'afar ZJ. Mouth health and treatment requirements for cleft lip and/or palate children in age group 3-12 years in Iraq. A master thesis, Department of Pedodontics and Preventive Dentistry, College of Dentistry, University of Baghdad, 2006.
 51. Addekey EO, Lavery KM. Cleft lip and palate in Nigeria children and adults. *Brit J Oral Maxillofac Surg* 1985; 3: 398-403.
 52. Natsume N, Kawai T. Incidence of cleft lip and cleft palate in 39690 Japanese born during 1983. *Int oral Maxillofac Surg* 1986; 15(5): 565-8.
 53. Al-Zubaidee AF, Hammash MH, Abdul Wahab S. Cleft lip and palate in primary school's student of Saddam City-Baghdad. *J Fac Med Baghdad* 1998; 40(30): 46-52.
 54. Al-Janabi MF. Clinical study on cleft lip and/or palate patients (A descriptive epidemiological comparative and cross sectional study). A master thesis, Department of orthodontics, College of Dentistry, University of Baghdad, 2001.
 55. Siegel B. A racial comparison of cleft patients in a clinic population, associated anomalies and occurrence rates. *Cleft Palate J* 1979; 16:193-7.
 56. Padilla GU, Gonzalez VM. Cleft lip and palate in Puertrorico: A thirty-three year study. *Cleft Palate J* 1986; 23: 48-57.
 57. Robent JS, Viki L, Siegel S. Anomalies associated with cleft lip and cleft palate or both. *Am J Med Gene* 1985; 20: 585-95.
 58. Conway H, Wagner KS. Incidence of cleft in New York city. *Cleft Palate J* 1966; 3: 284-90.
 59. Abdul-Khaliq AR. Clinicogenetic study for cleft lip and/or palate patients (epidemiological study). A master thesis, Department of orthodontics, College of Dentistry, University of Baghdad, 2003.
 60. Zarate YA, Martin LJ, Hopkin RJ, Bender PL, Zhang X, Saal HM. Evaluation of Growth in Patients With Isolated Cleft Lip and/or Cleft Palate official J American academy of pediatrics. 2010; 8:125-543.
 61. Luiz C, Montagnoli A, Barbieri H, Lazarini M, Luiz DS. Growth impairment of children with different types of lip and palate clefts in the first 2 years of life. *Jornal de Pediatria* 2005; 81(6): 461-5.
 62. Slavkin HC. Incidence of cleft lips, palates rising. *J Am Dent Assoc* 1992; 123(11): 61-5.
 63. Ingalls TH, Taube IE, Klingberg MA. Cleft lip and cleft palate. Epidemiologic considerations. *Plast Reconstr Surg* 1964; 34: 1-10.
 64. Romitti PA, Lidral AC, Munger RG, Hirsch S, Burns L, Murry JC. Candidate gene for non-syndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype environment interaction from application based case control study of orofacial clefts. *Teratol* 1999; 59(1): 59-70.
 65. Saxen I. Epidemiology of cleft lip and cleft palate; an attempt. To rule out chance correlations. *Br J Prev Soc Med* 1975; 29(2): 103-10.
 66. Nelson MM, Forfar JO. Associations between drugs administered during pregnancy and congenital abnormalities of the fetus. *Br Med J* 1971; 1: 523-7.