Corticosteroid Use and Risk of Orofacial Clefts

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Background: Maternal use of corticosteroids during early pregnancy has been inconsistently associated with orofacial clefts in the offspring. A previous report from the National Birth Defect Prevention Study (NBDPS), using data from 1997 to 2002, found an association with cleft lip and palate (odds ratio, 1.7; 95% confidence interval [CI], 1.1–2.6), but not cleft palate only (odds ratio, 0.5, 95%CI, 0.2–1.3). From 2003 to 2009, the study population more than doubled in size, and our objective was to assess this association in the more recent data. **Methods:** The NBDPS is an ongoing multi-state population-based case-control study of birth defects, with ascertainment of cases and controls born since 1997. We assessed the association of corticosteroids and orofacial clefts using data from 2372 cleft cases and 5922 controls born from 2003 to 2009. Maternal corticosteroid exposure was based on telephone interviews. **Results:** The overall association of corticosteroids and cleft lip and palate in the new data was 1.0 (95% CI, 0.7–1.4). There was little evidence of associations between specific corticosteroid components or timing and clefts. **Conclusion:** In contrast to the 1997 to 2002 data from the NBDPS, the 2003 to 2009 data show no association between maternal corticosteroid use and cleft lip and palate in the offspring.

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Key words: orofacial clefts; cleft lip and palate; corticosteroids; birth defects; pregnancy

Introduction

Orofacial clefts are one of the most common birth defects in humans, with a world birth prevalence of 1.7 per 1000 live births (Mossey et al., 2009). Orofacial clefts occur when the fusion of the lip and/or palate, which takes place during the first-trimester of pregnancy, is disrupted (Dixon et al., 2011). Corticosteroids are well-established as an experimental teratogen in animal models, causing cleft palate in mice (Fraser and Fainstat, 1951; Walker and Fraser, 1957). Several epidemiological studies have reported an association between corticosteroid use in early pregnancy in humans and delivering an infant with an orofacial cleft (Czeizel and Rockenbauer, 1997; Rodríguez-Pinilla and Luisa Martínez-Frías, 1998; Carmichael and Shaw, 1999; Edwards et al., 2003; Pradat et al., 2003; Carmichael et al., 2007), although others have not (Kallen et al., 1999; Källén, 2003; Hviid and Mølgaard-Nielsen, 2011).

The anti-inflammatory and immune modulating functions of corticosteroids are effective in the treatment of conditions such as asthma, allergic reactions, eczema, psoriasis, rheumatoid arthritis, and inflammatory bowel disease. These conditions are common and often affect women of reproductive age; however, the safety of corticosteroid medication during pregnancy is uncertain.

We previously reported that maternal corticosteroid use was associated with increased risk of cleft lip with or without palate (CLP) (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.1–2.6) but not cleft palate only (CPO) (OR, 0.5; 95%CI, 0.2–1.3), using data from the National Birth Defects Prevention Study (NBDPS) investigating deliveries from October 1997 through December 2002, including mothers of 1141 infants with CLP, 628 infants with CPO and 4143 controls (Carmichael et al., 2007). Since then, the study population has more than doubled in size, allowing the largest study of corticosteroids and clefts to date. Given continued uncertainty about the association between orofacial clefts and corticosteroid medications and the tentative findings from our earlier analyses, our objective here was to assess the association using larger and more recent NBDPS data.

Materials and Methods

We used data from the NBDPS, a population-based, multicenter case–control study of birth defects. Information on deliveries taking place from October 1997 through December 2009 was collected from the 10 NBDPS study centers (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah), although not all study sites contributed for all the study years. The study was approved by institutional review boards of the participating centers and the Centers for

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Disease Control and Prevention. More details on study methods and its surveillance systems can be found elsewhere (Yoon et al., 2001; Rasmussen et al., 2003).

Infants or fetuses with CLP or CPO were considered cases and analyzed separately. Case status was ascertained either through clinical or surgical records or autopsy reports. Medical records for all cases were assessed by a clinical geneticist who ensured that they fulfilled the eligibility criteria. Cases were ineligible if their clefts were believed to result from another defect (e.g., holoprosencephaly) or had a recognized or strongly suspected single-gene disorder or chromosomal abnormality. Cases were considered isolated if there were no accompanying major unrelated birth defects or as nonisolated if more than one additional major unrelated defect was present. Controls (live born infants, without birth defects) were randomly selected from hospital birth records or birth certificates at each study center.

Mothers were interviewed 6 weeks to 24 months after estimated date of delivery, using computer-assisted telephone interviews in English or Spanish; median time between estimated date of delivery and interview was 9.0 months for case mothers (interquartile range 8.0 months) and 8.0 months for controls (interquartile range 7.0 months). Overall participation from 1997 to 2009 was 72% for eligible mothers of infants with clefts and 65% for control mothers (participation in the two time periods declined from 76% to 67% for eligible mothers of infants with clefts and 68% to 61% for control mothers, with an overall decline from 70% to 63%).

In the questionnaires the mothers were asked whether they had specific medical conditions before or during pregnancy and then what medications they used to treat them. Mothers were also asked to list any other medication they had used that was not captured in response to the specific questions; indication was not reported for responses to this question. Mothers were asked for duration and frequency of use for each medication used from 12 weeks before conception to delivery. Medications were coded according to the Slone Epidemiology Center Drug Dictionary. We focused on periconceptional corticosteroid use by any administration route and component (systemic, nasal/inhaled and topical), defined as use that occurred between 4 weeks before through 12 weeks after conception.

We investigated the association between any corticosteroid use during the periconceptional period compared with no use. We also explored whether there was an association with specific timing of exposure, mode of administration, or corticosteroid component. Logistic regression models in SAS software were used to estimate ORs and their corresponding 95% CIs. ORs were only calculated if there were two or more exposed cases and two or more exposed controls. We also examined associations after adjustment for several covariates (maternal race-ethnicity, education, intake of folic acid-containing supplements, smoking, and study center) and after exclusion of nonisolated cases. We present results for deliveries from January 2003 through December 2009, and for pooled data for deliveries from October 1997 through December 2009.

TABLE 1. *Characteristics of mothers of 1577 infants with cleft lip with or without cleft palate (CLP), 795 infants with cleft palate only (CPO), and 5922 nonmalformed control infants*

	Percent (n)[a]		
Variable	**CLP**	**CPO**	**Controls**
Race/ethnicity			
Non-Hispanic white	59 (925)	59 (470)	56 (3330)
Non-Hispanic black	6 (92)	8 (62)	10 (618)
Hispanic	27 (426)	23 (182)	25 (1457)
Other	8 (133)	10 (81)	9 (507)
Unknown	<1 (1)	0	<1 (10)
Education			
<High school graduation	20 (316)	17 (134)	17 (997)
High school graduation	27 (421)	26 (206)	23 (1347)
1–3 years of college	25 (391)	28 (223)	26 (1529)
4+ years college	27 (418)	27 (213)	31 (1860)
Unknown	2 (31)	2 (19)	3 (189)
Smoking			
Any	22 (343)	21 (168)	17 (1008)
None	76 (1204)	77 (610)	80 (4744)
Unknown	2 (30)	2 (17)	3 (170)
Intake of folic acid-containing supplements[b]			
Any	84 (1326)	84 (668)	85 (5046)
None	14 (222)	13 (105)	12 (726)
Unknown	2 (29)	3(22)	3 (150)

NBDPS deliveries 2003–2009.

[a]Percentages may not add to 100% because of rounding.

[b]During the month before and first 3 months of pregnancy.

Results

From 2003 to 2009, the NBDPS enrolled mothers of 1577 children with CLP, 795 children with CPO, and 5922 control children. Demographic characteristics are outlined in Table 1. A total of 89% of the CLP cases ($n = 1402$) and 79% of CPO cases ($n = 631$) were isolated. Any use of corticosteroids four weeks prior through 12 weeks after conception was reported by mothers of 35 (2.3%) infants with CLP (OR, 1.0; 95% CI, 0.7–1.4) and mothers of 13 (1.7%) infants with CPO (OR, 0.7; 95% CI, 0.4–1.2), and by mothers of 137 (2.4%) control infants (Table 2). There was no association by route of administration (systemic, nasal/inhaled, topical or other use) or specific components of corticosteroids (Prednisone,

TABLE 2. *Association of Risk of Cleft Lip and Palate (CLP) and Cleft Palate Only (CPO) among Offspring Born to Women Who Used Maternal Corticosteroid Medications from 4 Weeks before through 12 Weeks after Conception, by Route of Administration and Component Corticosteroid.*

Route of administration and component	N 1997–2002	Odds Ratio (95% CI)[a] 1997–2002	N 2003-09	Odds Ratio (95% CI)[a] 2003-09	N 1997–2009	Odds rratio (95% CI)[a] 1997–2009
Any use						
CLP	33	1.7 (1.1, 2.6)	35	1.0 (0.7, 1.4)	69	1.2 (0.9, 1.6)
CPO	6	0.5 (0.2-1.3)	13	0.7 (0.4, 1.2)	19	0.6 (0.4, 1.0)
Controls	72		137		214	
Any systemic use						
CLP	9	2.1 (0.9, 4.7)	9	1.3 (0.6, 2.8)	18	1.6 (0.9, 2.8)
CPO	2	0.8 (0.2–3.6)	3	0.9 (0.3, 2.8)	5	0.8 (0.3, 2.1)
Controls	16		26		42	
Prednisone						
CLP	8	2.7 (1.1, 6.7)	6	1.4 (0.6, 3.6)	14	1.9 (1.0, 3.7)
CPO	2	1.2 (0.3–5.4)	1	–	3	0.8 (0.2, 2.6)
Controls	11		16		27	
Any nasal spray/inhaled use						
CLP	19	1.5 (0.9, 2.5)	26	1.0 (0.7, 1.6)	46	1.2 (0.8, 1.6)
CPO	5	0.7 (0.3, 1.8)	11	0.8 (0.5, 1.6)	16	0.8 (0.5, 1.3)
Controls	47		96		148	
Beclomethasone						
CLP	5	1.7 (0.6, 4.8)	0	–	5	1.7 (0.6, 4.8)
CPO	2	1.2 (0.3, 5.4)	0	–	2	1.3 (0.3, 5.7)
Controls	11		0		11	
Budesonide						
CLP	3	2.8 (0.6, 12.3)	1	–	4	0.7 (0.3, 2.2)
CPO	2	3.3 (0.6, 17.9)	1	–	3	1.0 (0.3, 3.5)
Controls	4		16		20	
Fluticasone						
CLP	8	1.3 (0.6, 2.9)	18	1.0 (0.6, 1.6)	26	1.0 (0.7, 1.6)
CPO	0	–	7	0.7 (0.3, 1.6)	7	0.5 (0.2, 1.1)
Controls	23		70		93	
Triamcinolone						
CLP	5	2.0 (0.7, 6.1)	2	1.9 (0.3, 10.3)	7	2.0 (0.8, 5.0)
CPO	1	–	0	–	1	–
Controls	9		4		13	
Any topical use						
CLP	2	0.9 (0.2, 4.3)	1	–	3	0.5 (0.2, 1.7)
CPO	0	–	0	–	0	–
Controls	8		14		22	
Other use						
CLP	4	2.9 (0.8, 11.0)	0	–	4	2.5 (0.7, 8.8)
CPO	0	–	0	–	0	–
Controls	5		1		6	

NBDPS deliveries 2003 to 2009*.

[a]Reference groups for the comparisons for the two time intervals included: 2003-09: 1542 CLP cases, 782 CPO cases, and 5785 controls with no exposure from 4 weeks before through 12 weeks after conception; 1997–2009: 2662 CLP cases, 1410 CP cases, and 9849 controls with no exposure from 4 weeks before through 12 weeks after conception. Odds ratios were estimated only if there were at least two exposed cases and two exposed controls.

Beclomethasone, Budesonide, Fluticasone, Triamcinolone). Furthermore, we did not find associations at more specific time windows of exposure (Table 3).

By combining the earlier data with more recent data, the total cohort included mothers of 2731 infants with CLP, 1429 infants with CPO, and 10063 controls, delivered from October 1997 through December 2009. Mothers of 69 (2.6%) infants with CLP (OR 1.2 95% CI, 0.9–1.6), 19 (1.3%) infants with CPO (OR 0.6, 95% CI, 0.4–1.0) and 214 (2.1%) controls reported using any corticosteroids from 4 weeks before 12 weeks after gestation (Table 2). We did not find an association by route of administration or component of corticosteroid in the combined data, with the possible exception of prednisone (OR, 1.9; 95% CI, 1.0–3.7) (Table 2). Results by time window of exposure were inconsistent (Table 3). For CLP, odds ratios ranged from 2.8 (95% CI, 1.3–5.9) for exposures only during week 1 to 4 and 5 to 8 after conception to 0.5 (95% CI, 0.1–1.6) for exposures during weeks 9 to 12.

For analyses of any corticosteroid use we adjusted for maternal race-ethnicity (Non-Hispanic white, Non-Hispanic black, Hispanic, Other, and unknown), education ($<$High school graduation, High school graduation, 1–3 years of college, $\geq$ 4years of college and unknown), intake of folic acid (any, none, and unknown), smoking (any [active], none, unknown), and study center (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah), and we excluded nonisolated cases in the pooled data. We conducted additional analyses restricting to states that participated in the study for the whole time period (Arkansas, California, Georgia, Iowa, Massachusetts, New York, and Texas). These modifications did not appreciably change our estimates. Length of time to interview was slightly shorter for mothers reporting corticosteroid use. This was true for both cases (mean time 9.2 months for mothers reporting corticosteroid use and 10.5 for no use) and controls (mean time 8.2 months for mothers reporting corticosteroid use and 9.1 for no use).

The main results from the two time periods (1997–2002 vs. 2003–2009) are illustrated in Figure 1.

Discussion

Recent data from the NBDPS provided no support for an association between maternal corticosteroid use during early pregnancy and delivering an infant with an orofacial cleft. This is in contrast to results from the first 6 years of the NBDPS, for which there was an association with CLP but not CPO (Carmichael et al., 2007). The component of corticosteroid most strongly associated with delivering an infant with CLP in the data from 1997 to 2002 was systemic prednisone; OR 2.7 (95% CI 1.1–6.7). This association was much weaker in the data from 2003 to 2009; OR 1.4 (95% CI 0.6–3.6).

When comparing corticosteroid use between the early and more recent data (1997–2002 vs. 2003–2009) there was increased use among controls (1.7–2.4%) and CPO cases (1.0–1.7%), however, there was a decrease among CLP cases (2.9 to 2.3%). This resulted in weaker associations with CLP in the more recent data. We are not aware of any significant changes in the study protocol, case ascertainment, or recruitment of cases or controls that could explain these differences. Given the small numbers, it is not possible to determine whether the frequency of reported use represents a trend or lies within the range of normal variation. We therefore suggest that our best estimates of the association of corticosteroids and orofacial clefts in the NBDPS data are those derived from the pooled data. Participation rates declined over the two time periods, from 70% to 63% overall. While this decline is substantial, participation is still in a range usually regarded as acceptable for observational studies.

The strongest association by component observed in the pooled data was for CLP and prednisone (OR, 1.9; 95% CI, 1.0–3.7). The number of control mothers reporting use of prednisone was stable at 0.3% during both time periods (1997–2002 and 2003–2009), while the proportion of case mothers (CLP) reporting prednisone went down from 0.7% to 0.4%. Given the substantial difference between the association in the earlier and later data (ORs of 2.7 vs. 1.4), and its marginal statistical significance, we recommend interpreting this result with caution. This also applies to associations between corticosteroid exposures by specific time period, because they were so variable. The strongest finding was for exposures during week 1 to 4 and 5 to 8 after conception (OR, 2.8; 95% CI, 1.3, 5.9, for the pooled data). The OR in the early data was 7.3 (95% CI, 1.8–29.4) and in the later data 1.9 (95% CI, 0.7–5.0). Although we recommend interpreting these results with caution, an association by timing of exposure cannot be dismissed completely. For comparison, a large US study reported that 0.8% of women received first trimester prescriptions for systemic corticosteroids (Andrade et al., 2004), with actual medication use probably less than 100% (Olesen et al., 2001). Furthermore, the prevalence is similar to what has been found in the National Health and Nutrition Examination Study (NHANES) during the years 1999 to 2008, where 0.5% of women aged 20 to 29 years and 0.6% of women aged 30 to 39 years reported use of oral corticosteroids (Overman et al., 2013). The NHANES data also indicate a trend toward lower prevalence of oral corticosteroid use from 1999 to 2008.

The earliest report of corticosteroids causing clefts was a study in mice (Fraser and Fainstat, 1951). Since then, studies have shown that corticosteroids are involved in cellular processes that lead to fusion of the palatal shelves, which can be disrupted by altering physiological corticosteroid levels (Pratt and Salomon, 1980; Piddington et al., 1983; Ziejewski et al., 2012). Studies have shown that teratogenicity can vary across species (Nau, 1986). Such

TABLE 3. *Association of Risk of Cleft Lip and Palate (CLP) among Offspring Born to Women Who Used Corticosteroids, by Timing of Exposure*

Exposure time period	N 1997–2002	Odds ratio (95% CI)[a] 1997–2002	N 2003-09	Odds ratio (95% CI)[a] 2003-09	N 1997–2009	Odds ratio (95% CI)[a] 1997–2009
Any exposure from 4 weeks before conception through 12 weeks after conception						
CLP	33	1.7 (1.1, 2.6)	35	1.0 (0.7, 1.4)	69	1.2 (0.9, 1.6)
Controls	72		137		214	
Exposed only during 4 weeks before conception						
CLP	5	2.3 (0.8, 7.0)	4	2.5 (0.7, 8.9)	9	2.4 (1.0, 5.5)
Controls	8		6		14	
Pregnancy exposure only during weeks 1–4 after conception						
CLP	3	1.4 (0.4, 5.2)	1	–	5	0.7 (0.3, 1.9)
Controls	8		17		26	
Pregnancy exposure only during weeks 5–8 after conception						
CLP	1	–	0	–	1	–
Controls	1		6		7	
Pregnancy exposure only during weeks 9–12 after conception						
CLP	2	0.7 (0.1, 3.0)	1	–	3	0.5 (0.1, 1.6)
Controls	11		11		23	
Pregnancy exposure during weeks 1–4 and 5–8 after conception						
CLP	6	7.3 (1.8, 29.4)	6	1.9 (0.7, 5.0)	12	2.8 (1.3, 5.9)
Controls	3		12		16	
Pregnancy exposure during weeks 5–8 and 9–12 after conception						
CLP	1	–	3	2.3 (0.5, 9.5)	4	2.1 (0.6, 7.2)
Controls	2		5		7	
Pregnancy exposure during weeks 1–4, 5–8, and 9–12 after conception						
CLP	15	1.4 (0.8, 2.6)	20	0.9 (0.6, 1.5)	35	1.1 (0.7, 1.6)
Controls	39		80		121	

TABLE 3. *Continued*

Exposure time period	N 1997–2002	Odds ratio (95% CI)[a] 1997–2002	N 2003-09	Odds ratio (95% CI)[a] 2003-09	N 1997–2009	Odds ratio (95% CI)[a] 1997–2009
Any exposure during weeks 1–4 or 5–8 after conception						
CLP	26	1.8 (1.1, 2.9)	30	0.9 (0.6, 1.6)	57	1.2 (0.9, 1.6)
Controls	53		120		177	

NBDPS Deliveries 2003–2009.

[a]Reference groups for the comparisons for the two time intervals included: 2003-09: 1542 CLP cases, 782 CPO cases, and 5785 controls with no exposure from 4 weeks before through 12 weeks after conception; 1997–2009: 2662 CLP cases, 1410 CP cases, and 9849 controls with no exposure from 4 weeks before through 12 weeks after conception. Odds ratios were estimated only if there were at least two exposed cases and two exposed controls.

studies have involved systemic corticosteroids, at doses that are 15 to 150 times human doses; thus, their comparability to the human condition is uncertain.

Previous epidemiological studies on corticosteroid use during early pregnancy and the risk of delivering an infant with an orofacial cleft are outlined in Table 4. Systemic corticosteroid use in early pregnancy has been associated with delivering an infant with CLP in some previous epidemiological studies in humans (Czeizel and Rockenbauer, 1997; Rodríguez-Pinilla and Luisa Martínez-Frías, 1998; Carmichael and Shaw, 1999; Pradat et al., 2003; Carmichael et al., 2007), one of which also reported an association with CPO (Carmichael and Shaw, 1999). Studies from Denmark, Norway, Sweden have found no association with systemic use in early pregnancy and orofacial clefts in the offspring, and a weak association with dermatological corticosteroids (Källén, 2003; Hviid and Mølgaard-Nielsen, 2011; Skuladottir et al., 2013). However, a recent population-based cohort study from the UK did not find an association between dermatological corticosteroids and clefts (Chi et al., 2013). In sum, the current literature is inconsistent regarding the association of first-trimester corticosteroid use and orofacial clefts in humans. The previous studies are limited by sample size, with number of cases (CLP and CPO combined) ranging from 8 to 1232.

The NBDPS included 4072 pregnancies resulting in either CLP or CPO, with 23 (0.6%) mothers reporting systemic corticosteroid use, making it the largest study exploring this potential association to date. Other strengths include the population-based design and the detailed assessment on corticosteroid mode, specific component used and the detailed time windows of exposure. We lacked information on dose and indication, which were limitations. Other potential limitations include recall bias (mean time to interview was slightly shorter for the mothers who reported corticosteroid use than the mothers who did not report use) and selection bias (participation was 72% for case mothers and 65% for control mothers). In the NBDPS questionnaire, there is no specific question for dermatological disease or treatment, and dermatological

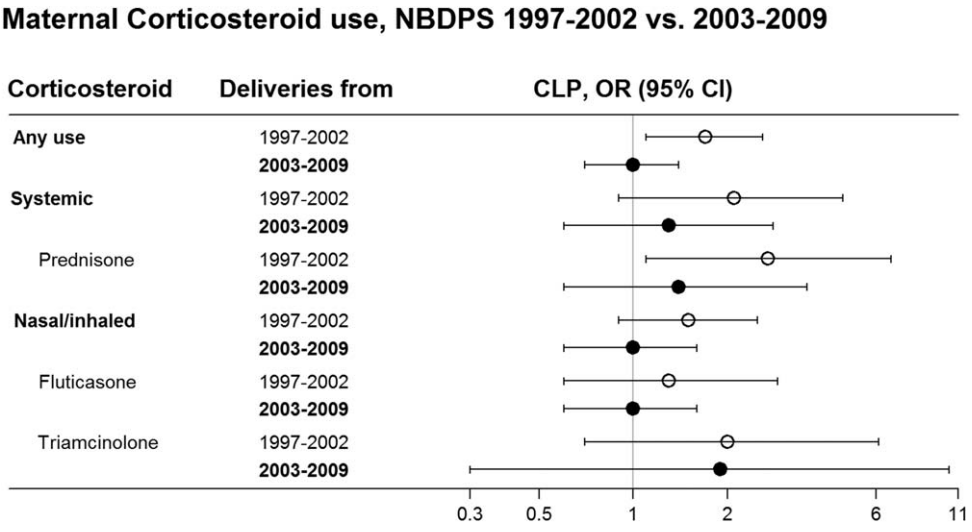

FIGURE 1. *Association of risk of cleft lip and palate (CLP) among offspring born to women who used maternal corticosteroid medications from 4 weeks before through 12 weeks after conception, comparing NBDPS deliveries 1997 to 2002 versus 2003 to 2009. Results are presented in a logarithmic scale.*

TABLE 4. *Summary of Previous Epidemiological Studies on Corticosteroid Use during Pregnancy and Risk of Orofacial Clefts*

	Country/study design/		Relative risk estimates (95% CI)		
Study (year)	**exposure assessment**	**Mode**	**All**	**CLP**	**CP**
Chi et al (2013)	United Kingdom/	Dermatologic	1.9 (0.2–15)		
	Population-based				
	Cohort Study/				
	Drug registry				
Hviid & Molgaard-	Denmark/	Any		1.1 (0.8, 1.4)	1.2 (0.8, 1.8)
Nielsen (2013)	Population-based	Inhaled		0.8 (0.3, 1.7)	0.9 (0.3, 2.9)
	Birth Cohort/	Nasal		0.5 (0.2, 1.2)	1.1 (0.4, 2.6)
	Prescription	Dermatologic		1.5 (1.0, 2.1)	1.5 (0.9, 2.5)
	Drug Registry	Other topical		1.0 (0.6, 1.8)	1.0 (0.4, 2.3)
Carmichael et al	USA/	Any		1.7 (1.1, 2.6)	0.5 (0.2, 1.3)
(2007)	Population-based	Systemic		2.1 (0.9, 4.7)	0.8 (0.2, 3.6)
	Case-control/	Nasal		1.5 (0.9, 2.5)	0.7 (0.1, 1.8)
	Questionnaire	Topical		0.9 (0.2, 4.3)	0
Kallen et al (2003)	Sweden/	Any	1.4 (1.0, 2.0)	1.1 (0.6, 1.9)	1.8 (0.9, 3.2)
	Population-based	Systemic	1.9 (0.8, 4.0)		
	Birth Cohort/	Inhaled	1.2 (0.7, 1.9)		
	Medical	Nasal drops	1.4 (0.6, 2.9)		
	Birth registry	Topical	2.0 (0.6, 5.2)		
Edwards et al (2003)	Australian/	Topical	13.2 (1.7, 586)	11.7 (1.4, 537)	12.0 (1.1, 600)
	Hospital-based				
	Case-control/				
	Questionnaire				
Pradat et al (2003)	Multi National/	Intestinal	0.6 (0.1, 2.9)	0	3.0 (0.7, 13)
	9 Birth	Dermatologic	0.5 (0.2, 1.6)	0.7 (0.2, 2.4)	0
	Defect Registries	Systemic	1.3 (0.9, 2.0)	1.8 (1.0, 3.1)	0.3 (0.0, 1.5)
	Case-control	Systemic combined	2.1 (1.0, 4.3)	2.6 (1.2, 5.7)	1.2 (0.3, 4.9)
		Inhaled	0.6 (0.2, 1.7)	0.7 (0.2, 2.2)	0.6 (0.1, 5.1)
		Nasal	1.7 (0.6, 4.3)	2.5 (1.0, 6.3)	0
Carmichael &	California,	Any		4.3 (1.1, 17)	5.3 (1.1, 27)
Shaw (1999)	USA/Population-based				
	Case-control/				
	Questionnaire				
Rodriguez-Pinilla	Spain/ Hospital-based	Systemic	5.2 (1.5, 17.1)	8.9 (2.0, 38)	
et al (1998)					
	Case-control				
Czeizel et al (1997)	Hungary/	Oral	1.27 (0.8, 2.0)		
	Population-based	Topical	2.21 (1.1, 4.4)		
	Case-control/				
	Questionnaire				

medication is consequently underreported and estimates are therefore inaccurate. Under-reported use of other types of corticosteroids is also possible but difficult to determine.

Conclusion

Maternal use of corticosteroids is not associated with delivering an infant with an orofacial cleft in the NBDPS. This analysis is consistent with recent results from large population-based studies (Källén, 2003; Hviid and Mølgaard-Nielsen, 2011; Skuladottir et al., 2013). These data help to inform the clinical risk-benefit decision for use of corticosteroids during the first trimester of pregnancy.

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