

## Study of risk factors related to the orofacial clefts in Eastern Azerbaijan, Iran: Population-based from 2000 to 2015

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### ABSTRACT

**Background and aims:** Nowadays, Orofacial clefts are known as the most common orofacial birth defects. Several factors are responsible for problem, such as environmental factors, genetic background, nutritional deficiencies such as Vitamins, zinc, iron, maternal diseases, exposure to teratogenic agents, smoking, drugs, organic solvents. The aim of this study was to evaluate the of risk factors frequency of orofacial clefts in our region.

**Methods:** This is an epidemiological study with retrospective database including parent's age, family history, medical and drug history in pregnancy, toxin exposure, urbanistic habituation and parent's job.

**Results:** A total of 670 patients with orofacial cleft were studied. Parents were in 15-35 years old range. The frequency of cleft history in parents was 12.7%. Passive smoking (7%) and depression were the most common predisposing factor and most common maternal disease, respectively. Amoxicillin was the most common drug used in pregnancy period. Most of patients (92.5%) did not live in high risk areas. The most common job in fathers was agricultural.

**Conclusion:** Orofacial clefts are the multifactorial disease. Due to its prevention, there is a need to focus on the local risk factors to be able to reach further information to reduce its occurrence rate and also to find a better way to reduce the related costs on both patients and healthcare system.

**Keywords:** Birth defects, Orofacial clefts, Risk factor, children, epidemiological study.

Original article

### INTRODUCTION

Non-syndromic orofacial clefts are the most common orofacial birth defects worldwide, and occurs in 1 per 500 to 2,500 births. Their incidence rate varies markedly in terms of geographical location, being more common among Asians than in Caucasians and least common among Afro-Caribbean

populations.<sup>1</sup> Reports in Asian populations put overall rates around 1.76 to 1.81, reflecting the higher prevalence in this region.<sup>2,3</sup>

In the United States, approximately 7500 infants are born with cleft malformation each year.<sup>4</sup> A report characterized the prevalence of CL/P and CP at 2.3 per 1,000 newborns in

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Taiwan in 2000.<sup>5</sup> Defects arising from neural tube and the neural crest are the most devastating in terms of mortality and morbidity, stillbirths, and spontaneous abortions.<sup>6</sup> Several interactions between genes and environmental factors are responsible for orofacial clefts.<sup>7-10</sup>

Some materials such as Vitamins (especially folic acid with or without vitamins) vitamin B1 and B6, myo-inositol, zinc, iron and riboflavin are protective factors in orofacial clefts.<sup>11-13</sup> However, some conditions such as maternal diseases (chronic or infectious, during or before pregnancy), diabetes<sup>8</sup>, obesity<sup>14</sup> exposure to teratogenic agents<sup>15</sup>, smoking<sup>16</sup>, using drug during pregnancy (amoxicillin, phenytoin, oxprenolol, thiethylperazine, oxytetracycline, and carbamazepine)<sup>17</sup>, and exposure to organic solvents.<sup>18</sup> Children with lip/palate cleft need multidisciplinary birth-care until adulthood; they have higher morbidity and mortality throughout life.<sup>19,20</sup> Individuals born with lip and/or palate cleft, have a shorter lifespan, with increased risk for all major causes of death, when compared with individuals born without clefts.<sup>20,21</sup>

Recognition of frequent factors in association with orofacial clefts in each region will help to control of them and decrease its prevalence. In the present study, we decided to evaluate the concomitant factors in our region and their prevalence in cleft patients in order to get a reliable data in this regard and be able to use them for controlling this disease occurrence and also to manage for the upcoming cases and make them a better life plus to inform the individuals regarding the environmental factors control which affect this process.

## METHODS

This population-based epidemiologic cross-sectional study was conducted on children referred to Tabriz children hospital from 2000 to 2015. Data were collected from

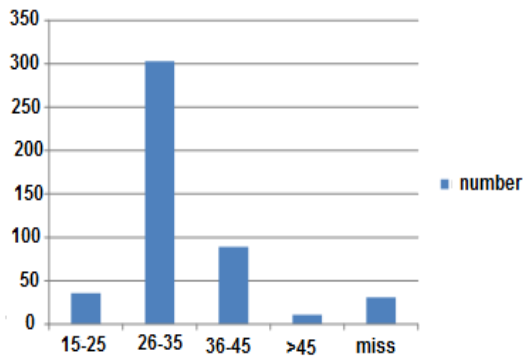
the hospital records of almost 670 births with cleft lip or cleft palate or both over the fifteen years period that all were alive. This study was approved by Tabriz University of medical sciences. All Patients information remained confidential.

Collected data contained both parents age, family history (having any condition associated with cleft lip and/or palate in the proband or a sibling, and mother's diabetes), previous pregnancy history, medical history in family members, history of drug consumption by mother/father before and during the pregnancy (OCP, antibiotic, ASA, antiemetic, antihypertention, antipsychotic...), toxin exposure history, live in neighbouring the industrial centers, residency in rural or urban areas, and location of delivery of child and parent's job were included in analysis. Then, A maxillofacial surgeon diagnosed cleft lip and/or palate cases based on the Kernahan classification.<sup>30</sup> Independent variables were determined through a questionnaire administered to parents that were collected in recent years from each patient. The obtained data were analyzed by using SPSS, statistical software.

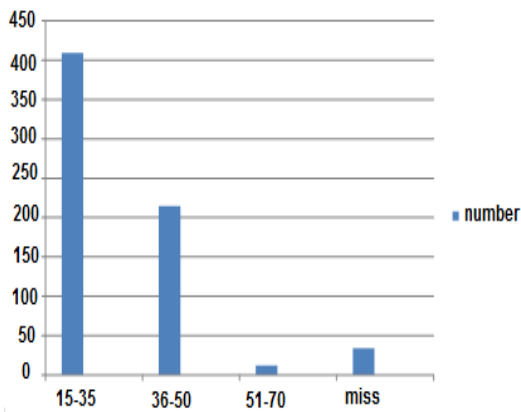
## RESULTS

Data were collected from a total of 670 births with cleft lip or cleft palate or both over the fifteen years period that all were alive. Distributions of parent's age are shown in Figure 1 and Figure 2. The most common age group in mothers and fathers are 15-35 years old (84.4%) and 15-35 years old (64.3%), respectively (mean=28.6,33.4 and SD=6.9,7.1, respectively). This age group is the most common time for delivery in Iran. Then, the cleft is seen more than the other groups, but pregnancy in teenagers can be a risk factor because of low primary care. Table 1 shows variables related to the family history background. Having a sibling (1.6%) with cleft lip and/or palate was not as strong as the parents' disease (12.7%) in cleft lip and/or palate. Then, the frequency of cleft was

greater in parents in this study. Whereas having any other child with cleft was at least. Table 2 shows maternal predisposing factors affecting the child phenotype. The most common factor was passive smoking (7%) and then, depression (4.2%), hypertension (3.6%), severe anemia (3.4%), diabetes (3.1%). Fortunately smoking is rare in Iranian women and most of maternal exposure with smoke is due to their father's abuse. Having psychotic disease especially depression in mothers was a dominant disease in this study. Then, it is necessary to evaluate the frequency of this disease in our country and its relation to maternal disease such as cleft.



**Figure 1:** Distribution of mothers age in orofacial cleft children in Tabriz children hospital in Iran, 2000-2015



**Figure 2:** Distribution of fathers age in orofacial cleft children in Tabriz children hospital in Iran, 2000-2015

**Table 1:** Cleft distribution in orofacial cleft families in Eastern Azerbaijan in Iran, 2000-2015

| Variable         | Frequency | Percent |
|------------------|-----------|---------|
| Sibling          | 11        | 1.6     |
| Parents          | 85        | 12.7    |
| Second degree fa | 71        | 10.6    |
| Far families     | 22        | 3.2     |
| Total            | 189       | 28.2    |
| Miss             | 481       | 71.8    |
| Total            | 670       | 100.0   |

**Table 2:** Maternal disease in association with orofacial clefts in Eastern Azerbaijan in Iran, 2000-2015

| Variable       | Frequency | Percent |
|----------------|-----------|---------|
| Diabetes       | 21        | 3.1     |
| Sizzure        | 10        | 1.5     |
| Depression     | 28        | 4.2     |
| Obesity        | 2         | .3      |
| Smoking        | 2         | .3      |
| Passive smoker | 47        | 7.0     |
| Hypertention   | 24        | 3.6     |
| Anemia         | 9         | 1.3     |
| Sever anemia   | 23        | 3.4     |
| Total          | 166       | 24.8    |
| Miss           | 504       | 75.2    |
| Total          | 670       | 100.0   |

Drug history was positive in 156(23.3%) and negative in 456(68.1%) patients. Drug history was missed in 58 patients. The most common drug history in mothers was Antibiotic (24 cases) (3.6%). Amoxicillin had much greater prevalence. Second line was related to NSAIDs (15 cases), and then, acetaminophen (6 cases), insulin (5 cases), antisizure (5 cases), OCP (4 cases). Other drugs with lower consumption rate were (1 or 2 cases) abortion drugs, antiemetic, antihypertensive and etc. Toxin exposure rate was 5.5% ,and 92.5% had negative history for toxins. Thirteen patients (1.9%) were missed. Birth in the west Tabriz that is nearest to the urban centers can be a risk factor. In this study

most of patients (92.5%) did not live in high risk areas (Table 3), but most of cleft child's family were not from village (67.9% in city and 29.1% in village with 3%miss). May be clefts reffered from city had much better possibity to call on?

**Table 3:** Urban exposure in cleft patiens in Eastern Azerbaijan in Iran, 2000-2015

| Cleft | Frequency | Percent |
|-------|-----------|---------|
| Yes   | 37        | 5.5     |
| No    | 620       | 92.5    |
| Total | 657       | 98.1    |
| Miss  | 13        | 1.9     |
| Total | 670       | 100.0   |

As addressed in Table 4, the incidence of smoking, addiction and alcohol abuse were 10.3%, 0.9% and 0.4%, respectively. One of the challenging factors in multifactorial disease such as cleft is father's job. In this study, the most common job was farmer (11.5%) and then: Staff (10%), transporter (8.5%), building workers (5.8%) and metal worker (4.9%) (Table 5). In metal welding workers, turnery and armature worker had more frequencies. Most of the mothers were house wife (89.3%) and only 3.3% were staff.

**Table4:** Distribution of drug abuse in cleft child fathers in Eastern Azerbaijan in Iran, 2000-2015

| Variable  | Frequency | Percent |
|-----------|-----------|---------|
| Smoking   | 69        | 10.3    |
| Addiction | 6         | 0.9     |
| Alchol    | 3         | 0.4     |
| Other     | 12        | 1.8     |
| Total     | 90        | 13.4    |
| Miss      | 580       | 86.6    |
| Total     | 670       | 100.0   |

As addressed in Table 4, the incidence of smoking, addiction and alcohol abuse were 10.3%, 0.9% and 0.4%, respectively. One of the challenging factors in multifactorial disease such as cleft is father's job. In this study, the most common job was farmer (11.5%) and then: staff (10%), transporter (8.5%), building workers (5.8%) and metal worker (4.9%) (Table 5). In metal welding workers, turnery and armature worker had more frequencies. Most of the mothers were house wife (89.3%) and only 3.3% were staff.

**Table 5:** Distribution of father'job in cleft diseasein Eastern Azerbaijan in Iran, 2000-2015

| Variable        | Frequency | Percent |
|-----------------|-----------|---------|
| Free job        | 152       | 22.6    |
| Farmer          | 77        | 11.5    |
| Staff           | 67        | 10      |
| Transporter     | 57        | 8.5     |
| Building worker | 39        | 5.8     |
| Metal worker    | 33        | 4.9     |
| Repair worker   | 25        | 3.7     |
| Education       | 22        | 3.2     |
| No job          | 19        | 2.8     |
| Soldier         | 12        | 1.7     |
| Timber worker   | 4         | 0.5     |
| Other worker    | 153       | 22.8    |
| Total           | 670       | 100.0   |

## DISCUSSION

Orofacial defects are undoubtedly important oral health issue. The present study established some of the most important risk factors related to cleft lip and/or palate in Tabriz, Iran. The most common age group in parents was 15-35 years old. Parents were not old. May be this age group is the most

common time for delivery in Iran and this frequency can be related to this reason or maybe it is related to low parent education, low socioeconomic level, or dietary folate deficiency. Although this study did not measure the genetic influence on cleft occurrence, the role of family history factors (assessed by cleft lip and/or palate background in the family) was evident. These results have been observed in other epidemiological studies focused on cleft lip and/or palate with some differences and confirmed the strong influence of genetic background. Positive history in parents was more significant than siblings (12.5% vs. 1.6%) in this study. The importance of genetic background has been confirmed.<sup>22-26</sup>

Any factor that could prevent the facial processes from reaching each other by slowing down migration, multiplication or both of neural crest cells by stopping tissue growth and development for a time or by killing some cells that are already in that location, would cause a persistence of a cleft.<sup>27</sup> Studies of role of smoking in TGF- $\beta$ 1 and MSX1 genes as covariates have suggested that the risk for orofacial clefting may be influenced by maternal smoking alone as well as combination with the presence of uncommon TGF- $\beta$ 1 allele.<sup>28</sup> In this study smoking was the most common associated factor with cleft but it should be done other studies for analysis of the influence of this factor. Between maternal smoking and risk for orofacial cleft, the current data support the possibility that smoking has a different effect on cleft risk among women which may reflect a role for genetic susceptibility factors in cleft development. In our study, passive smoking was more related to cleft patients. Information

to habitual change in smoking is a preventable behavior in cleft disorders. Depression was the second maternal factor in cleft group. May be socioeconomic level, dietary deficiency or drug consumption and its toxicity due to concurrent backgrounds were responsible for this result. It is not clear that depression is a risk factor for cleft or its treatment and complications are responsible for this problem. In this history we must review all habituations and daily life style of patient's mother. From this list, anemia is preventable problem before pregnancy. Maybe hypoxemia due to anemia is the most common hypothesis for tissue breakdown that can cause cleft deformity.

Low socioeconomic status and low maternal education seemed to be risk factors for having a child with orofacial clefts similar to Kraples and Mirilas study.<sup>29,30</sup> Low socioeconomic status as a risk factor should be considered because it can be a marker of parental health and life style. Individuals with low education tend to smoke more and have less healthy diets and nutrients. In this study, most of patients (90.3%) did not live in high risk areas around the occupational cantors may be clefts referred from city had much better possibility to call on. Chlorinated solvents was associated with neural tube defects, but no solvent class was associated with orofacial clefts in Defrosters TA study in 2012.<sup>31</sup>

The most common drug history in mothers was Antibiotic. Amoxicillin usage had much greater prevalence among drugs (then ampicillin and macrolids). Other drugs were NSAIDs, acetaminophen, insulin, antizure, OCP. Lin KJ, Mitchell AA and coworkers in 2012 reported the amoxicillin influence on oral cleft increase (2 folds).<sup>32</sup> In

results of national birth defects study, there was not positive correlation between penicillin group and oral cleft.<sup>33-35</sup>

Van Gelder MM and Roeleveld did not find any correlation between NSAIDs and occurrence of congenital heart disease and orofacial defects.<sup>36</sup> In Hill L and Murphy M study in 1988, the most common drug history in pregnant women with oral cleft child was steroid and others were antibacterial and analgesics.<sup>37</sup> This study was similar to our study. The association between antibiotics and orofacial clefts is unknown but maybe it is due to some nutritional deficiencies in combination with drug usage.

Father's job was very different and most of them have low socioeconomic level in this study. May be this factor affects on maternal nutrition or primary care or particle toxicity in their home. Building worker, staff, farmers and metal workers had high frequency. Chia SE and Shi LM reviewed association of occupational group with some disease such as painters with cleft palate and spina bifida.<sup>38-41</sup>, fireman with cleft lip, farmer with cleft lip and palate, metal workers with cleft lip and palate, motor vehicle operator with cleft palate, vehicle manufacturers with cleft lip.<sup>29</sup> In Desrosiers TA and Herring AM study in 2012, farmers and mechanics were one of the most common occasions with birth defects.<sup>42</sup> In this study, cleft lip and Palate were associated with artists, cleaners, shippers, electrical workers, chemical workers and motor vehicle operators.<sup>42</sup> The most common job in fathers of cleft patients was agriculture. The question is orofacial cleft common in farmer's family. Maybe nutritional deficiencies due to low socioeconomic status in these families are the most important cause of its high prevalence.

One of the common jobs was working with metals. Welding, turnery and armature worker had more frequencies. Maybe metal combinations in these jobs have a prominent effect on cleft patients. Some of deficiencies such as Iron, or some overloads such as copper may induce anemia and cause cleft deformity but some other studies are necessary to distinguish all metal toxicity. We must inform the possibility of orofacial deformities with these jobs. Other researches in cleft epidemiology can clarify this question. This means, there is a need for further studies and evaluation to get more reliable results and data in this regards. So, more studies with larger sample size and long time period evaluation are recommended.

## CONCLUSION

Orofacial clefts are multifactorial disease which we must control the environmental and genetic factors to prevention them. To determinate these etiologies multivariate some studies must be done. We assess some of these factor's frequencies in this epidemiologic study. Cleft was mostly presented in non urban families with normal jobs. May be nutritional defects are more responsible in our area.

## CONFLICT OF INTEREST

The authors declare that there was no conflict of interest.

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