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Maternal obesity is a risk factor for orofacial clefts: a meta-analysis

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Abstract

Orofacial clefts are the most prevalent birth defects that affect craniofacial structures and implicate genetic and environmental factors in their aetiology. Maternal metabolic state and nutrition have been related to these and other structural malformations, and studies of maternal obesity before pregnancy have shown controversial results about its association with the risk of orofacial clefts in their offspring. Our aim was to assess the combined effect of several single studies of maternal obesity on the risk of orofacial clefts using meta-analysis. We searched for these reports in the PubMed database, and selected 8 studies that met our criteria for eligibility. As a result of this analysis, and using maternal normal weight as a reference, we found that maternal obesity does increase the risk of orofacial clefts in their offspring (OR 1.18, 95% CI 1.11 to 1.26). When these clefts are considered separately, maternal obesity is associated with cleft lip with or without cleft palate (OR 1.13, 95% CI 1.04 to 1.23), and with cleft palate alone (OR 1.22, 95% CI 1.09 to 1.35). Our results support the relation between maternal obesity and orofacial clefts, and confirm two previous meta-analyses that considered fewer studies. However, the molecular mechanisms underlying this statistical evidence have not been fully elucidated.

Keywords: Orofacial clefts; Cleft lip with or without cleft palate; Cleft palate; Maternal obesity; Meta-analysis

Introduction

Among birth defects cleft lip with or without cleft palate and cleft palate alone grouped together as orofacial clefts are the most common birth defects that affect the craniofacial skeleton. The prevalence of cleft lip and palate (1/1000 births) and of cleft palate alone (1/1600 births) varies according to the ethnic origin, geographical location, and socioeconomic group, among other factors.[1] Around 350 syndromes include orofacial clefts among their features, and they comprise about 30% of all clefts. The remaining 70% are isolated (non-syndromic) orofacial clefts.[1] Given their prevalence and the complexity of their rehabilitation plus medical costs and the emotional burden to patients and their families, these malformations are a worldwide public health problem.[2] The aetiology of orofacial clefts can be explained by the interaction between functionally-altered genes and environmental factors.[3] Maternal conditions such as diabetes, alcohol consumption, and smoking before and during pregnancy, have also been associated with these birth defects.[1,4]

According to the World Health Organization (WHO) about 27% of the world's adult population is overweight or obese, with about 300 million obese women.[5] Maternal overweight and obesity before pregnancy have been associated with an increased risk of maternal complications such as pre-

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eclampsia and gestational diabetes, together with perinatal death and congenital malformations.[6] Although the reported effect is modest (around 27% incremental risk), maternal obesity before pregnancy has been identified as a risk factor for orofacial clefts in cohort studies,[7,8] but some case-control studies have failed to pick up the association.[9,10]

Our aim was to evaluate the effect of maternal obesity before pregnancy on the risk of development of orofacial clefts in the offspring using a meta-analysis that combined the individual effects of several relevant studies reported in a scientific database.

Subjects and methods

Extraction of data

We searched the database PubMed up to October 2014 with no restrictions for date of early studies and including the "Related articles" option. For this purpose we used the following terms: "orofacial clefts" OR "cleft lip palate" OR "cleft palate only" OR "oral clefts" AND "maternal obesity" OR "maternal body mass index", and included case-control and cohort studies. This search was made independently by two of us who identified the authors, year of publication, journal, sample size, maternal normal weight before pregnancy, classification criteria for obesity, and results (number of cases and controls among mothers of normal weight and obese).

Statistical analyses

To estimate the effect of maternal obesity before pregnancy we calculated the combined odds ratio (OR) with 95% confidence interval (95% CI), using the effect of maternal normal weight as reference. The presence of heterogeneity among the selected studies was assessed based on the Cochran Q statistic, which is calculated by summing the squared deviations for the effect of each study related to the pooled effect.[11] In addition, heterogeneity was quantified using the I^2 test, which indicates the percentage of between-studies variability that is explained by heterogeneity.[11] The combined effect was therefore estimated using fixed-effects or random effects methods according to the respective absence ($I^2 < 50$) or presence of heterogeneity ($I^2 > 50$).[12] Publication bias was evaluated by visual inspection of the Begg's funnel plot, on which each trail is presented around a central estimator (Napierian logarithm of pooled OR in the ordinate) compared with the standard error (as estimator or study size). If reports are located symmetrically (as a funnel) one can conclude the absence of publication bias (that is, that studies have been published independently of their sample size and of their positive or negative effect).[12] In addition, visual inspection of a funnel plot was complemented by the computation of Eggers statistic, which detects asymmetry from this plot based on a regression model of precision (inverse of standard error) compared with the effect.[12] All tests were calculated with the aid of the statistical package Epidat 3.1.

Results

The initial result of our search showed 26 reports. The reading of the full text of each of these papers permitted us to exclude several studies for the reasons detailed in Fig. 1. Eight reports were then considered for the meta-analysis (Table 1). All these papers classified mothers according to their body mass index (BMI) before pregnancy as normal (BMI 18.5-24.9 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2), the only exception being Cedergren and Källen[7] who classified normal as BMI 19.8-26 kg/m^2 and obese as BMI > 29 kg/m^2, respectively. The number of affected and non-affected children delivered by these mothers is shown in Table 1 as total orofacial clefts, and as cleft lip and palate, and cleft palate alone, separately.

When we considered the total number of orofacial clefts, the meta-analysis showed no evidence of heterogeneity among the 8 studies (Q = 9.38; p = 0.227; I^2 = 25.4%), so the combined effect was estimated by means of fixed effects. Using maternal normal weight as the reference, maternal obesity significantly increased the risk of orofacial clefts in the offspring (OR = 1.18; 95% CI 1.11 to 1.26) (Fig. 2). The individual OR for each study and its contribution (weight (%)) are shown in Fig. 2. The analyses of publication bias showed a borderline asymmetry as can be seen in the Begg's funnel plot (Fig. 3). However, we found no significance in the result of the Egger test (p = 0.907), which shows that this kind of bias is not present in our selection.

Many authors have considered cleft lip and palate and cleft palate alone as two different entities,[3] and so we also assessed the combined effect of segregating by type of orofacial cleft. Six of the 8 studies included data about cleft lip and palate and cleft palate alone separately (Table 1). When we evaluated the overall effect for 6 studies about maternal obesity and the risk for cleft lip and palate in the offspring, the results allowed

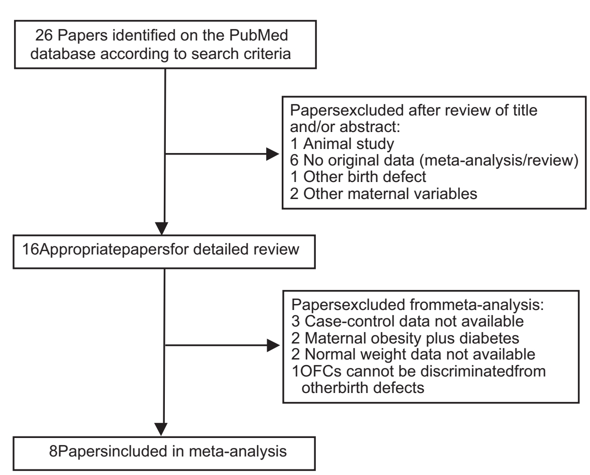

Fig. 1. Algorithm showing how the studies were selected.