Maternal smoking during pregnancy is associated with a higher risk of non-syndromic orofacial clefts in infants

Is there an association between maternal tobacco smoking during pregnancy and nonsyndromic orofacial clefts in infants?

Little J, Cardy A, Munger RG. *Tobacco smoking and oral clefts: a meta-analysis. Bull World Health Organ. 2004; 82:213–218*

Data sources Medline and Embase were searched to 2002 using the search terms “cleft lip”, “cleft palate”, “smoking”, “tobacco”, “cigarette”, “mother” and “maternal”. Reference lists from retrieved articles and a monograph on neural tube defects were also examined for more studies.

Study selection Case-control and cohort studies that reported data on smoking by women during pregnancy were included. The outcomes were orofacial clefts (OFC) in infants, specifically cleft lip with or without cleft palate (CL±P) and cleft palate only (CP). Isolated or multiple defects were included, but syndromic cases were excluded wherever possible.

Data extraction and synthesis Meta-analyses were carried out for CL±P, CP and total clefts. The analyses of CL±P and CP were repeated following stratification by the presence or absence of malformations in addition to the cleft, after the exclusion of studies that used malformed controls. Heterogeneity was assessed using the Q test and a random effect model was used if the *P* value was less than 0.1. Tests for publication bias and presence of a linear dose-response effect were also carried out when suitable data were available.

Results The search identified 32 articles, of which 24 met the inclusion criteria (15 case-control and nine cohort studies). Statistically significant associations were found between maternal smoking and CL±P (relative risk, 1.34; 95% confidence interval, 1.25–1.44), and between maternal smoking and CP (relative risk, 1.22; 95% confidence interval, 1.10–1.35). There was evidence of a modest dose-response effect for CL±P, but the evidence was not clear for CP. No strong evidence of publication bias could be found.

Conclusions This study showed a consistent, moderate association between maternal tobacco smoking during pregnancy and nonsyndromic OFC in infants. The effect was observed for both isolated and multiple clefts, and was stronger and more consistent for CL±P than for CP.

Commentary

The health risks of tobacco smoking are of great interest. Partial and total bans on smoking in public places are being debated in society at present. Often patients ask for advice concerning the potential damaging effects of tobacco smoking. Meanwhile, prevention of OFC would help to reduce the adverse effects of the condition on individuals and families and reduce the burden to health resources. This study aims to answer a clearly defined question regarding the possible increased risk of OFC with maternal tobacco smoking.

Overall, this is an extremely well-conducted review of the available literature. A rigorous search strategy was used. This included the use of appropriate MeSH (Medical Subject Headings) terms relating to both the participants and exposure of interest. Electronic searching only identifies 50% of studies¹ and therefore relevant journals and reference lists from electronically identified studies were also searched by hand. No mention was made of whether publications other than those in the English language or unpublished data were included. This can be a source of bias in study selection with meta-analysis.

The type of studies identified was appropriate. Low-frequency outcomes in causation studies mean that case-control and cohort studies are the only way to evaluate causation effectively.

The search identified 32 studies for possible inclusion. Once reports of the same groups were excluded, 24 cohort and case-control studies were included. This allowed for comparison of more than 15,500 incidents of OFC compared with almost eight million control births with no OFC.

Subtle selection bias may be present in these types of study. This was recognised and a qualitative assessment of potential confounding was undertaken. Heterogeneity and publication bias are dealt with in the method. A description of the potential bias of the primary data is highlighted, such as recall bias in some investigations. Therefore, potential biases are appreciated by the investigators.

A relative risk of more than one implies that exposure is associated with increased risk for an outcome measure, here OFC. It has been suggested that, because of the inherent bias from known and unknown patient confounders, a relative risk should be at least three before definite evidence of the increased risk is established.² Lower values may be acceptable when the outcome is serious, however, as in OFC. Other evidence is discussed to explain the relative risk results, with the suggestion that other aetiological factors are present besides maternal smoking. Other investigators agree that there is multifactorial aetiology for nonsyndromic OFC.³

The results are well interpreted with easy-to-follow guidance regarding anticipated effects of maternal smoking on the increased risk of birth with either CL±P (30%) and CP only (20%).

The authors have suggested that this evidence may be used for helping with cessation of smoking and initial uptake. Previous systematic reviews have demonstrated the difficulty of this approach, however. That evidence shows only a small positive effect on smoking cessation after advice from a healthcare

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professional⁴ or intervention programmes in pregnancy.⁵ A similar result has been seen in the dental practice setting.⁶ Further developments in intervention programmes may allow effective advice. The evidence from this meta-analysis may become an established component of the information given to potential mothers in the future.

Practice point

- Evidence shows only a small positive effect on smoking cessation after advice from a healthcare professional or intervention programmes in pregnancy.

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