

# Non-syndromic oral clefts: a glimpse on environmental risk factors- a mini-review

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## Introduction

Worldwide, oral clefts (OC) are considered among the most common birth defects with an estimated rate of 1 per 500-1000 live births.<sup>1</sup> Disparities in prevalence of OC are largely related to ethnic, geographic and socioeconomic variations such that the highest rates have been reported among Asians and Native American whereas Africa-based populations are at the lowest risk to develop such defects.<sup>2</sup> Typical orofacial clefts which comprise cleft lip with or without cleft palate (CL/P) and isolated cleft palate (CP) are mostly non-syndromic and occur as isolated defects. Only 30% are associated with other structural or systemic defects as a part of a recognized syndrome.<sup>2,3</sup>

Children with OC tend to suffer from feeding problems and hence delayed growth, difficulties in speech, hearing disorders and physical disfigurement. This in turn leads to low self-esteem, social isolation and impairs a child's ability to integrate into the surrounding environment.<sup>4,5</sup> In low income countries, where resources and multidisciplinary cleft care including surgical repair, dental treatment, speech therapy and psychological support are lacking, infant mortality has become common due to poor nutrition and high risk to acquire infectious diseases.<sup>6</sup> Having a child with oral cleft substantially imposes negative psychosocial and financial burdens for the affected family.<sup>7</sup>

## Etiology

Though there is no global agreement on the exact etiology of OC yet it is well known that a complex interplay between both genetic factors and environmental teratogens contributes to their development. Understanding the developmental disturbances associated with OC and identifying the modifiable environmental factors offer an excellent opportunity for devising programs for primary prevention of these deformities.

Multiple environmental exposures contributing to OC have been extensively researched including maternal obesity, stress, diabetes and tobacco use as well as alcohol or drugs consumption. Though several studies have lent support to the hypothesis that maternal tobacco use and exposure to passive smoking during the first trimester are positively associated with CL/P<sup>9,10</sup> however a recent meta-analysis failed to confirm a dosage response relationship. (11) As revealed in many studies, the risk of OC is also high among expectant mothers using anticonvulsants such as valproic acid and phenytoin in early gestation.<sup>12,13</sup>

Despite the existing controversies regarding the relationship between maternal pre-pregnancy weight and development of oral clefts, it has been lately confirmed that obese women are at higher

risk to deliver children with CL/P.<sup>14</sup> Moreover, it was suggested that both overweight and underweight interfere with the process of palatal development.<sup>15</sup> This could be linked to maternal nutritional deficiencies and imbalanced dietary patterns during pregnancy which have been strongly associated with the development of OC. In many studies, it has been reiterated that mothers whose dietary intake contains low levels of essential micronutrients present in liver per se such as vitamin B6 and B12, zinc and folate are at higher risk to have infants with OC.<sup>16-19</sup> It has been claimed that using folate supplements alone reduces the risk of oral clefts (20) Nevertheless, recently it was revealed that maternal use of multivitamins containing folic acid rather than folic acid-only when combined with proper dietary patterns rich in fruits, vegetables, whole grains, low-fat dairy food, nuts and liver has a stronger impact on decreasing the risk of OC thereby implying that several micronutrients have a role in that.<sup>19-22</sup> In obese women having pre-pregnancy diabetes, it was also found that the synergistic effect of hyperglycemia coupled with obesity could increase the odds of cleft lip with cleft palate per se.<sup>23</sup>

## Implications

Public health strategies need to be set to promote smoking cessation programs among women with childbearing potential and ensure their access to preconception orientation and awareness sessions on plausible risk factors of oral clefts and importance of adequate dietary patterns as a routine part of prenatal care. These strategies should primarily focus on vulnerable groups including poor and uneducated women to ensure health equity.

Genetic counseling should be conducted for families at high risk of having children with oral clefts.

Health professionals should be well trained to educate pregnant women about various risk factors of OC and to provide parents having a child with cleft with postnatal psychological assistance and adequate information on proper feeding practices and required rehabilitative treatment.

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## Conflicts of interest

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