Maternal Cigarette Smoking and Oral Clefts: A Population-Based Study

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Abstract: Analyses of 1984 data from the Maryland Birth Defects Reporting and Information System indicate that mothers of infants with oral clefts (cleft lip with or without cleft palate; and cleft palate) smoked more during pregnancy than mothers of infants with other defects (odds ratio OR of 2.56 and 2.39, respectively). There was a dose-response relation between the daily amount smoked and the risk of clefting. Adjustment for available confounding variables did not account for the association between smoking and oral clefts. (*Am J Public Health* 1987; 77:623–625.)

Introduction

Although it is generally accepted that cigarette smoking during pregnancy increases the risk of intrauterine growth retardation, prematurity, perinatal mortality, and spontaneous abortion,[1–3] controversy still exists as to whether or not cigarette smoking increases the risk of congenital malformations.[1] While several studies have reported positive associations between smoking and specific malformations,[4–8] particularly oral clefts,[9–11] others did not find such relationships.[12–21]

In this study, we examined the association between cigarette smoking and oral clefts using data from the Maryland Birth Defects Reporting and Information System (BDRIS). We discuss the importance of grouping malformations into homogeneous categories[22–25] in etiologic studies.

Methods

The Maryland BDRIS is a birth defects monitoring program that has been in operation since September 1983. Details on the system can be found elsewhere.[26] Briefly, BDRIS ascertains infants (live births or fetal deaths more than 500 g or 20 weeks) born with any one of 12 sentinel defects: anencephaly, spina bifida, hydrocephalus, cleft lip with or without cleft palate (CL), cleft palate (CP), esophageal atresia, anal/rectal atresia, hypospadias, reduction and other deformities of upper limbs, reduction and other deformities of lower limbs, congenital dislocation of the hip, and Down syndrome. Cases are ascertained at birth and reported by hospitals on a special form which includes demographics, obstetric variables, and information concerning prenatal illnesses and exposures. Smoking history during pregnancy is usually obtained by an obstetric nurse directly from the mother. Two questions are asked: 1) Did you smoke at any time during pregnancy?; and 2) if yes, how many cigarettes a day? (1–5, 6–10, 11–20, >20). No questions are asked about pre-pregnancy smoking or about smoking status by trimester of pregnancy. Details on the completeness of reporting of the system and descriptive epidemiology of sentinel defects for 1984 are reported elsewhere.[26]

We investigated the 1984 completed BDRIS data. Clefts were divided into CL and CP, and by whether the clefting is the only abnormality or whether it exists with other malformations. The frequency of maternal smoking was compared between the cleft groups and a control group that consisted of all other defects combined, except for Down syndrome. This latter group was excluded because of the reported negative association between smoking and Down syndrome.[27] Although other defects are presented in aggregate, the frequency of smoking was examined among each defect group and was found to be homogeneous. A dose-response effect of smoking on the risk of CL and CP was evaluated using data on the reported amount of smoking (grouped into 0, 1–10, 11–20, >20 cigarettes per day). A linear trend in the effect of smoking on the odds of clefting was tested using the weighted regression model described by Rothman.[28] In further analyses, to examine whether the association between smoking and oral clefts is confounded by demographic variables (such as race, sex, residence, maternal age, parity, etc., or by prenatal events such as drug intake, environmental exposures, and illnesses), stratified analysis was used to examine the effects of smoking on the risk of oral clefts within different levels of other variables (such as among Whites and Blacks separately). Adjusted odds ratios were obtained using the Mantel-Haenzel procedure.[29]

Results

During 1984, the Maryland BDRIS ascertained 28 cases of cleft lip with or without cleft palate (CL) and 26 cases of cleft palate (CP) for rates of 5.0 and 4.6 per 10,000 live births, respectively. In addition, there were 209 cases of other sentinel defects (excluding Down syndrome). Only mothers with known smoking status during pregnancy are included in the analysis (CL: 27/28, CP: 26/26, other defects: 198/209).

As shown in Table 1, cigarette smoking during pregnancy was associated with clefting (odds ratios of 2.56 and 2.39 for CL and CP, respectively). Table 2 shows that, with

TABLE 1—Maternal Cigarette Smoking during Pregnancy and Oral Clefts, Maryland Birth Defects Reporting and Information System, 1984

	Cleft lip ± cleft palate (N = 27)	Cleft palate (N = 26)	Other defects* (N = 198)
No. Smokers	15	14	65
Odds Ratio	2.56	2.39	1.0
95% Confidence intervals	1.13–5.78	1.04–5.45	—

*Other defects include: anencephaly, spina bifida, hydrocephalus, esophageal atresia, anal/rectal atresia, limb reduction deformities, hypospadias, congenital dislocation of the hip. Mothers with unknown smoking status are excluded.

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TABLE 2—Odds Ratios for the Effect of Maternal Cigarette Smoking on Oral Clefts, by Amount Smoked, Maryland Birth Defects Reporting and Information System, 1984

Amount Smoked	Cleft lip ± Cleft palate (N = 25) N	Crude Odds Ratio (95% CI)	Predicted* Odds Ratio (95% CI)	Cleft palate (N = 25) N	Crude Odds Ratio (95% CI)	Predicted* Odds Ratio (95% CI)
0	12	1.0	1.0	12	1.0	1.0
1–10	4	1.17 (.4–3.8)	1.68 (.8–3.3)	7	2.04 (.7–5.6)	2.00 (1.1–3.7)
11–20	6	4.16 (1.4–12.6)	3.04 (1.0–9.5)	4	2.77 (.8–9.6)	4.00 (1.6–9.9)
21+	3	4.75 (1.1–20.8)	4.50 (1.2–16.3)	2	3.17 (.6–17.0)	6.01 (2.2–16.5)

*Predicted odds ratios are obtained by fitting a weighted regression line to case-control odds as described by Rothman.[29]
For CL: odds ratio = 1 + .14 X (X = number cigarettes smoked)
For CP: odds ratio = 1 + .20 X (X = number cigarettes smoked)

TABLE 3—Odds Ratio for the Effects of Maternal Cigarette Smoking on Oral Clefts, by the Presence of Associated Malformations, Maryland Birth Defects Reporting and Information System, 1984

Associated Malformations	Cleft lip ± Cleft palate (N = 27) N	Odds Ratio	95% CI	Cleft palate (N = 26) N	Odds Ratio	95% CI
None	21	3.33	1.3–8.4	17	1.82	.67– 4.9
Multiple	6	1.02	.2–5.7	9	4.09	.99–16.9

TABLE 4—Odds Ratios for the Effect of Maternal Cigarette Smoking on Oral Clefts, Adjusted for Potential Confounding Variables, Maryland Birth Defects Reporting and Information System, 1984

Variables	Cleft lip ± Cleft palate (N = 27) Odds Ratio	95% CI	Cleft palate (N = 26) Odds Ratio	95% CI
Race				
White/Black	2.58	1.1–6.3	2.23	.5–9.4
Sex				
Males/Females	2.55	1.1–6.1	2.67	.7–8.8
Residence				
Baltimore/Other	2.52	1.0–6.2	2.33	.6–8.5
Maternal age (years)				
>30/≤30	2.58	1.0–6.6	2.27	.6–8.0
Parity				
≤2/>2	2.53	1.0–6.2	2.15	.6–8.3
Perceived maternal exposures				
No/Yes	2.44	1.0–6.0	2.28	.6–9.3
Use of birth control				
No/Yes	2.44	1.0–6.0	2.56	1.6–11.0
Drug use				
No/Yes	2.40	.8–6.5	2.30	.6–9.3
URI during pregnancy				
No/Yes	2.63	1.1–6.4	2.23	.6–8.3
Nausea/vomiting				
No/Yes	2.68	1.1–6.4	1.87	.5–7.0

Mothers with unknown status for a variable were excluded.

increasing amounts of smoking, there is a more pronounced association between smoking and clefts for both CL and CP.

When oral clefts were divided into those that occur isolated (about two-thirds of the cases) and those that occur in conjunction with other defects (Table 3), the association between smoking and CL holds only for the isolated CL but not the multiple defect group (odds ratios of 3.33 and 1.02, respectively). For CP, there is a tendency for the reverse to occur (but not statistically significant).

As shown in Table 4, adjustment for a series of potential confounding demographics and perceived exposure variables did not appreciably change the magnitude of association between smoking and clefts. Other available variables such as maternal epilepsy, anticonvulsant use, diabetes, cancer, and emotional disturbances occurred too infrequently to be used for adjustment. Because of the small number of cases in this series, these variables were adjusted one at a time using the Mantel-Haenzel procedure, rather than in a multivariate model.

Discussion

This study has some limitations. Aside from the small sample size, these include:

- the inability to refine the timing of smoking during pregnancy into exposure that occurred during the vulnerable embryological time in the first trimester. Since this misclassification problem is nondifferential among infants with clefts and other defects, its net effect will be to bias the association towards the null;
- underreporting of clefts to the Maryland BDRIS. As shown elsewhere,[26] about 20 per cent of sentinel defects were not reported to the BDRIS in 1984. This underreporting is due, in part, to the loss of cases to District of Columbia area hospitals, but there is no reason to believe it is related to cigarette smoking during pregnancy;
- the possibility of unmeasured confounding variables (for example, a factor not routinely collected via BDRIS is maternal alcohol consumption during pregnancy); and
- the absence of a normal control group.

Although there is much debate in the literature about the appropriate control group in birth defects studies,[30] the use of abnormal controls can be defended here on the basis of two arguments: First, the frequency of smoking among mothers of infants with other defects is similar to the frequency of smoking among females of childbearing age in general, and is within the range of reported smoking frequency among pregnant women in particular.[1] Second, oral clefts stand out as the most consistently found association with smoking,[9–11] and is supported by our inability to find meaningful differ-

ences in the frequency of smoking among mothers of infants with other defects when broken down into specific types of defects. Nevertheless, these findings should be viewed as conservative in the sense that if smoking increases the risk of some other defects, the odds ratios measured here will tend toward unity and against finding an association.

Many previous studies of smoking and birth defects have not refined cases into embryologically and pathogenetically homogeneous categories. Since it is highly unlikely that any putative teratogen can cause an increased risk of all malformations, a negative association between smoking and all defects combined[12,16,19] is not illuminating. Furthermore, because of cumulating evidence from epidemiologic,[23,31] family,[24,32] and embryologic studies[22,25] that the same clinical phenotype (such as cleft palate) may be related to different etiologic and embryologic mechanisms, it is not revealing to report negative associations between smoking and defects of major organ systems (such as cardiovascular musculoskeletal).[16,17] Even studies of specific defects such as oral clefts do not usually separate cases into cleft lip and cleft palate, and into isolated cleft and those with multiple abnormalities[9,18] despite the epidemiologic heterogeneity between the two groups of clefts.[31] The presence of associated defects may point to a chromosonal or Meadelian etiology.[23,32]

If smoking is related to isolated CL but not CL associated with other anomalies, as suggested here, lumping all clefts together for analysis, or with major organ structures (such as craniofacial), may dilute the magnitude of the association between smoking and the specific defect group.

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REFERENCES

1. Schardein JL: Chemically Induced Birth Defects. New York, Basel: Marcel Dekker Inc., 1985; 764–800.
2. Landesman-Dwyer S, Emanuel I: Smoking during pregnancy. Teratology 1979; 10:119–126
3. Johnston C: Cigarette smoking and the outcome of human pregnancies: a status report on the consequences. Clin Toxicol 1981; 18:189–209.
4. Fredrick J, Alberman E, Goldstein H: Possible teratogenic effect of cigarette smoking. Nature 1971; 231:529–530.
5. Kelsey JL, Dwyer T, Holford TR: Maternal smoking and congenital malformations: a community study. J Epidemiol Community Health 1978; 32:102–107.
6. Himmelberger DU, Brown BWm, Cohen EN: Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. Am J Epidemiol 1978; 108:470–479.
7. Naeye RL: Relationship of cigarette smoking to congenital anomalies and perinatal death: a prospective study. Am J Pathol 1978; 90:289–293.
8. Aro T: Maternal diseases, alcohol consumption, and smoking during pregnancy associated with limb reduction defects. Early Hum Dev 1983; 9:49–57.
9. Ericson A, Kallen B, Westerholm P: Cigarette smoking as an etiologic factor in cleft lip and palate. Am J Obstet Gynecol 1979; 135:348–351.
10. Andrews J, McGarry JM: A community study of smoking in pregnancy. Br J Obstet Gynecol 1972; 79:1057–1073.
11. Saxen I: Cleft lip and palate in Finland: parental histories, course of pregnancy and selected environmental factors. Int J Epidemiol 1974; 3:263–270.
12. Kullander S, Kallen B: A prospective study of smoking and pregnancy. Acta Obstet Gynecol Scand 1971; 50:83–94.
13. Hemminki K, Mutanen P, Saloniemi I: Smoking and the occurrence of congenital malformations and spontaneous abortions: multivariate analysis. Am J Obstet Gynecol 1983; 145:61–66.
14. Yerushalmy J: The relationship of parents citarette smoking to outcome of pregnancy—implications as to the problem of inferring causation from observed associations. Am J Epidemiol 1971; 93:443–456.
15. Heinonen OP, Slone O, Shapiro S: Birth Defects and Drugs in Pregnancy. Littleton, MA: Publishing Sciences Group, 1977.
16. Christianson RE: The relationship between maternal smoking and the incidence of congenital anomalies. Am J Epidemiol 1980; 112:684–695.
17. Evans DR, Newcombe RG, Campbell H: Maternal smoking habits and congenital malformations: a population study. Br Med J 1979; 2:171–173.
18. Saxen I: Epidemiology of cleft lip and palate: an attempt to rule out chance associations. Br J Prev Soc Med 1975; 29:103–110.
19. Comstock GW, Shah FK, Meyer MB, Abbey H: Low birth weight and neonatal mortality rate related to maternal smoking and socio-economic status. Am J Obstet Gynecol 1971; 111:53–59.
20. Underwood P, Hester LL, Laffitte T, Gregg KV: The relationship of smoking to the outcome of pregnancy. Am J Obstet Gynecol 1965; 91:270–276.
21. Shiono PH, Klebanoff MA, Berendes HW: Congenital malformations and maternal smoking during pregnancy. Teratology 1986; 34:65–71.
22. Spranger J, Benirschke K, Hall JG, *et al:* Errors of morphogenesis: concepts and terms. J Pediatr 1982; 100:160–165.
23. Khoury MJ, Erickson JD, James LM: Etiologic heterogeneity of neural tube defects: clues from epidemiology. Am J Epidemiol 1982; 115:538–548.
24. Khoury MJ, Erickson JD, James LM: Etiologic heterogeneity of neural tube defects: II. clues from family studies. Am J Hum Genet 1982; 34:980–987.
25. Opitz JM, Gilbert EF: CNS anomalies and the midline as a developmental field. Am J Med Genet 1982; 12:443–445.
26. Khoury MJ, Weinstein A, Panny S, *et al:* Epidemiology of sentinel birth defects in Maryland, 1984. Md Med J 1986; 35:837–845.
27. Hook EB, Cross PK: Cigarette smoking and Down syndrome. Am J Hum Genet 1985; 37:1216–1224.
28. Rothman KJ: Modern Epidemiology. Boston: Little, Brown and Company, 1986; 341–346.
29. Mantel N, Haenzel W: Statistical aspects of the analysis of data from retrospective studies of disease. JNCI 1959; 22:719–748.
30. Bracken MB: Methodologic issues in epidemiologic investigations of drug-induced malformations. *In:* Bracken MB (ed): Perinatal Epidemiology. New York: Oxford University Press, 1984; 423–449.
31. Emanuel I, Culver BH, Erickson JD, *et al:* The further epidemiologic differentiation of cleft lip and palate: a population study of clefts in King county, Washington, 1956–1965. Teratology 1973; 7:271–281.
32. Holmes LB, Driscoll SD, Atkins LA: Etiologic heterogeneity of neural tube defects. N Engl J Med 1976; 294:365–369.