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Risk factors involved in orofacial cleft predisposition – review

Abstract: Clefts that occur in children are a special topic. Avoiding risk factors, and also an early diagnosis of cleft possibility can result in minimizing or avoiding them. If on the other hand when clefts occur they require a long-term, multistage specialized treatment. Etiology of clefts seems to be related to many factors. Factors such as genetic, environmental, geographic and even race factors are important. Identification of risk factors can lead to prevention and prophylactic behaviors in order to minimize its occurrence. Exposure to environmental factors at home and work that lead to cleft predisposition should not be disregarded. It seems that before planning a family it would be wise to consult with doctors of different specializations, especially in high-risk families with cleft history in order to analyze previous lifestyle. Clefts are very common in hereditary facial malformations and are causing a lot of other irregularities in the head and neck region. In this paper after a brief papers review authors present socio-geographic, environmental and also work place related factors that are influencing pregnant women condition and should be taken under serious consideration.

Keywords: Clefts; risk factors; lifestyle; predisposing factors; environmental factors

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1 Introduction

According to Mayo Health Book, several factors can be involved with orofacial cleft (OFC) predispositions: geographic factors, race, family history, sex, exposure to risk factors in pregnancy, such as alcohol consumption and tobacco smoking, poor nutrition, viral infections, drugs and also teratogens in the workplace and home. Recent studies show that even obesity during pregnancy may be related with cleft lip and palate [1].

Orofacial clefts are very common world-wide with an incidence of 1.7 per 1000 babies being diagnosed with OFC [2]. Different factors are related with its occurrence. It seems that geographic and climatic factors are also quite important. In different part of the world, thanks to mass communication, people traveling and migration, geographic borders can be moved and cleft occurrence in different part of the world might change.

Asia has an incidence of 17/1000, American Indians 3,6/1000, African Americans 0,4/1000. Gender ratio is also higher in boys. Cleft palate is more frequent in males, but females more often have only cleft palate (about 0,5:1000). According to the Mayo Health Book authors, isolated cleft palate and cleft lip with or without cleft palate are present in 1,7 children per 1000 live births, but ethnic and geographic variations greatly influence this issue [3-5].

2 Facial morphogenesis and related diseases

In order to fully understand the etiology of OFC it is very important to know how facial embryogenesis and morphogenesis takes place. After activity of various risk factors in different stages of facial morphogenesis OFC clefts might occur with characteristic intensity.

Face morphogenesis consists of five processes. The frontonasal process and two maxillary and mandibular processes made from mesenchyme surrounded with



epithelium lining that also surrounds and covers entire oral cavity. It is well known that the human skull consists of desmocranium, chondrocranium and viscerocranium. All parts have a great effect on proper growth [6]. During embryogenesis various factors might interrupt or change the proper course in facial development at any moment during pregnancy. Facial processes have their own growth outline. The frontal process grows out from medial nasal and lateral nasal processes which surround the bilateral nasal pits. The next stage is a fusion of processes anteriorly with the maxillary processes to form upper lip, alveolus and primary palate [7]. For example oral clefts, such as cleft lip and cleft palate have different congenital failure episodes and occurrence. Cleft lip is related to a failure in the fusion of maxillary and median nasal processes. Cleft palate is related with a failure of the palate to fuse properly. Moved posteriorly the maxillary processes fuse to form the secondary palate. Because of the multifactor etiology of orofacial clefts and impact of cleft inducing factors, clefts can be unilateral, bilateral, have different sides and consist of various types [8,9].

In many cases orofacial clefts can also occur with various syndromes and have also other manifestations. Also genetic disorders have a great influence on cleft occurrence. Many different gene mutations and diseases are the cause of facial defects.

It is also very important to notice that clefts can be related to various syndromes and defects. Most common one is Pierre-Robin sequence. Other Syndromes related with clefts, are: van der Woude's, Opitz, Stickler, Apert's, DiGeorge's, CHARGE syndrome (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness) Waardenburg's, Hedgehog's, trisomy 13 Patau's syndrome, Trisomy 18 Edwards' syndrome, amniotic band anomaly, Fryn's, Meckel's Treacher Collins, velo-cardio-facial syndrome (VCF), oculo-auriculo-vertebral spectrum (OAV, Goldenhar syndrome, hemifacial microstomia) and other syndromes [10,11]. Many studies also conclude that females have a higher risk of breast cancer, primary brain malignancy while males have a higher risk of primary lung cancer [12]. Also Quality of Life (QOL) of patients suffering from clefts is different, because of behavioral problems, anxiety, depression, lack of self-esteem and others [13].

Also dental, facial or combined abnormalities might occur with clefts. Cleft occurrence with or without any other orodontal abnormalities or syndromes is less common [14,15].

3 Factors related with orofacial clefts

Many factors are related with clefts; however they are depend on the time, place and moment of morphogenesis and proper facial formation [16,17]. We present the most important risk factors such as: geographic, family history and genetics, alcohol and tobacco, diet, medication intake during pregnancy, infections, and occupational hazards influencing orofacial cleft occurrence.

4 Geographic-related factors

It is quite important to notice that prevalence of OFC world-wide and its relation with geographic, climate, and socio-epidemiological factors is still a focus of many studies. Maybe perhaps because of those findings OFC could be more predictable.

Predisposition to oral clefts is also different in geographic regions. Many different studies were performed world-wide in various geographic regions, climates and continents. Because of those results authors describe a very important ethnic and social dependence. Asians have the highest risk marked at 14:10000 births but a special geographic occurrence in regions such as Japan, Korea and China should be more carefully evaluated. Other races followed by caucasian have 10:10000 births, followed by African Americans 4:10000 births.

Studies shows that African children are least likely to have clefts, however cleft lip and palate is most common in American Indian and Asian children. Geographic location of Africa, its history, different cultural and ethnical factors makes it a very special place for evaluation and describing orofacial cleft occurrence and predisposition. Butali review study performed in Africa suggest that it is necessary to set up a diagnostic system in order to fully measure cleft occurrence in different regions in Africa and more studies and researches need to be performed to fully evaluate this issue [18]. Adetayo et al performed survey questionnaires in West Africa in 2007, and conclude that geographic situation of Africa, its geographic and social status has a great effect on cleft patient's life [19,20]. For example not only funding, infrastructural, education and care are important.

Both in Japan and in western Asia regional occurrences and cleft predisposition is different. Elahi et al conclude that many geographic and epidemiologic studies were carried out worldwide. Therefore authors

performed a study in northern Pakistan based on birth registry [21]. 117 cases from 61156 live births were found. Those results seem to confirm that cleft lip and/or palate was 1.91 per 1000 births, however boys had more cleft lip and lip with palate and girls had more often isolated cleft palates. This study can not only mark the prevalence of clefts in Pakistan, but also can show special geographic and cultural differences in clefts. On the other hand Dai et al study made in China between 1996 and 2000, concludes that cleft palate (CP) was identified in 499 perinatals among 2218616 births and was quite different in rural and urban areas [22]. The highest rate of 2.84 per 10000 live births was found in maternal age group more than 35 years, and also geographic variation between provinces is different. Authors also conclude that because of poor birth quality, perinatals diagnosed with syndromic CP had a poor prognosis.

Studies performed by Pradubwong et al in Thailand with usage of special Geographic Information System (GIS) indicate that most patients with clefts lived in central and northern Northeast Thailand, and most in Khon Kaen province [23]. Thanks to usage of such systems not only surgeries and treatments can be planned but also routine patient check-ups and improvement of patient's life can be achieved.

It is also worthy to note, that not only geographic factors are very important in cleft occurrence, but also in opioid administration in children. A study performed by Rabbits et al concludes that operated cleft children in Central and South America received less opioid intra-operatively than African and Indian children and more research are need to take place to evaluate this extraordinary finding [24]. Root describes a special neighborhood-level socioeconomic status (SES) conditions and factors that influence health outcomes [25]. Border crossing, illegal residency, refugees and a great amount of influx of peoples to the USA has a great effect on orofacial cleft predisposition. Because of presence or lack of social insurance that affects socio-epidemiological status, people's treatment and detection of clefts is varying.

North, Central and South Americas have a greater differences in their orofacial cleft predisposition, occurrence and treatment. Salemi et al indicate that FBDR (Florida Birth Defects Registry), which is used to collect data at geographic area in Florida is very accurate and helpful to describe and mark every 9 from 10 born infants. In conclusion a special tool to set up geographic regions and borders is very important [26]. Study performed in Colorado, USA, between 1982–1988 performed by Amidei et al marks out that country of residence, Hispanic or non-Hispanic

newborns, born in metropolitan and non-metropolitan areas have greater range difference of occurrence [27].

Socioeconomic risk factors have to be carefully evaluated. Acuña-González et al study performed in Mexico marks that the following factors have a and are related with OFC: low socioeconomic status, birth in southern Mexico region, home delivery or public hospital delivery, familial history, other siblings or family malformations, and infections during pregnancy [28].

According to study performed by Rodrigues et al that consisted of evaluation of data gathered between 1998 to 2002, on 15786107 live births 5764 newborns had OFC Study also shows that cleft occurrence in Brazil was 0.36 per 1000 live births. Ratio of OFC prevalence was more common in 1.6 men for 1 female with greater prevalence in southern and midwest regions with a very low rate in the northern region of Mexico. It seems that geographic and climatic variances have a great effect on OFC occurrence [29]. Study performed in 10 South America countries performed by Poletta et al also concludes that not only geographic region of South America has a great influence, but also familial history and family members living and traveling in different countries and continents is very important [30].

Ulucan et al conclude that regional differences in nutritional habits and life style have various effects in non-syndromic cleft lip with/without palate occurrence in Turkey [31]. This might be related with Europe-Asian ethnics and habits.

According to Silberstein et al, in the Negev region in Israel their study among Bedouin and Jewish in a well-defined geographic area describes that Bedouin population has a greater decrease of facial clefts than the Jewish population [32]. In some cases natural and traditional habits related with geographic regions might decreased greatly amount of clefts.

Studies made in Europe conclude some very important facts. For example refugees and the opening of borders of United Europe might be related with migration of peoples with different predisposition to clefts and familial history of its occurrence. Even studies made by Dai et al, confirm that in order to fully describe and measure orofacial cleft occurrence in the borders of countries, a special surveillance system is required [33].

Durning et al studies performed in Wales between 1982 and 2003 indicate that 831 babies were born with orofacial cleft, equating to 109 clefts per 100,000 live births. Authors conclude that serious association between material deprivation and orofacial clefts is essential and more studies are needed to take place in order to fully evaluate this problem [34].

Croatian study consisted of the analysis of 525298 live-births since 1988 to 1998, and marked out that OFC incidence grown slowly and was different in some geographical areas [35].

On the other hand, habitants of Australia and Oceania have different rates of orofacial cleft occurrence. Australian findings from a study on a group of newborns from 1980 to 2009 conclude that within occurrence of cleft lip with/without cleft palate and cleft and palate was 1.9 and 1.3 times higher respectively, for Aboriginal Australians. This finding may conclude that geographic and ethnic factors are very important [36].

Geographic factors have a great meaning in orofacial cleft predisposition, occurrence and treatment methods. Because habits, social conditions, access to drugs and tobacco, alcohol, its consumption in different geographic regions during pregnancy is highly related with hereditary disease occurrence and predisposition. If more risk factors accumulate it is more possible for many diseases to appear.

5 Family history and genetic factors

Family history involving any present or past members of family can induce a higher risk of having baby with a cleft. Therefore genetic counselling should be offered.

On the other hand Lace *et al* conclude that different population predisposition to OFC is related with several genes, for example European gene might be related with mitochondrial DNA (mtDNA) haplotypes. As a result authors conclude that it is unlike that mtDNA has a direct role in cleft lip and palate predisposition [37]. Therefore all newborns and their parents should be closely evaluated, examined and had special data gathered, which might be very useful in diagnosis and prevention of orofacial clefts. It seems that genetic consults have a great impact of early hereditary disease findings.

It is very important to routinely gather data about newborn's, OFC and other hereditary diseases occurrence. Another study made in US by Johnson *et al*, suggests that the number of prenatally diagnosed orofacial clefts is very low, and this tendency should be changed in order to decrease number of its occurrence [38].

Cousley *et al* study made after evaluating Yorkshire regional cleft database seems to confirm that a special diagnostic system should be used to clarify and evaluate local occurrence of clefts. Author indicates that a special program should be used to identify OFC newborns, their

complete diagnosis, familial history and geographic region assessment [39].

Males have cleft lip with or without cleft palate almost twice as often, and females have cleft palate without cleft lip.

Many different factors are involved in cleft predisposition. Parent's age, especially mother's age. Studies performed by Shaw, Baird, Vieira, DeRoo seem to confirm that maternal age is related to oral cleft risk; however not in all older studied maternal groups clefts occur [40,41,42,43].

6 Alcohol and tobacco

Exposure to risk factors in pregnancy such as alcohol may induce cleft lip and palate. When alcohol is combined with other factors, such as tobacco, drugs, and also other socio-geographic factors cleft risk is greatly higher.

It seems that both combined factors are increasing risk of OFC. Miller *et al* study performed in Russian region Murmansk in baby homes and orphanages suggest that geographic region of Murmansk and its greater expression of prenatal exposure to alcohol. Because of that children's growth, maturation and even occurring symptoms are more common [44].

Environmental factors in study made by Molina-Solana indicates that in cleft lip and/or palate main factors are: tobacco 1.48, alcohol 1.28, folic acid intake 0.77, obesity 1.26, stressful events 1.41, low blood zinc levels 1.82 and fever during pregnancy 1.30 [45]. Tobacco intake seems to have the most serious influence on OFC according to Lebbey *et al*, 1.66 ratio [46]. On the other hand, study performed by Leite *et al* concludes that mother's smoking in first trimester of pregnancy was not statistically significant, but increased alcohol use increases the risk of cleft lip with or without cleft palate and cleft palate alone to 3.41 and 8.30 and within the higher dose of drugs ratio of OFC seems to increase [47].

Tobacco and alcohol are well known factors involved in OFC occurrence. Honein *et al* study describes association between periconceptional maternal smoking, environmental tobacco smoke and cleft lip with or without cleft palate and cleft palate only in infants born between 1997 and 2001. The authors conclude that periconceptional smoking was associated with bilateral cleft lip and palate. Smoking more than 25 cigarettes per day was related with higher amounts of bilateral CLP and even Pierre Robin sequence [48].

Diaz Casado *et al*, confirm that orofacial clefts have many factors that might induce clefts and also studies explaining their origin seems to have few theories. Low

social status with abuse of tobacco, alcohol and/or drug addiction have a great effect on predisposition to orofacial clefts, and also use during pregnancy is causing not only OFC but also other congenital syndromes and malformations [49]. Genetic factors involved in orofacial clefts are still being considered in serious studies being performed world-wide [50].

When orofacial clefts occur they have a great impact on infant feeding, speech, language and voice formation, breathing, oral functions, bite, teeth formation and other related topics. Because of that newborns with OFC should be carefully treated by many specialists. Studies made in the USA indicate that more cleft surgeries are made in teaching hospitals than in nonteaching hospitals which have some positive effects on OFC treatment (decreased number of complications), for both patients and parents [51].

7 Diet

Factors such as diet including folic acid, vitamins, zinc and other microelements have a great effect on pregnancy. Some authors also point out that drinking cola and tea might have some influence on pregnancy. Drugs, medicine, corticosteroids, antibiotics and local and general agents used in pregnancy have a great effect on OFC predisposition. Other quite important matters are health status and infections present in pregnant women. Viral infections and diseases related with elevated body temperatures also have a great effect on hereditary disease occurrence. Work and factors related with work, such as radiation, high temperatures, chemical agents, light, electromagnetic field and others are influencing women's health in early stages of pregnancy when in some cases pregnant women don't even know about their condition.

One of the most important factors related to OFC is diet, because the diet of pregnant women influence the infant growth.

In a case-control study of 203 mothers of children with a cleft lip or cleft palate and 178 mothers with non-malformed offspring Vujkovic et al proved that the use of the maternal Western diet—high in meat, pizza, legumes, and potatoes, and low in fruits—increases the risk of offspring with a cleft lip or cleft palate approximately two fold. That means that dietary and lifestyle profiles should be included in preconception screening programs [52]. Other studies performed world-wide also seem to confirm those findings.

Shaw et al investigated whether a woman's periconceptional use of multivitamins containing folic acid was associated with a reduced risk of orofacial clefts. Authors found that a reduced risk of orofacial clefts is more common in mothers that had used multivitamins containing folic acid during the period from one month before through two months after conception. In this study woman using multivitamins containing folic acid periconceptionally had a 25-50% reduction in risk for offspring with orofacial clefts compared to women who did not use such vitamins [53].

According to O'Neill and a national population-based case-control study performed in Norway folic acid supplements during early pregnancy (400 microgram per day) seem to reduce the risk of isolated cleft lip (with or without cleft palate) by about one third. Moreover the author claims that other vitamins and dietary factors such as a diet rich in fruits, vegetables and other high-folate-containing foods may provide additional benefit. According to this study the lowest risk of cleft lip was among women who ate foliate-rich diets and also took folic acid supplements and multivitamins. Folic acid did not provide protection against cleft palate alone [54].

Moreover the population-based infant study cohort of the national Growing Up in Ireland performed by Kelly et al which was focused on 11,134 9-month-old infants also suggests that taking folic acid may partially prevent cleft lip and palate occurrence [55]. Wilcox et al also claim that folic acid supplements during early pregnancy seem to reduce the risk of isolated cleft lip (with or without cleft palate) by about one third. According to them other vitamins and dietary factors may provide additional benefit [56]. It seems that folic acid intake is the most important factor, but combined with other rational health food intake might cumulate positive effects on pregnancy.

On the other hand Little et al in a U.K.-based case-control study focused on determination of the associations between non-syndromic cleft lip with or without cleft palate and cleft palate only and maternal intake of dietary foliate and supplemental folic acid, in an area where the prevalence at birth of neural tube defects has been high and flour is not fortified with folic acid. There was no overall association between CL-P and CP and either energy-adjusted total foliate intake or supplemental folic acid use, irrespective of dosage. Also the same authors concluded that overall, higher intakes of total foliate do not appear to prevent oral clefts in this population [57]. Perhaps genetic predisposition and familial history has a greater influence on OFC occurrence than folic acid intake.

Badovinac *et al* meta-analysis undertook to test the hypothesis that non-syndromic oral cleft birth prevalence is different for those whose mothers took folic acid-containing supplements and for those whose mothers did not. The results support the hypothesis of a protective effect of folic acid-containing supplement intake during pregnancy on the risk for oral clefts [58].

It seems that improving our knowledge of the role of nutrition in the pathogenesis of orofacial clefts may stimulate the development of nutritional interventions for orofacial clefts prevention in the future. Folic acid fortification in the United States became mandatory from January 1st 1998 in order to reduce the occurrence of neural tube defects (NTDs). Yazdy *et al* evaluated the impact of folic acid fortification on orofacial clefts using United States birth certificate data for 45 states and the District of Columbia. Authors compared orofacial cleft prevalence among births prefortification and postfortification. According to this study folic acid fortification in the United States was associated with a small decrease in orofacial cleft prevalence, but the decline was much smaller than that observed for NTDs [59]. Also results of Canfield *et al* study indicated statistically significant decrease in the birth prevalence for cleft palate, which suggest some modest benefit from the folic acid fortification on the prevalence of cleft palate [60].

On the other hand it appears that folic acid fortification had very little or no effect on the prevalence of oral clefts in infants born in Texas [61]. Maybe geographic factor is related to these findings.

Levels of vitamin intake during pregnancy are also related with fetus formation, however in some geographic regions normal diet is better than vitamin supplementation.

Wong *et al* suggest that elevated mean serum concentrations of homocysteine may be a risk factor for having non-syndromic orofacial cleft offspring [62].

Munger *et al* suggest that poor maternal vitamin B-6 status is associated with an increased risk of cleft lip/palate at two sites in the Philippines. They also suggest that associations between foliate status and CL/P risk appear to be a result of statistical interaction between foliate, vitamin B-6, and case-control status that produced different results in study areas of higher versus lower prevalence of vitamin B-6 deficiency [63].

For example according to a population-based case-control study in Norway between 1996 and 2001 performed by Johansen *et al* maternal intake of vitamin A is associated with reduced risk of cleft palate only, and there is no evidence of increased risk of clefts among women with the highest 5% of vitamin A intake [64].

It is very important to point out that in different geographic regions of the world vitamin intake may differ. This finding is essential for proper diet planning in different part of the world.

Hozyasz *et al* suggest that also microelements can play role in the pathoetiology of clefts, especially low levels of zinc, and elevated level of cooper in mother's serum [65]. Authors investigated the relation between concentrations of maternal zinc and copper and the risk of an infant being born with an orofacial cleft. The results suggest that association between concentrations of maternal zinc and the risk of orofacial clefts in offspring are noticeable [66].

Munger *et al* reported that poor maternal zinc status was a risk factor for OCs in the Philippines, where OC prevalence is high and maternal plasma zinc concentration (PZc) is low. No such association was found in Utah, what suggest that poor maternal zinc status may become a risk factor only when zinc status is highly compromised [67].

According to Tamura *et al* higher plasma zinc concentrations in Filipino women in reproductive age were associated with a lower risk for oral clefts in their children [68].

Krapels *et al* in their study demonstrate that zinc and myo-inositol are important in the etiology of CL/P, because a low maternal serum myo-inositol concentration (<13.5 mmol/L) and a low red blood cell zinc concentration (<189 mmol/L) increased cleft lip palate risk. The cleft lip and palate children and their mothers had significantly lower red blood cell zinc concentrations than controls [69].

According to Huber *et al* oral clefts did not appear to be significantly associated with estimated dietary intake of nitrate, nitrite, and nitrosamines [70].

Consumption of drinks such as tea, caffeine, coke and other drinks is related in some cases with OFC occurrence. There are also evidence that tea consumption is associated with a reduced odds ratio of both cleft lip with or without cleft palate and cleft palate only. There is also little evidence of an association between caffeine exposures to clefts when all sources of caffeine are present in diet [71]. On the other hand Collier *et al* didn't suggest an association between maternal dietary caffeine intake and orofacial clefts. The authors claim that caffeine-containing medications require further additional study [72].

Bille *et al* study is focused on the association between oral clefts and first trimester maternal lifestyle factors based on prospective data from the Danish National Birth Cohort (approximately 100,000 pregnancies). Results of this study did not find statistically significant associations with drinking more than 1 l of cola per week and oral clefts [73].

8 Medicaments intake during pregnancy

Not only are diet and nutritional factors important for OFC predisposition, but also medicament intake is related with significant OFC risk.

In some clinical situations it is necessary for woman to take medicaments during pregnancy. According to FDA (Food and Drug Administration) drugs are classified into five categories (category A, B, C, D, X), which describe the potential benefits and risks of use of the drug in pregnant women. The use of medicaments during pregnancy requires careful consideration. Some epidemiological studies have explored that relationship between orofacial clefts and medicaments during pregnancy is very important. Because of that also additional educational campaigns are need to take place, for example for reducing OTC (over the counter) accessible drugs.

Bronchodilators are most often prescribed for the treatment and control of symptoms of obstructive lung diseases such as asthma and chronic obstructive pulmonary disease.

Munsie et al assessed whether mothers who used bronchodilators during early pregnancy were at an increased risk of delivering infants with orofacial clefts, and observed a statistically significant association between maternal bronchodilator use during the periconceptional period and the risk of CLO after controlling for other risk factors. However authors pay attention to the fact that it is still unclear whether the increased odds ratio observed in this study are due to the bronchodilators, the severity of asthma, or both, or are not related to each other [74].

Also anticonvulsant drugs were considered to cause an increased risk of clefts, however still other studies are taking place to fully explain this risk. Data confirming the association between diazepam and orofacial clefts risk are divergent. Marinucci et al in their review analyze accessible data from international studies investigating the combined genetic and environmental causes of cleft lip with or without cleft palate and describe successes and limitations in identifying underlying genetic and environmental factors. Authors suggest that more studies are needed to characterize the effects of diazepam during gestation on the child's development, particularly on orofacial clefts [75].

Association of another anticonvulsant drug – lamotrigine – with oral clefts was a subject of Holmes et al study who noticed increased frequency of isolated cleft palate in infants exposed to lamotrigine during pregnancy.

That means the infant exposed in the first trimester of pregnancy to the anticonvulsant drug lamotrigine has an increased risk to have an isolated cleft palate or cleft lip deformity [76].

Puhó et al evaluated the possible association between all kinds of drug treatments during pregnancy and isolated cleft lip with or without cleft palate and posterior cleft palate in the offspring. Authors confirmed the orofacial cleft inducing effect of phenytoin, carbamazepine, oxytetracycline, and thiethylperazine and suggested a possible association between orofacial clefts and oxprenolol and amoxicillin. However authors pay attention to the fact those drugs may have only a limited role in the origin of isolated OFC [77].

To examine whether maternal corticosteroid use during pregnancy is associated with delivering an infant with an orofacial cleft Carmichael et al performed a study, which results suggest a moderately increased risk of cleft lip/palate among women who use corticosteroids during early pregnancy stages [78].

Park-Wyllie et al suggest that prednisone does not represent a major teratogenic risk in humans at therapeutic doses [79]. Corticosteroids are used to treat many diseases during pregnancy, such as inflammatory diseases. The association between the risk of orofacial clefts in infants and the use of corticosteroids during pregnancy is still unclear from the available evidence. The results of the study of Hviid et al did not show an increased risk of orofacial clefts after usage of corticosteroids during pregnancy. Investigation of the pattern of association between orofacial clefts and the use of dermatologic corticosteroids during pregnancy indicated that this result did not statistically mark out a causal connection and more likely arose from multiple statistical comparisons [80].

Park-Wyllie et al collected prospectively and followed up 184 women exposed to prednisone in pregnancy and 188 pregnant women who were counseled for non-teratogenic exposure. In study there was no statistical difference in the rate of major anomalies between the corticosteroid-exposed and control groups. Authors suggest a marginally increased risk of major malformations after first-trimester exposure to corticosteroids. In addition, summary odds ratio for case-control studies after examining oral clefts was significant (3.35 [95% CI 1.97, 5.69]). Although prednisone does not represent a major teratogenic risk in humans at therapeutic doses, it does increase risk of OFC studies performed on animals [81].

On the other hand Bay Bjørn et al performed a prevalence study of 83,043 primiparous women who gave birth to a single live-born in northern Denmark, in 1999-2009. Authors did not find evidence of an association between

use of corticosteroids in early pregnancy and risk of congenital malformations in offspring [82].

Another group of drugs which is used during pregnancy are antibiotics. According to the study of Mølgaard-Nielsen *et al* who investigated the association between antibiotic use in early pregnancy and the risk of isolated orofacial clefts in a Danish nation-wide cohort study, antibiotic use in early pregnancy is not a major risk factor for isolated orofacial clefts [83]. On the other hand results of the study performed by Lin *et al* suggests that maternal use of amoxicillin in early pregnancy may be associated with an increased risk of cleft lip with or without cleft palate for third-gestational-month use [84].

9 Infections

Viral infections such as HSV are very common and have a great influence in any hereditary disease occurrence.

Infections of HIV and AIDS in which pregnant women require antiretroviral prophylaxis additional approaches are necessary. The aim of these drugs is to prevent vertical HIV transmission to the offspring from infected mothers. Association between antiretroviral prophylaxis and risk of oral clefts was investigated. Albano *et al* and Vassiliki *et al* did not find evidence for increased risk of cleft lip or cleft palate among infants exposed to antiretroviral drugs during pregnancy. Vassiliki additionally analyzed 5 years of available data from the Food and Drug Administration's Adverse Events Reporting System (Medwatch program) and calculated reporting odds ratios (RORs) and their associated 95% confidence intervals. The results suggest there were infants exposed to antiretroviral drugs (such as lamivudine, the combination abacavir sulfate/lamivudine/zidovudine, and nelfinavir, followed by nevirapine, lopinavir/ritonavir, and lamivudine/zidovudine) during pregnancy in the Antiretroviral Pregnancy Registry (APR) and haven't been born with increased risk of cleft lip or cleft palate [85, 86].

Antineoplastic drugs during pregnancy are associated with increased risk of oral clefts. According to this data there are evidences regarding the association of medications use in pregnancy and congenital malformations in offspring. This subject requires additional researches.

10 Occupational factors

Occupational factors related with job and job-related factors have a great influence on OFC predisposition.

Social factors do not allow every woman not to work during pregnancy. The environment of working place can be a place, where the women are exposed to many factors which can potentially increase risk of oral clefts.

Maternal occupations, which have been reported to increase risk of oral clefts, are services such as hairdressing, agriculture, and leather or shoe manufacturing as well as exposure to pesticides, lead, and aliphatic acids. Studies made by Bianchi *et al*, Garcia *et al*, Lorente *et al*, Wyszynski *et al* seem to confirm those findings [87, 88, 89, 90].

Bianchi *et al* in their study performed on data derived from the Florence Eurocat registry surveillance program, indicates a notable, significant relation between maternal occupation as a pelt or leather worker and orofacial clefts in offspring [91]. The results of a study presented by Garcia *et al* suggest that the mothers who were involved in agricultural activities during the month before conception and the first trimester of pregnancy have increased risk for oral clefts in offspring. The authors consider possible association between exposures to pesticides during agriculture activities [92].

Romitti *et al* in meta-analysis consisted of reviewing 230 studies on pesticides and orofacial clefts confirm some findings. The results of this meta-analysis suggest that maternal exposure to pesticides is associated with a modest but marginally significant risk of cleft. The authors claim that in order to better understand the relationship between pesticide exposure and orofacial clefts, future studies should consider evaluation of multiple routes of parental exposure, etiologically homogenous phenotypes, and individual genetic susceptibility [93].

Organic solvents and other chemicals are often present in women's occupational and domestic environment. This presence is quite dangerous. Those agents can be found in both work and in home. That means that identification of the agent responsible for specific reproductive outcome is difficult. Maybe carefully performed questionnaires could be useful.

The association between organic solvents and risk of oral clefts was the subject of the study performed by Chevrier *et al*. The authors investigated the role of maternal occupational exposure to organic solvents at the beginning of pregnancy in the risk of non-syndromic oral clefts. Authors collected data from a case-control study conducted in France between 1998 and 2001 at seven hospitals. The results suggest that the risk of oral clefts

increases linearly with level of exposure within the three subgroups of oxygenated solvents—aliphatic alcohols, glycol ethers, and other oxygenated solvents (including esters, ketones, and aliphatic aldehydes) [94].

Laumon et al in their case-control study conducted in the Rhône-Alpes region of France during the years 1985 to 1989 compared maternal exposure to any organic solvent between 200 infants with cleft lip and/or cleft palate and 400 controls. Both groups were compared to exposures to nine subgroups of solvents. They found association between halogenated aliphatic solvents and oral clefts [95].

Pregnant women working during pregnancy might be potentially exposed to different risk factors. During years and civilization expansion and advancement more risk factors had occurred. The study of Lorente et al was performed to investigate the role of maternal exposures at work during pregnancy and the occurrence of oral clefts. The authors examined occupational exposures of 851 women (100 mothers of babies with oral clefts and 751 mothers of healthy referents) who worked during the first trimester of pregnancy. All data was analyzed. The women were part of a multicenter European case-referent study conducted using 6 congenital malformation registers between 1989 and 1992. Analysis suggests that occupational exposures such as aliphatic aldehydes, glycol ethers, lead compounds, biocides, antineoplastic drugs, trichloroethylene, and aliphatic acids are associated with orofacial clefts [96].

Although results of many studies suggest that maternal occupational exposure to organic solvents during pregnancy may lead to increased risk of oral clefts, these results should be interpreted cautiously, because of multiple exposures during pregnancy.

Environmental factors considered to be risk factors of orofacial clefts are electromagnetic fields and also other light and electric sources that after long exposure might be dangerous.

Shaw et al investigated whether the periconceptional use of electric blankets, bed warmers, or electrically heated waterbeds increases the risk of women to deliver infants or fetuses with orofacial clefts. The results suggest that women, who reported more frequent use of a bed-heating device, or longer duration of use, did not appear to have a higher risk for delivering offspring with anomalies than were women who reported less frequent or shorter-duration use [97].

11 Conclusion

We conclude that there are many factors, which can be involved in OFC predispositions. Many of them require additional research to confirm their significance in etiology of these orofacial malformations. Also a quite important matter in OFC is an adequate and precise measuring device of etiology and occurrence of OFC while using a special data base performed just after delivery of newborns would be highly useful. In many cases lack of documentation and proper medical examinations leads to misinformation and misdiagnosis, both very important factors in OFC management.

Improving our knowledge about the risk factors and potential risk factors leading to oral clefts can be very useful in their prevention. Education of future mothers about behaviors before and during pregnancy, which can increase the risk of oral clefts is very important. It might cause decrease in the OFC occurrence and improve local health systems, however lack of information and people's lack of education might have a great impact on OFC.

The parent's attitude in OFC patients and their response to prognosis and treatment is very important. Most parents do not perceive oral clefts as a severe condition and they didn't consider the termination of pregnancy because of OFC in the offspring. Because of a great but long term treatment of OFC the patient's quality of life can be greatly improved if treatment takes place just after childbirth and lasts almost their entire life.

On the other hand the real vision of future life of the child with OFC is not so optimistic. The children require a multidisciplinary approach. Also complications are common. Among complications which are connected with OFC are: chronic glue ear, hearing loss, soft palate muscle malformation which influence hearing, speaking and swallowing, dental cavities with displaced teeth or lack of teeth, poor speech and quite often the value of problems related with OFC are not related to the size of the defect. Nasal breathing, articulation, rehabilitation of occlusion often require treatment until the end of maturation.

It is also important for physicians to educate the patients and prescribe medicaments if necessary with low teratogenic risk. Without proper drug administration and not referring to physician recommendations, some complications connected with OFC might occur.

The results of many studies are divergent. Further understanding of environmental risk factors in different geographic and ethnic regions requires more study.

Next challenges are related with continuation of European and national programs not only helping

patients with OFC but also gathering socio-geographical data and their evaluation.

Patients suffering from orofacial clefts have decreased functioning levels because of malocclusion, biting problems, hipodontia and other co-existing problems. Facial aesthetics, social acceptance and well-being are related with their quality of life, self-acceptance and contacts with others. Multidisciplinary approaches with long-term treatment are very important to improve health and life.

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