Tobacco and Alcohol Use During Pregnancy and Risk of Oral Clefts

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ABSTRACT

Objectives. This study examined the relationship between maternal tobacco and alcohol consumption during the first trimester of pregnancy and oral clefts.

Methods. Data were derived from a European multicenter case–control study including 161 infants with oral clefts and 1134 control infants.

Results. Multivariate analyses showed an increased risk of cleft lip with or without cleft palate associated with smoking (odds ratio [OR] = 1.79, 95% confidence interval [CI] = 1.07, 3.04) and an increased risk of cleft palate associated with alcohol consumption (OR = 2.28, 95% CI = 1.02, 5.09). The former risk increased with the number of cigarettes smoked.

Conclusions. This study provides further evidence of the possible role of prevalent environmental exposures such as tobacco and alcohol in the etiology of oral clefts. (*Am J Public Health*. 2000; 90:415–419)

Tobacco use and alcohol consumption during pregnancy have been associated with unfavorable pregnancy outcomes, but their teratogenic effects in humans are still debated. Some studies have shown an elevated risk of oral clefts with tobacco smoking during pregnancy,[1–10] whereas other studies have not.[11–15] A recent meta-analysis[16] estimated, for both types of clefts (cleft lip with or without cleft palate and cleft palate only), a small but significant increase in risk; the existence of a dose–response effect is still controversial.

Recently, several studies have suggested an interaction in the risk of oral cleft between maternal smoking and polymorphism of several candidate genes of susceptibility to oral clefts[7,10,14]; other studies have not confirmed this interaction.[9,15] Excessive alcohol consumption during pregnancy is responsible for fetal alcohol syndrome,[17–19] and in 10% of such cases oral cleft has been described.[18] In several case–control studies, alcohol consumption during pregnancy has been reported as a risk factor for oral cleft[20–24]; associated consumption levels vary widely from one study to another, however, and the specific role of high consumption rates or binge drinking has been questioned.

The objective of the present study was to test the existence of a relation between maternal alcohol or tobacco use during the first trimester of pregnancy and oral clefts.

Methods

Data were obtained from a multicenter case–control study conducted between 1989 and 1992 in 4 countries (France [Paris and Bouches du Rhône], the United Kingdom [Glasgow], Italy [Emilia Romagna and Toscana], and the Netherlands [Groningen]) by 6 congenital malformation registries that are part of the European Registration of Congenital Anomalies. The Groningen and Glasgow centers recruited case patients and controls from the general population. In the other centers, recruitment was hospital based for both case patients and controls. The methods used in this investigation have been described in detail elsewhere.[25]

A case patient was defined as any liveborn or stillborn child or fetus from a therapeutic abortion with a major congenital malformation diagnosed prenatally or during the perinatal period (0 to 6 days). In the present analysis, only case patients with a diagnosis of oral cleft (British Paediatric Association Classification of Diseases codes 749.01–749.29[26]) were selected. Cases were then subcategorized as isolated defects (no other major congenital anomalies) or multiple defects.

Despite efforts at exhaustiveness, mothers of only 63% of the eligible case patients could be interviewed, either because the mother left the hospital before the interview or because of refusals from the mother or her physician. In all, 984 cases of malformation, including 161 oral clefts, were included in this study.

One control baby (2 in Glasgow), normal at birth, was selected for each case patient. Controls were born immediately after the case patients and identified in maternity wards in all centers except Groningen and Glasgow, where controls were selected from birth records of the area and matched for date of birth and residence. Refusals were rare in hospital-based centers (less than 10%). In population-based centers, a number of the control mothers who were contacted for participation did not respond (40% in Groningen

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This brief was accepted October 5, 1999.

and 14% in Glasgow); in these instances, infants were replaced by the next child meeting the same criteria.[25] In all, the study included 1134 controls.

We have no information on the families of case patients who were not included in the study, and the direction of the potential bias introduced by this nonparticipation is difficult to infer. With regard to controls, an additional survey in the Netherlands, where participation rates were lowest, indicated that participating mothers were, on average, of higher socioeconomic status than nonparticipants. Because alcohol and tobacco consumption during pregnancy are also socially determined, adjustment for socioeconomic status was necessary in this study.

Medical data concerning birth or abortion were extracted from medical records. Mothers of case patients and controls were interviewed in the maternity hospital or at home (Glasgow, Groningen) by the same investigators; the standardized questionnaire investigated various sociodemographic and medical variables and lifestyle habits. The average delays between birth or abortion and interview were 6.7 days for case patients and 4.6 days for controls in hospital-based centers; in population-based centers, the average delay for both case patients and controls was 1 month.

Smoking and alcohol intake were categorized as follows. The reference categories were nonsmokers (i.e., women who reported that they had never been regular smokers) and nondrinkers (i.e., women who reported consuming less than one drink per day during the first trimester of pregnancy both during the week and on the weekend). Ex-smokers had smoked regularly at some period during their life but had not smoked during pregnancy. Ex-drinkers were women who reported having more than one drink per day before pregnancy but who stopped or decreased to less than one drink per day during the first trimester of pregnancy.

Weekly alcohol consumption, in grams per week, was estimated via computation of a weighted sum of the number of different kinds of drinks (wine, beer, cider, liquor) consumed on weekdays and on weekends during the first trimester of pregnancy. Two categories of weekly consumption were defined according to the median based on the control population: less than 70 g and 70 g or more.

Because our analysis was part of a larger investigation, 2 types of controls were available: controls matched to case patients with oral clefts (n=183) and controls matched to case patients with other malformations (n=951). We verified that these 2 categories of controls did not differ significantly in terms of sociodemographic characteristics, and we chose to consider the overall control group (n=1134) in the analysis. In addition, as a check for consistency, both matched and unmatched estimates were computed in some instances.

A logistic regression model (BMDP software, Statistical Solution, Cork, Ireland) was used in evaluating odds ratios (ORs) and 95% confidence intervals (CIs) associated with tobacco use or alcohol consumption for each type of cleft (cleft lip with or without cleft palate and cleft palate only) and for isolated cleft only. Multivariate models included the following factors: center, maternal age (4 classes), mother's socioeconomic status (4 classes), and area of residence (rural vs urban). Urban residence was defined as residence in a village, small town, or city of 1000 inhabitants or more. We also took alcohol use during the first trimester (yes vs no) into account in analyses of the effects of tobacco, and vice versa.

Results

The investigation included 109 cases of cleft lip with or without cleft palate and 52 cases of cleft palate only. Because of the small number of subjects, the 2 Italian centers were combined in the analysis.

There were no significant differences between the case patients and controls with respect to mother's socioeconomic status, country of birth, age, or chronic illness and obstetric history (Table 1). However, mothers of case patients were more likely to live in rural areas (9.3% vs 4.1%) and reported more infectious diseases during the first trimester (8.1% vs 3.9%). Also, they reported more frequent treatment for insomnia (6.2%) than did control mothers (1.9%).

Depending on the center, between 46% and 64% of mothers of controls were nonsmokers at the time of the pregnancy, and between 5% and 25% were ex-smokers. The adjusted odds ratios for first-trimester maternal smoking (Table 2) were 1.79 (95% CI=1.07, 3.04) for cleft lip with or without cleft palate and 0.86 (95% CI=0.40, 1.87) for cleft palate only. When we considered only the matched controls and performed a conditional logistic regression, the odds ratio estimates for first trimester maternal smoking became 1.69 (95% CI=0.73, 3.94) for cleft lip with or without cleft palate and 1.15 (95% CI=0.30, 4.43) for cleft palate only.

For both types of clefts, offspring of ex-smokers did not have an increased risk, and risks did not vary with time since quitting. For cleft lip with or without cleft palate, we found a significant increase in risk from 1.28 to 2.23 (P<.01) with increasing amounts smoked daily during the first trimester of pregnancy. Restricting these computations to isolated cases did not substantially modify the estimates.

Approximately 17% of the control mothers reported drinking alcohol once a day or more during pregnancy; rates varied substantially between centers, from less than 10% in Groningen to approximately 30% in the Italian centers. Depending on the center, between 2% and 30% of women reported that they had stopped drinking when they became pregnant. For alcohol consumption during the first trimester, we found a significant increase in risk only for cleft palate (OR=2.28, 95% CI=1.02, 5.09) (Table 3). Risks were elevated among ex-drinkers as well. Limiting the calculation to isolated clefts only strengthened the association between alcohol use and both types of clefts (Table 3).

We did not find any increase in risk according to dose for either type of cleft. Restricting the analysis to matched controls in a conditional logistic regression, we obtained odds ratio estimates of 1.38 (95% CI=0.76, 2.52) for cleft lip with or without cleft palate and 1.24 (95% CI=0.66, 2.33) for cleft palate only.

Half of the mothers who reported drinking during the first trimester of pregnancy consumed alcohol only on weekends (n=106). The adjusted odds ratios associated with total weekend consumption (2.5 days) were 2.3 (95% CI=1.0, 5.2) for cleft palate only and 1.1 (95% CI=0.5, 2.1) for cleft lip with or without cleft palate. No increased risk was found when we considered total consumption during the week only (4.5 days); the odds ratio associated with cleft palate was 1.3 (95% CI=0.4, 4.4), and that associated with cleft lip with or without cleft palate was 0.6 (95% CI=0.2, 2.0). Moreover, when we considered consumption on weekend days, we found an increased risk of cleft palate with increasing consumption levels (below the median [31.5 g per weekend], OR=2.04, 95% CI=0.76, 5.47; above the median, OR=2.83, 95% CI=0.88, 9.11).

Tobacco use during the first trimester of pregnancy was significantly associated with consumption of alcohol; among the control mothers, 26% of the smokers drank, compared with 19% of the nonsmokers ($P<.01$). Quantitative consumptions of alcohol and tobacco were correlated. Adjusting the smoking risk estimate for alcohol consumption strengthened the association between smoking and cleft lip with or without cleft palate, while the association between smoking and cleft palate disappeared (Table 2). In contrast, taking smoking into account in a logistic regression model had little effect on the relation between alcohol use and both types of

TABLE 1—Mothers' Sociodemographic and Medical Characteristics: 4-Country Multicenter Study, Europe, 1989–1992

Characteristic	Case Patients (n = 161)		Controls (n = 1134)	
	CP, No. (%) (n = 52)	CL(P), No. (%) (n = 109)	Matched, No. (%) (n = 183)	Other, No. (%) (n = 951)
Socioeconomic status (most recent job before delivery)				
Scientific, technical, professional, managerial	10 (20)	25 (24)	45 (25)	285 (31)
Administrative, sales, services	28 (55)	57 (54)	93 (51)	472 (51)
Agricultural, production	5 (10)	12 (11)	20 (11)	70 (7)
Student, not employed (never worked)	8 (15)	12 (11)	23 (13)	104 (11)
Unknown	1	3	2	20
Country of origin				
Same as child	44 (85)	95 (87)	151 (85)	790 (84)
Foreign	8 (15)	14 (13)	26 (15)	145 (16)
Unknown	. . .	. . .	6	16
Age, y				
≤24	11 (21)	15 (14)	32 (17)	162 (17)
25–29	19 (37)	55 (50)	69 (38)	351 (37)
30–34	13 (25)	24 (22)	57 (31)	287 (30)
≥35	9 (17)	15 (14)	25 (14)	150 (16)
Unknown	. . .	. . .	. . .	1
Residence				
Rural	3 (6)	12 (11)	6 (3)	41 (4)
Urban	49 (94)	97 (89)	177 (97)	909 (96)
Unknown	. . .	. . .	. . .	1
Infectious disease during first trimester of pregnancy				
Yes	5 (10)	8 (7)	5 (3)	39 (4)
No	47 (90)	100 (93)	178 (97)	909 (96)
Unknown	. . .	1	. . .	3
Insomnia treatment				
Yes	6 (12)	4 (4)	4 (2)	17 (2)
No	46 (88)	105 (96)	178 (98)	931 (98)
Unknown	. . .	. . .	1	3

Note. CP = cleft palate only; CL(P) = cleft lip with or without cleft palate. Missing values are excluded from the percentages.

clefts (Table 3). Additional adjustment for treatment for insomnia or infectious disease during the first trimester of pregnancy did not modify these estimates.

Discussion

In regard to cleft lip with or without cleft palate, the magnitude of the odds ratio associated with smoking found in our study is consistent with that found in other studies.[4–9] Specificity in the evaluation of the relation between tobacco and oral clefts was not improved when our analysis was limited to isolated clefts. The finding of an increased risk of cleft lip with or without cleft palate with increasing numbers of cigarettes smoked daily is in accordance with the results of previous studies.[4,5,7] The association observed between smoking and cleft palate disappeared after adjustment for alcohol consumption.

Several previous studies have suggested an association between various levels of alcohol use during the first trimester of pregnancy and primarily cleft lip with or without cleft palate.[20–24] Our study indicated an increased risk, especially of cleft palate, without any dose effect. The analysis limited to isolated clefts resulted in an improved specificity for both types, with an increase on the order of 20% of the value of the odds ratios. Taking smoking into account in examining the relationship between alcohol consumption and oral clefts did not change the relations that we observed.

The high odds ratio observed among ex-drinkers is puzzling and may be explained by our definition of ex-drinkers: women who consumed more than 1 drink per day up to the few weeks before pregnancy and who reported having stopped at the beginning of pregnancy. Some of them may, in fact, have maintained their drinking habits up until pregnancy was recognized.

Interpretation of our work is necessarily limited by the small number of cases, which could explain some of the artifacts in the results. Although only 63% of mothers of eligible case patients were interviewed, there were no systematic reasons for noninclusion that could have led to a selected case group.[25] Two groups of controls (matched and unmatched) were available, and we made sure that the choice of the overall control group did not induce any gross inconsistencies in estimates. Potential confounding by socioeconomic status, as a result of control participation bias in some centers, was taken into account in the analysis via adjustment for this variable.

Measures of tobacco and alcohol consumption were obtained from the mothers via questionnaire and may therefore be subject to recall bias. We compared the proportion of control mothers who reported smoking or drinking during pregnancy with national surveys when available and found similar figures (in France, 22% smokers vs 25% expected, 23% drinkers vs 25% expected).[27] A recent survey carried out in Scotland reported that 36% of Scottish women were current smokers at the time of the survey.[28] In our study, 48% of the controls in Glasgow reported smoking before pregnancy. Also, in our control group, we did find the expected association between smoking and low birthweight. Finally, the specificity of the associations found (between smoking and cleft lip with or without cleft palate and between consumption of alcohol and cleft palate only) tends to indicate that recall bias was not a major problem in our study; otherwise, both types of clefts would have been associated with these exposures.

In conclusion, this study adds another piece of evidence to the possible role of

TABLE 2—Odds Ratios Associated With Smoking During the First Trimester of Pregnancy: 4-Country Multicenter Study, Europe, 1989–1992

	All Clefts							Isolated Clefts					
	Case Patients, No. (%)	Controls, No. (%)	Crude OR	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI	Case Patients, No. (%)	Crude OR	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI
CL(P) (n = 109)													
Nonsmokers	48 (46.1)	630 (56.9)	1.00	1.00	. . .	1.00	. . .	43 (47.8)	1.00	1.00	. . .	1.00	. . .
Ex-smokers	16 (15.4)	177 (16.0)	1.19	0.84	0.46, 1.62	0.96	0.34, 1.51	12 (13.3)	0.99	0.69	0.34, 1.40	0.72	0.33, 2.89
Smokers	40 (38.5)	299 (27.0)	1.76	1.56	0.98, 2.50	1.79	1.07, 3.04	35 (38.9)	1.72	1.47	0.89, 2.43	1.61	0.92, 2.81
No. of cigarettes per day													
1–9	15 (14.4)	136 (12.3)	1.45	1.09	0.56, 2.09	1.28	0.62, 2.73	13 (14.4)	1.40	1.01	0.50, 2.04	1.12	0.50, 2.53
≥10	25 (24.0)	163 (14.7)	2.01	2.08	1.19, 3.62	2.23	1.23, 4.12	22 (24.4)	1.98	1.96	1.09, 3.54	2.03	1.07, 3.85
CP (n = 52)													
Nonsmokers	27 (51.9)	. . .	1.00	1.00	. . .	1.00	. . .	22 (51.2)	1.00	1.00	. . .	1.00	. . .
Ex-smokers	9 (17.3)	. . .	1.19	1.00	0.45, 2.22	1.01	0.43, 2.38	7 (16.3)	1.13	0.93	0.38, 2.27	0.91	0.35, 2.44
Smokers	16 (30.8)	. . .	1.25	1.21	0.62, 2.34	0.86	0.40, 1.87	14 (32.6)	1.34	1.33	0.65, 2.73	0.92	0.74, 2.17
No of cigarettes per day													
1–9	6 (11.5)	. . .	1.03	0.91	0.39, 2.29	0.66	0.22, 2.03	6 (14.0)	1.26	1.09	0.42, 2.80	0.83	0.26, 2.61
≥10	10 (19.2)	. . .	1.43	1.54	0.69, 3.42	1.06	0.43, 2.37	8 (18.6)	1.41	1.63	0.67, 3.98	1.01	0.34, 2.99

Note. Five women among CL(P) cases, and 28 among controls, had unknown smoking status. OR = odds ratio; CI = confidence interval; CL(P) = cleft lip with or without cleft palate; CP = cleft palate only. Missing values are excluded from the percentages.
[a]Adjusted for study center, age, socioeconomic status, and area of residence.
[b]Adjusted for study center, age, socioeconomic status, area of residence, and mother's alcohol consumption.

prevalent environmental exposures such as tobacco and alcohol in the etiology of oral clefts. Whereas our results on the association between tobacco smoking and oral clefts are in accordance with previous studies in terms of cleft lip with or without cleft palate, no association with cleft palate only was found in those studies. Similarly, our specific association between alcohol consumption and cleft palate has not been confirmed in other studies, in which an association with cleft lip with or without cleft palate is mainly found. This demonstrates that the mechanism of action of tobacco and alcohol (if any) in regard to the risk of orofacial cleft is still to be clarified. Determining the role of interacting polymorphisms may be a way of interpreting these divergent findings across populations of various genetic backgrounds. □

Contributors

C. Lorente and S. Cordier were responsible for data analysis and the initial writing of the paper. S. Cordier, J. Goujard, S. Aymé, F. Bianchi, E. Calzolari, H. E. K. De Walle, and R. Knill-Jones were responsible for the planning of the study. Data

TABLE 3—Odds Ratios Associated With Alcohol Consumption During the First Trimester of Pregnancy: 4-Country Multicenter Study, Europe, 1989–1992

	All Clefts							Isolated Clefts					
	Case Patients, No. (%)	Controls, No. (%)	Crude OR	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI	Case Patients, No. (%)	Crude OR	Adjusted OR[a]	95% CI	Adjusted OR[b]	95% CI
CL(P) (n = 109)													
Nondrinkers	78 (71.6)	757 (67.0)	1.00	1.00	. . .	1.00	. . .	65 (69.1)	1.00	1.00	. . .	1.00	. . .
Ex-drinkers	15 (13.8)	184 (16.3)	0.79	0.73	(0.39, 1.36)	0.73	(0.36, 1.45)	14 (14.9)	0.89	0.75	(0.39, 1.43)	0.72	0.35, 1.48
Drinkers	16 (14.7)	189 (16.7)	0.82	1.23	(0.68, 2.24)	1.10	(0.56, 2.17)	15 (16.0)	0.92	1.45	(0.77, 2.72)	1.38	0.69, 2.76
Consumption, g/wk													
<70	10 (9.2)	93 (8.2)	1.04	1.53	(0.74, 3.18)	1.30	(0.57, 2.96)	9 (9.6)	1.13	1.78	(0.82, 3.86)	1.65	0.93, 2.82
≥70	6 (5.5)	96 (8.5)	0.61	0.92	(0.37, 2.25)	0.87	(0.32, 2.39)	6 (6.4)	0.73	1.12	(0.45,2.80)	1.07	0.39, 2.99
CP (n = 52)													
Nondrinkers	29 (56.9)	. . .	1.00	1.00	. . .	1.00	. . .	21 (50.0)	1.00	1.00	. . .	1.00	. . .
Ex-drinkers	8 (15.7)	. . .	1.13	1.55	(0.64, 3.75)	1.70	(0.65, 4.43)	8 (19.1)	1.57	2.35	(0.92, 5.99)	2.42	0.89, 6.60
Drinkers	14 (27.4)	. . .	1.93	2.32	(1.14, 4.70)	2.28	(1.02, 5.09)	13 (30.9)	2.48	2.99	(1.38, 6.45)	2.78	1.16, 6.65
Consumption, g/wk													
<70	10 (19.6)	. . .	2.53	3.15	(1.41, 7.06)	2.76	(1.08, 7.03)	9 (21.4)	3.15	4.10	(1.70, 9.91)	3.31	1.18, 9.25
≥70	4 (7.8)	. . .	1.21	1.41	(0.47, 4.25)	1.74	(0.55, 5.51)	4 (9.5)	1.68	1.88	(0.60, 5.86)	2.22	0.67, 7.34

Note. One woman among CP cases, and 4 among controls, had unknown alcohol status. OR = odds ratio; CI = confidence interval; CL(P) = cleft lip with or without cleft palate; CP = cleft palate only.
[a]Adjusted for study center, age, socioeconomic status, and area or residence.
[b]Adjusted for study center, age, socioeconomic status, area of residence, and maternal smoking.

collection was coordinated by J. Goujard, S. Aymé, F. Bianchi, E. Calzolari, H. E. K. De Walle, and R. Knill-Jones. All of the authors contributed to the writing of the final version of the paper.

Acknowledgments

This study was supported by the following: in France, the Ministry of Research and the Ministry of Health; in Italy, Emilia Romagna Regional Administration and Toscana Regional Administration; in the Netherlands, the Directorate General of Labour of the Ministry of Social Affairs and Employment; in Great Britain, the Health and Safety Executive (grant 1/LMD/126/360/88) and the Greater Glasgow Health Board (Research Support Group); and, in Europe, the European Registration of Congenital Anomalies and BIOMED Concerted Action (grant BMH1-CT93-1585).

We thank the Fondation pour la Recherche Médicale for its financial support. This study was approved when necessary by national committees in charge of confidentiality laws.

The members of the Occupational Exposure and Congenital Malformation Working Group are as follows: Bouches du Rhône, France: S. Aymé and J. Pompili; Emilia Romagna, Italy: E. Calzolari and S. Candela; Glasgow, Scotland: R. Knill-Jones, I. Dale, and A. Nielsen; Groningen, the Netherlands: H. E. K. De Walle, M. C. Cornel, E. Y. Haayer, G. S. Kiel, M. Y M. C. Smeets, and T. M. Pal; Lyons, France: A. Bergeret, B. Dananché, and J. Fevotte; Paris, France: J. Goujard, C. de Vigan, V. Vodovar, and O. Boiron; Toscana, Italy: F. Bianchi, A. Seniori-Costantini, A. Scarpelli, and A. Pierini; and Villejuif, France: S. Cordier, M. C. Ha, and L. Mandereau.

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