Review Article

Prevention of oro-facial clefts in developing world

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ABSTRACT

Oro-facial cleft (OFC) remains a prominent health issue in developed and developing countries alike. It is the commonest craniofacial birth defect in humans. Mounting evidence suggest a polygenic, multifactorial and a list of epigenetic events. Primary prevention of OFC is based on recognition of the etiologic and risk factors. While a number of preventive strategies are in place for OFC in most developed countries of the world, the majority of developing countries are distant from achieving this goal for a number of reasons. Notable among these are a huge knowledge and practice gap in the field of genetics and dearth of accurate data. In addition, improper coordination and absenteeism from antenatal care contributed greatly to this set back. With ongoing efforts aimed at determining the genetics of nonsyndromic OFC in developing countries, researches directed at identifying environmental factors should equally be in place. Pending the outcome of these, implicated environmental and attitudinal risk factors in other populations could serve as preventive template in health education and interventions. Since risk factors vary between populations, definitive and effective preventive strategies and models would vary from place to place and from time to time. Frantic effort directed at identifying specific implicated risk factors in developing countries should include developing and keeping comprehensive national perinatal database and centralization of antenatal care protocol. Additionally, active health education at every level and a focus on developing manpower in the field of genetics should be in place. These would be designed and tailored toward identified, proven, and emerging risk factors.

Keywords: Oro facial cleft, prevention, limited resource setting, developing world

INTRODUCTION

Oro-facial cleft (OFC) remains a prominent health issue in developed and developing countries alike. With a worldwide prevalence of approximately 1.2/1000 live births, OFCs are the commonest craniofacial birth defects in humans.[1] They are categorized as syndromic (S) if accompanied by additional structural and/or developmental abnormalities and nonsyndromic (NS) if they occur in isolation without other apparent abnormalities. About 70% of cleft lip with or without palate (CL/P) and 50% of isolated cleft palate (CPO) are NS.[2] The prevalence of NS CL/P is known to vary according to ancestral origin[3] and socioeconomic status[4] ranging from ~1/500 in individuals of Asian and Amerindian origin to ~1/1000 in European and ~1/2500 in African populations.[5] These patterns do change from time to time with changing lifestyles. Some exceptions are observed in isolated geographic regions where the prevalence differ from that of the surrounding ancestral background a discrepancy generally attributed to cofounder effects or specific environmental factors. For instance, the Scandinavian populations, tend to have a higher prevalence of cleft lip defects than most other European populations.[5–7]

Mounting evidence suggests that interplay of multiple genes and environmental factors influence the risk of OFCs, either individually or through their interactions in complex biological pathways.[8]

Extensive medical and behavioral interventions are needed to treat these common structural birth defects which impose considerable economic, psychological, and personal health burden.[9] Consequently, its prevention is cost effective and extremely desirable particularly in developing countries where

access to comprehensive care is limited.

Although the causes of OFC are not completely understood, its prevention remains the ultimate goal of several research endeavor in OFC today. Outcomes of some of these researches constitute the bedrock of existing preventive programs in most developed countries. This manuscript hopes to propose ways of bridging the existing gaps in the prevention of OFC between developed and developing countries.

PREVENTION DEFINED AND APPLIED

Three levels of prevention (primary, secondary, and tertiary) have been identified. Primary prevention refers to steps taken to ensure that a disease process does not begin. Secondary prevention on the other hand involves prompt diagnosis and management of a condition while tertiary prevention addresses limiting the debilitation resulting from a disease process. Most efforts at primary prevention are predicated on eliminating identified etiologic and risk factors.

Secondary prevention on the other hand has been developed to include steps like prenatal diagnosis and counseling, earliest possible presentation in the hospital (at birth), and receiving every available care promptly. Available cares include a range of support, for example, psychosocial, nutritional, medical, surgical, dental, etc.

Tertiary prevention involves psychosocial care of OFC patients and their proper integration into every system in life. Speech, orthodontic as well as orthognathic surgical care among other secondary surgical procedures are included.

Of these, primary prevention of OFC is most desirable. It is the only step that aims at eliminating the disease process absolutely and will form the major thrust of this paper.

Foundation of existing preventive programs

Although a very young and growing field, successful preventive OFC programs all over the world are founded on identified etiologic and risk factors. In Denmark for instance, the presence of validated nationwide population and health registers ensure correct identification of children with OFC.[6] Furthermore, all medical and dental treatment of children in Denmark is free and centralized ensuring high ascertainment of OFC.[10] Additionally, reviews of birth registries over the decades (1936 to date)[6] and comparison with subsequent years have enabled the study of changes in birth prevalence. These have also formed the basis for introducing a number of preventive programs.

A number of researches (observational, epidemiological studies, etc.) have contributed greatly to the detection of etiologic and risk factors and consequently have enhanced prevention.[11]

Etiology of oro-facial clefts: The journey so far

Our knowledge of OFC up to date suggests that it is of multifactorial etiology.[8] Interplay of genetic and environmental factors has been implicated. Genetic factors and environmental factors are, however, ethnicity-specific and, in many places throughout the world, location-specific. Importantly, this understanding helps direct our attention toward prevention.

Genetic causes of syndromic clefts have received a lot of attention. They are widely studied, explored and understood than the NS types.

Epidemiological and experimental data suggest that environmental risk factors might be important in NS cleft lip and palate. A number of factors have been identified over the years with varying degrees of certainty. Maternal exposure to tobacco smoke, alcohol, poor nutrition, viral infection, medicinal drugs, and teratogens in the workplace and at home in early pregnancy and effect of pregnancy planning have all been investigated among many other factors.[12,13]

Maternal smoking during pregnancy has been linked consistently with increased risk of both cleft lip with or without cleft palate and isolated cleft palate, with a population-attributable risk as high as 20%.[14,15] This association might be underestimated because passive exposure to smoke has not been assessed in most studies. Maternal alcohol use is a well known cause of fetal alcohol syndrome; however, the role of alcohol in isolated OFCs is less certain, with positive associations reported in some studies[16–18] but not in others.[19,20] Social and dietary contexts of alcohol consumption are varied and complex and can include modifying or confounding effects of nutrition, smoking, stress,[21] or drug use.[14]

Advanced maternal and paternal ages (another risk factor for OFC) are known to result in gene mutation and chromosomal abnormalities.[22] Findings of observational studies suggest a role for maternal nutrition in OFCs. Assessments of dietary intake or biochemical measures of nutritional status are challenging and generally unavailable in many impoverished populations with the highest rates of OFCs. It is desirable to enhance and harmonize measurement of exposure across board in future studies.

Maternal use of multivitamin supplements in early pregnancy has been linked to decreased risk of OFCs; in a meta-analysis,[23] evidenced by 25% reduction in birth prevalence of OFCs with multivitamin use. Data suggest a possible interaction between maternal hyperthermia during pregnancy and use of vitamin supplements, such that supplementation diminishes the increased risk for OFCs associated with hyperthermia.[24]

Previous trials investigating the role of maternal multivitamin supplementation in the prevention of OFC have been inadequate because of small sample sizes and insufficient data to allow evaluation of results.[25] In a Hungarian trial of multivitamins for primary prevention of birth defects the rate of neural-tube defects was significantly lowered, but the sample was too small to ascertain whether multivitamins prevented OFCs.[26] The control group received trace elements, including zinc, which could be protective against cleft lip, cleft lip and palate, and cleft palate alone, therefore possibly obscuring a treatment effect. In another randomized controlled trial, in which women choosing to take folic acid supplements before or during pregnancy were randomly

allocated either high-dose (2.5 mg) or low-dose (1.0 mg) folic acid,[27] prevalence of OFCs was higher in the high-dose group than in the low-dose group.

Folate deficiency causes clefts in animals,[28] and folate antagonists are associated with increased risk of OFCs in humans.[29] The role of dietary or supplemental intake of folic acid in human cleft disorders is uncertain. Biomarkers of poor vitamin B6 status were associated with increased risk of OFCs in the Netherlands[30] and in Philippines.[31] Vitamin B6 deficiency is typical in populations with high intakes of polished rice in Asia, and these groups also seem to have high rates of cleft lip, cleft lip and palate, and cleft palate alone.[31]

Zinc is important in fetal development, and deficiency of this nutrient causes isolated cleft palate and other malformations in animals.[32] Mothers of children with cleft lip, cleft lip and palate, or cleft palate alone in the Netherlands had lower concentrations of zinc in erythrocytes than did mothers of children without clefts. Similar differences were noted between children with and without these defects.[33] In the Philippines, zinc deficiency is widespread, and high maternal amounts of zinc in plasma were associated with low risk of OFCs with a dose-response relation.[34] Other nutrients that could play a part in development of OFCs include riboflavin[35] and vitamin A.[36,37] Fetal exposure to retinoid drugs can result in severe craniofacial anomalies[38] but the relevance of this finding to dietary exposure to vitamin A is uncertain.

Maternal occupational exposure to organic solvents[39] and parental exposure to agricultural chemicals[40,41] have been associated inconsistently with cleft lip, cleft lip and palate, and cleft palate alone. Anticonvulsant drugs, notably diazepam, phenytoin, and phenobarbital,[42–44] increase risk of these anomalies. Positive associations with maternal corticosteroid use in pregnancy have also been reported.[45] Such findings must, however, be interpreted with caution because of possible publication bias.

Other maternal factors associated with increased risk for oral clefts in other studies include history of a fever or cold; use of analgesic and antipyretic drugs; poor ventilation during heating; and consumption of pickled vegetables >6 times per week during pregnancy.[46] Maternal alcohol consumption,[47] maternal stress, maternal diabetes, proton pump inhibitor, antibacterial medication, maternal use of bronchodilator, and acetaminophen have been implicated. Others are use of native concoction/herbal preparations,[48] exposure to smoke, carbon monoxide, mould, arsenic, formaldehyde, mycotoxins, radioactive substances in water, obesity,[49] birth rank, pregnancy illness, parental age, young parents, and consanguineous marriages.[50,51]

Genetic factors

Cleft lip with or without cleft palate is listed as a feature of more than 200 specific genetic syndromes, and isolated cleft palate is recorded as a component of more than 400 such disorders.[52] The proportion of OFCs associated with specific syndromes is between 5% and 7%.[2] If specific genetic disorders are excluded, the recurrence risk to siblings is greater than that predicted by familial aggregation of environmental risk factors.[53]

Various genetic polymorphisms have been investigated in population-based association studies. Some gene products studied are growth factors (e.g., TGFA, TGFβ3), transcription factors (e.g., MSX1, IRF6, TBX22), or factors that play a part in xenobiotic metabolism (e.g., CYP1A1, glutathione S-transferase μ1 [GSTM1], *N*-acetyltransferase 2 [NAT2]), nutrient metabolism (e.g., methylenetetrahydrofolate reductase [MTHFR], retinoic acid receptor α [RARA]), or immune response (e.g., PVRL1, IRF6). The most intensively investigated variants have been of the *TGFA*[54–56] and *MTHFR*66,[57,58] genes. Inconsistencies in data have been indicative of the challenges of researching gene–disease associations and related interactions.[59]

Gene–environment interaction

Examining the gene–environment interaction is important for a number of reasons. Independent appraisal of genetic or environmental factors could be prejudiced, hence it is imperative to evaluate their interaction.[60] Second, results of such studies will improve our knowledge of cause and pathogenesis of OFC and should influence decisions made about public health policies.

Unfortunately, findings of these studies on interactions have been highly inconclusive.

Reasons for uncertainty include low statistical power to detect or exclude interaction; differences between studies in the individuals who have been genotyped (e.g., mother alone or with infant). Furthermore, researches are confined to populations in a few industrialized countries. The need to establish collaborative groups was proposed through the WHO International Collaborative Research on Craniofacial Anomalies project. This should help to undertake meta-analyses and pooled analyses of studies of relations between craniofacial anomalies and putative genetic polymorphisms.

THE GAP BETWEEN DEVELOPED AND DEVELOPING COUNTRIES

Most of the researches designed to identify the etiology of OFC have been conducted in the developed countries where there are accurate records of births and deaths as well as their causes. Such registries have formed ready sources of information backing up observational studies. A number of risk factors attributable to birth defects have been discovered thereby.

The reverse is the case in most developing countries where accurate records of antenatal care, births and deaths are not available. Some of the factors enhancing poor records include poverty, ignorance, settling for alternatives, unavailability, and/or poor access to antenatal care.

Unlike developed countries, indiscriminate prescription, purchase over the counter and use of drugs is possible in many developing countries. This has been reflected in a few studies[48] as a potential risk factor for OFC.

The use of herbal preparations and native concoction is deeply entrenched in some cultures in developing countries.[48] There are

places where people believe that herbal preparations are superior to orthodox medicine. Unfortunately most of these preparations are not prescribed in known doses, neither are they proven to be free from teratogenic agents.[48]

Some cultural practices and beliefs about birth defects have helped to compound preexisting poor health seeking behaviors.[61] Nevertheless, a few hospital-based studies in many developing countries have generated list of potential risk factors, which can be termed inconclusive but may serve as guide for prospective studies in those population.

While the role of clinical geneticist in accurate diagnosis cannot be over emphasized,[62] these specialists are lacking in most developing countries. This constitutes another major setback encountered by the developing countries. To say the obvious, preconception care is largely missing in developing countries. Most developing countries also do not have centralized treatment for most citizens. This makes it difficult to introduce interventions and monitor their outcome. Poor records have gone on to hamper detection of specific risk factors, introduction of preventive measures, and monitoring outcomes.

In Denmark, a decline in birth defect prevalence was attributable to increase in folic acid supplementation or decrease in smoking among fertile women,[10,63] In Taiwan, the presence and use of registries have helped to achieve successful comparison between ethnic groups.[64]

Cooper *et al*. pointed out that careful delineation of the data (whether for singleton and/or multiparous, for live births and/or stillbirths, type of syndromes, cleft type) in population-based studies of oro-facial defects prevalence is crucial when examining ethnic differences,[3,65] These are not feasible in most developing countries with defective or nonexisting database. Regrettably, government policies in most of the developing countries do not suggest appropriate prioritization of issues like birth defects and registries. Infection control and malnutrition may occupy top priority positions for obvious reasons.

There are indications that awareness about preventive strategies for OFC among health workers in developing countries may be very low.[66] Although the importance of folic acid in the prevention of OFC was recognized and accepted worldwide,[66–72] its practical implementation has eluded reality. The main reason for this is the extremely low degree or, in certain cases, lack of awareness among the medical population and health care providers who actually interact with affected people.[73–75]

For instance, awareness about the role of folic acid and its influence on neural tube defects and cleft lip and palate was very poor in the groups studied by Elavenil *et al*., with the specialists having a marginal edge.[66]

ORO-FACIAL CLEFT PREVENTION TODAY

Available knowledge on risk factors have been applied in cleft preventive programs in most parts of the world with varying results. It has been found that proper counseling of prospective mothers and their education is the best means of achieving the goal of prevention.[74-76] For this to occur, health care providers need to be aware and thoroughly educated on the various preventive strategies available. For instance, the knowledge of the benefits of folic acid have been put to use and yielded positive results.[66]

It is known that genetic factors and environmental factors are ethnicity-specific and, in many places throughout the world, location-specific. Thus, a specific protocol for cleft prevention are being worked out based on genetic and nutritional studies of each specific population group to ensure effectiveness. This is always the ultimate goal.[72]

A projection on the effect of complete elimination of smoking among pregnant women in the Danish population has been analyzed, produced and made available to educate the populace (National Health Service of Denmark, 2004). A 10% decrease in smoking (from 34% in 1989 to 24% in 2001) would result in a 4% decrease in occurrence of CL/P.

With better understanding of these health problems, steps have been taken toward modification of lifestyle and diet thus helping to prevent 'environmental factors' from triggering the inherited mutated genes.[77] In Denmark, no decrease in birth prevalence of CL/P was observed during an update period (1988 through 2001) despite reduced smoking and introduction of folic acid. This was attributed to possible poor compliance with consumption of folic acid, the presence of another risk factor or a weak causal association between folic acid and smoking and the occurrence of CL/P.[10,18]

The role of folic acid in the prevention of clefts has been proven beyond doubt by various studies,[66–71,78] The use of folic acid as a prophylactic therapy to any woman of child-bearing age has been proven to decrease the incidence of OFC by as much as 85%, besides the other proven benefits of folic acid as a nutritional supplement.[9,67,70,78]

ACTION PLAN FOR DEVELOPING COUNTRIES

For most developing countries, access to comprehensive care for OFC is still poor. Health policies in such countries focus on 'pressing issues' like infection control, malnutrition, etc. With time, reduction or eradication of these problems will project the problem of birth defects to a more prominent position.

A necessary proactive step for such countries is to position primary prevention of OFC (like other birth defects) high on their priority list. Borrowing a leaf from the existing programs that have been improved upon over the years, a preventive program for these countries should begin with establishment of prospective databases at every level in the nations. This should include all antenatal, birth, death, and birth defect registries but with emphasis on OFC. Variables in such registers should be comprehensive and ethnicity conscious and specific.

To ensure a wide coverage and accuracy, National government

would have to standardize, centralize, and heavily subsidize antenatal care at every level. Such care should be made available at every location in the country including private hospital and traditional birth attendant centers. While data catchments goes on at every center, (rural, urban, or sub-urban) efforts such as incentives should be put in place to surmount poor health seeking behaviors especially among women of child-bearing age.

Determining the birth outcome of every pregnancy accurately regardless of where deliveries take place will help to determine the incidence of birth defects and OFC in such countries, a feat which many have tried and failed to achieve severally. Moreover, since it is known that genetic and environmental factors implicated in OFC are ethnicity and location-specific in many places throughout the world, studying input in these registries should help to generate a reliable pattern. A follow-up on the pattern of risk factors found will then initiate a preventive process. This will include modifications of maternal and paternal lifestyles and following up to determine the effects on outcome.

Additionally educative programs on prevention of OFC should be put in place and kept ongoing for different groups in the societies. First, all health workers should be thoroughly educated on the subject, likewise those who come in contact with individuals of child-bearing age (all potential mothers). Target group should include schools, media houses, churches, mosques, markets, all clinics, and locations where women and men of child-bearing age are found. Communication with these groups of people will have to be adapted to their levels in understandable terms if knowledge will be imparted effectively.

Centralized and subsidized antenatal care, will help to implement preventive measures like vitamin supplementation. Other strategies like dietary counseling; occupational health counseling could be introduced at the supplement delivery points.

Secondary prevention will address situations in developing countries where people do not know of the possibilities of surgical care. Educating the public on this will form part of a preventive program. Furthermore, providing a directory of the locations where such cares are available in every health care delivery center will enhance early presentation for care. Posters of pre- and postoperative cases, with hospital's contact details will enhance information dissemination.

The genetic model is an essential part of a complete preventive package. Ongoing collaborative efforts aimed at detecting the genetic patterns in NS OFC at specific locations should be sustained and extended to every developing country. More importantly, the need to develop genetics in most developing countries is long overdue. A campaign for genetics in the authors' opinion will begin with career counseling to school age children and undergraduates studying in related specialties.

Where there is manpower, government policies and funding should be directed at enhancing researches aimed at determining the specific genetic factors in various groups. These action plans can be classified into time-related goals built into government policies and worked at steadily to achieve a desired end.

CONCLUSION

Considering the total cost (financial, emotional, psychological, etc.) that goes into comprehensive cleft care, every effort directed at the prevention of OFC is worthwhile. Measures aimed at prevention of OFC are ongoing in developed countries and can be achieved in developing countries too. Identifying the specific genetic and environmental factors in each location is a necessity. Hindrances peculiar to the developing countries and hampering preventive programs have been identified. These can be overcome if there is a determination to do so at every level. The roles of government and health workers in policy formulation and implementation are central and cannot be overemphasized. For the developing countries, where cleft care is not so readily available, prevention remains the best and cheapest option.

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