First Trimester Exposure to Corticosteroids and Oral Clefts

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BACKGROUND: The possible association between oral cleft in the newborn and maternal exposure to corticoids during pregnancy is still controversial. The aim of this study was to test this association by a case-control analysis using the large multicentric MADRE database. **METHODS**: The MADRE database is a collection of information on malformed infants with a history of maternal first-trimester drug exposure. Nine malformation registries participate in the data collection. Cases were defined as infants presenting with a cleft palate or cleft lip, and exposure was defined by the use of corticosteroids during the first trimester of pregnancy. **RESULTS:** After 12 years of data collection, the database includes data on 11,150 malformed infants. A slight association is observed between exposure to corticoids for systemic use and the occurrence of cleft lip with or without cleft palate (OR, 2.59; 95% CI, 1.18–5.67). **CONCLUSIONS:** If the observed association is real, an interpretation is suggested, based on a likely interaction between corticosteroids and environmental dioxins. It is indeed possible that human fetuses may become sensitive to the teratogenic effect of corticosteroids when they are exposed in utero to environmental pesticides as well. *Birth Defects Research (Part A) 67:968–970, 2003.* © 2003 Wiley-Liss, Inc.

INTRODUCTION

Because glucocorticoids cause cleft palate in sensitive mouse strains (Fraser and Fainstat, 1951), the possible association between use of corticosteroids during pregnancy and occurrence of oral clefts in the newborn has been discussed for many years, and the results are controversial. Some studies recently reported an increased risk for oral clefts after maternal corticosteroid use (Rodriguez-Pinilla and Martinez-Frias, 1998; Carmichael and Shaw, 1999; Park-Wyllie et al., 2000; Edwards et al., 2003), whereas in other studies, no evidence of association appears (Fraser and Sajoo, 1995; Czeizel and Rockenbauer, 1997; Källén et al., 1999). The aim of this study was to test the possible association between corticosteroid exposure and oral clefts using the large MADRE database, which is a collection of information on malformed infants with maternal first-trimester drug exposure (Robert et al., 1994; Arpino et al., 2000).

MATERIALS AND METHODS

Data Collection

The MADRE project collects data yearly on malformed infants exposed to drugs in different parts of the world. Cases with multiple congenital anomalies, recognized syndromes, or known causes such as chromosomal anomalies are also included in the database. Nine malformation registries participate in the data collection and the collected material is stored centrally and coded in a uniform way. After 13 years of data collection (1990–2002), 11,150 cases of congenital malformations (including live births, stillbirths, and induced abortions) with a positive history of first-trimester drug exposure of the mother were reported to the registries participating in the network.

Coding of Malformations and Drugs

Congenital malformations were coded using the ninth revision of the World Health Organization (WHO) International Classification of Diseases, adapted by the British Paediatric Association, known as ICD9/BPA (British Paediatric Association, 1987), and drugs were coded using the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organization, 1990) after exact identification of the drugs reported from different countries (Reynolds, 1989).

Case and Exposure Definition

In the present study, cases were defined as infants presenting with a malformation belonging to one of the following groups—group I: code 749 (cleft palate or cleft lip); group II: code 749.0 (cleft palate); and group III: code 749.1 or 749.2 (cleft lip or cleft lip with cleft palate). Controls were defined as infants presenting with any other birth defect. Exposure

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was defined by the use of corticosteroids (alone or in combination) during the first trimester of pregnancy.

Statistical Analysis

The association between corticosteroid use and presence of malformation was estimated by calculating the crude odds ratios for each registry. To evaluate whether the risk differed across registries, the homogeneity of the odds ratios was tested using the Breslow Day test. Using the Mantel-Haenszel method, registry-adjusted odds ratios with 95% confidence intervals, were calculated.

RESULTS

The ATC list contains 20 hierarchical codes referring to corticosteroids. They are shown in Table 1, which also indicates the drug categories for which there were no exposed infants (NE) in the MADRE database, and those for which there was no infant with oral cleft (NC).

The results of the analysis conducted to test the possible association between corticosteroid use and facial clefts are presented in Table 2. No association appears when all corticosteroids are lumped together, but a slight risk increase is observed for H02B* (ATC group "corticosteroids for systemic use, combinations") and clefts belonging to group I (cleft palate or cleft lip, nine cases) or group III (cleft lip or cleft lip with cleft palate, seven cases). Although not significant, a slight increase is also observed for the ATC group "corticosteroids for systemic use, plain." If all cases exposed to corticosteroids for systemic use (H02A or H02B) are lumped together (24 cases), a decreasing trend in the number of cases per year is observed (11 cases in 1990–1992, 8 cases in 1993–1995, 4 cases in 1996–1998, and 1 case in 1999–2002; Poisson regression; $p < 0.001$).

Table 1
ATC Codes Referring to Corticosteroids

Code		Label
A01AC*	NE	Corticosteroids for local oral treatment
A07EA*		Intestinal antiinflammatory agents/corticosteroids for local use
C05AA*	NC	Products containing corticosteroids
D07*		Corticosteroids, dermatological preparations
D10AA*	NC	Corticosteroids, combinations for treatment of acne
G01B*	NC	Antiinfectives/antiseptics in combination with corticosteroids
H02A*		Corticosteroids for systemic use, plain
H02B*		Corticosteroids for systemic use, combinations
M01BA*	NE	Antiinflam/antirheum. agents in combination with corticosteroids
N02CB*	NE	Corticosteroid derivatives
R01AD*		Decongestants and other nasal prep. for topical use/corticosteroids
R03BA*		Other anti-asthmatics, inhalants/glucocorticoids
S01BA*	NE	Ophthalmologicals/corticosteroids, plain
S01BB*	NE	Ophthalmologicals/corticosteroids and mydriatics in combination
S01CA*	NC	Ophthalmologicals/dexamethasone and antiinfectives
S01CB*	NE	Corticosteroids/antiinfectives/mydriatics in combination
S02B*	NE	Otologicals/corticosteroids
S02C*	NC	Otologicals/corticosteroids and antiinfectives in combination
S03B*	NE	Ophthalmological and otological preparations/corticosteroids
S03C*	NE	Ophthalmological and otological preparations/corticosteroids and antiinfectives in combination

NE, no exposed malformed child; NC, no case of oral cleft.

DISCUSSION

Our findings are based on 11,150 records presently constituting the MADRE database. In a previous analysis based on the first two years of data collection (i.e., 1448 records collected in 1990–1991), Robert et al. (1994) already observed a significant association between the group of cleft palate and cleft lip and corticosteroids for systemic use (ATC code H02) (OR, 3.16; 95% CI, 1.08–7.91). All exposed cases were cleft lip, with or without cleft palate. In our study, if all corticoids for systemic use are lumped together (H02*), the association with cleft lip—with or without cleft palate—remains significant (OR, 1.88; 95% CI, 1.16–3.02). It is noteworthy that the only observed significant association is with corticosteroids for systemic use, which are more likely to reach the embryo than the topical ones. A limitation of our study is the lack of information concerning the underlying maternal condition motivating the steroid use, which could be responsible for some of the increased risk. However, the observed association is unlikely the result of the presence of drugs associated with steroids since only bronchodilators and β-mimetics are among these combinations, and none of these compounds has ever been suspected of having teratogenic effects.

The other epidemiologic studies published during the 1990s on this specific association present inconsistent results. Furthermore, since multiple tests were performed in our analysis, the findings might reflect a random association. We nevertheless suggest a possible explanation for these inconsistent findings. In their metaanalysis, Park-Wyllie et al. (2000) found no significant association between corticosteroids and major malformations in cohort studies, and a clearly significant one in case-control studies. The two series of epidemiological studies differ not only in their design, but also in their period of data collection; most of the cohort studies were conducted in the 1950s, 1960s, or 1970s, while case-control studies were conducted from the end of the 1970s to the end of the 1990s. This difference may reflect a difference in other exposures of the populations, especially to pesticides. Different authors (Birnbaum et al. 1986; Abbott et al., 1994) have shown on mice that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a widespread environmental contaminant, was able to interact synergistically with corticosteroids to induce cleft palate. Human fetuses may become sensitive to the teratogenic effect of corticosteroids when they are exposed in utero to environmental pesticides as well. Risk differences seen among various populations may also reflect differences in pesticides in their environment.

Dioxins are largely spread in the air, land, and water (Dyke et al., 1997). Nevertheless, efforts have been made to reduce the exposure, which has declined in the last few years (Päpke, 1998; Stanley et al., 1998). One would therefore expect a decreasing trend in the number of exposed cases, which is confirmed in our material.

Although we have no direct evidence that any of our cases were associated with maternal dioxin exposure during pregnancy, animal experiments may be considered as an indirect argument in favor of an interaction between corticosteroids

Table 2
Odds Ratios With 95% Confidence Intervals for Each Combination of Oral Cleft and Corticosteroid Exposure[†]

	Type of malformation[a]								
	Group I, cleft palate or cleft lip (n = 982)			Group II, cleft palate (n = 304)			Group III, cleft lip or cleft lip with cleft palate (n = 645)		
ATC code	N[b]	OR[c]	95% CI	N	OR	95% CI	N	OR	95% CI
All corticoids* (n = 387)	37	1.05[e]	0.74–1.49	6	0.64	0.28–1.45	30	1.31[e]	0.90–1.92
A07EA* (n = 14); intestinal antiinflammatory agents/corticosteroids for local use	2	0.63	0.14–2.87	2	2.98	0.68–13.13	0	0	0.00–5.96
D07* (n = 53); corticosteroids, dermatological preparations	3	0.52	0.16–1.64	0	0	0.00–3.41	3	0.73	0.23–2.37
H02A* (n = 155); corticosteroids for systemic use, plain	15	1.25	0.72–2.15	1	0.25	0.04–1.53	13	1.75[e]	0.98–3.11
H02B* (n = 61); corticosteroids for systemic use, combinations	**9**	**2.10**	**1.03–4.26**	2	1.17	0.28–4.92	**7**	**2.59**	**1.18–5.67**
R01AD* (n = 30); decongestants and other nasal prep. for topical use/corticosteroids	5	1.66	0.64–4.31	0	0	0.00–5.88	5	2.48	0.98–6.26
R03BA* (n = 68); other anti-asthmatics, inhalants/ glucocorticoids	4	0.60	0.21–1.67	1	0.64	0.08–5.06	3	0.69	0.22–2.22

[†]Total number of records: n = 11,150; group I may be greater than the sum of group II and group III, since some infants may have an unspecified cleft lip or cleft palate without belonging to group II or III, e.g., code 749.

[a]Group I: ICD code 749 (cleft palate or cleft lip); group II: code 749.0 (cleft palate); and group III: code 749.1 or 749.2 (cleft lip or cleft lip with cleft palate).

[b]Note that the sum of the number of cases exposed to the different steroid categories is greater than the total reported for "all corticoids" since one fetus may be exposed to more than one preparation.

[c]OR, Mantel-Haenszel odds ratio after stratification by Registry.

[d]Heterogeneity between registries.

*Including all subcategories in the hierarchical classification.

Significantly increased odd ratios are indicated in bold.

and dioxins. Furthermore, if maternal dioxin treatment of pregnant mice has been shown to only produce cleft palate in the offspring, there is good evidence from epidemiologic studies that cleft lip and cleft palate share several epidemiological characteristics (Robert et al., 1996), and various environmental factors, such as maternal smoking (Ericson et al., 1979) or use of anticonvulsants, have been shown to increase the risk for both types of clefts (Bossi, 1983).

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