Corticosteroid use during pregnancy and risk of orofacial clefts

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Abstract

Background: The association between the risk of orofacial clefts in infants and the use of corticosteroids during pregnancy is unclear from the available evidence. We conducted a nationwide cohort study of all live births in Denmark over a 12-year period.

Methods: We collected data on all live births in Denmark from Jan. 1, 1996, to Sept. 30, 2008. We included live births for which information was available from nationwide health registries on the use of corticosteroids during pregnancy, the diagnosis of an orofacial cleft and possible confounders.

Results: There were 832 636 live births during the study period. Exposure to corticosteroids during the first trimester occurred in 51 973 of the pregnancies. A total of 1232 isolated orofacial clefts (i.e., cleft lip, cleft palate, or cleft lip and cleft palate) were diagnosed within the first year of life, including 84 instances in which the infant had been exposed to corticosteroids during the first trimester of pregnancy. We did not identify any statistically significant increased risk of orofacial clefts associated with the use of corticosteroids: cleft lip with or without cleft palate, prevalence odds ratio (OR) 1.05 (95% confidence interval [CI] 0.80–1.38]; cleft palate alone, prevalence OR 1.23 (95% CI 0.83–1.82). Odds ratios for risk of orofacial clefts by method of delivery (i.e., oral, inhalant, nasal spray, or dermatologic and other topicals) were consistent with the overall results of the study and did not display significant heterogeneity, although the OR for cleft lip with or without cleft palate associated with the use of dermatologic corticosteroids was 1.45 (95% CI 1.03–2.05).

Interpretation: Our results add to the safety information on a class of drugs commonly used during pregnancy. Our study did not show an increased risk of orofacial clefts with the use of corticosteroids during pregnancy. Indepth investigation of the pattern of association between orofacial clefts and the use of dermatologic corticosteroids during pregnancy indicated that this result did not signify a causal connection and likely arose from multiple statistical comparisons.

The anti-inflammatory and immunosuppressive properties of corticosteroids in pharmacotherapeutic doses has a wide range of clinical uses, such as for the treatment of asthma, atopic dermatitis and other allergic conditions, autoimmune diseases and cancer. However, caution is warranted for the use of corticosteroid medications during pregnancy. Corticosteroid use during pregnancy has been associated with orofacial clefts in animals, and similar risks in humans are suspected.[1,2] The available epidemiologic evidence favours an association, but many of the studies that have been done have been limited by recall bias and a lack of statistical power. The association between risk of orofacial clefts and the use of corticosteroids during pregnancy remains unclear.[3–10]

We conducted a nationwide cohort study in Denmark with independent and prospective determination of corticosteroid use during pregnancy and the diagnosis of orofacial clefts. Our study comprised all live births from January 1996 to September 2008.

Methods

Study cohort

The Danish Medical Birth Registry was established in 1968 and contains information on all births in Denmark.[11] Each record in the registry includes the following information: the personal identification number (a 10-digit number assigned to all people living in Denmark and used in all nationwide registries) of the mother, the father (when known) and the newborn (for all live births); the date and time of birth; any complications during pregnancy or delivery; and the gestational age, birth weight and other physical characteristics of the newborn, including any malformations diagnosed at birth. Estimation of gestational age is primarily done by ultrasound.[12] However, the date of the last menstrual period is sometimes used.

Using the information in the medical birth registry, we constructed a cohort of all live births in Denmark from Jan. 1, 1996, to Sept. 30, 2008. The date on which each pregnancy began was estimated by subtracting the estimated gestational age from the date of birth. Births with missing gestational age (7371 births [0.9%]) were excluded, and the final cohort included 832 636 births.

Use of corticosteroids during pregnancy

Information on all corticosteroid prescriptions given to women in the cohort and filled during the period starting four weeks before pregnancy and ending at birth was obtained from the Danish Prescription Drug Register. This register contains information on all prescriptions filled at Danish pharmacies, the only places in Denmark where prescription drugs can legally be purchased, since 1995. Each record is indexed using the recipient's personal identification number and includes the date on which the prescription was filled, the Anatomic Therapeutic Chemical (ATC) code of the drug (available from www.whocc.no/atc_ddd_index/), the number of packages dispensed, the size of the package dispensed and the number of daily defined doses in the prescription. For the purposes of our study, the date on which the prescription was filled was considered the date of use. We included corticosteroid drugs with the following ATC codes in the study: A01AC, A07EA, C05AA, D07, D10AA, G01B, H02A, H02B, M01BA, N02CB, R01AD, R03BA, S01BA, S01BB, S01CA, S01CB, S02B, S02C, S03B and S03C. We grouped corticosteroid drugs according to the route of administration (oral, inhalant, nasal spray, and dermatologic and other topicals).

Orofacial clefts and other diagnostic information

Infants with orofacial clefts (clefts) were identified through the National Hospital Discharge Register.[13] This registry was established in 1977 and contains information on hospital contacts indexed by the personal identification number. The registry includes information on the dates of admission and discharge as well as the diagnoses at discharge. We had access to data for the period covering Jan. 1, 1996, to Mar. 31, 2009. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was used to code diagnostic information. Clefts were subcategorized as cleft lip with or without cleft palate (ICD-10 codes Q36 and Q37) and cleft palate alone (ICD-10 code Q35). Only diagnoses made during the first year of life were included.

Clefts were further characterized as isolated or as one of multiple birth defects (any diagnosis of a birth defect other than clefts, ICD-10 codes Q00–Q89, during the first year of life) using information from the discharge registry. Orofacial clefts in isolation were used as the main outcome measure.

We excluded children with chromosomal abnormalities (ICD-10 codes Q90–Q99) diagnosed during the first year of life from the cohort.

Potential confounders

We included information on many potential confounders. These confounders were selected using previously described associations with clefts found in the literature.[14–23]

Information on maternal age at the start of pregnancy, parity and smoking status during pregnancy was obtained from the Danish Medical Birth Registry; the mother's place of origin and her place of residence at the start of pregnancy were obtained from the Danish Central Person Register, which contains complete and continually updated demographic information on all Danish residents;[24] the level of education and socioeconomic status of the mother during the year in which pregnancy started was obtained from Statistics Denmark.

Information on the following maternal morbidities was obtained from the discharge registry: infections during the first trimester (ICD-10 codes A00–B99), infections of the genitourinary tract during the first trimester (ICD-10 code O23), diabetes (ICD-10 codes O24 and E10–E14) and epilepsy (ICD-10 codes G40 and G41).

Information on the use of the following additional drugs during the first trimester was obtained from the Danish Prescription Drug Register: antiepileptic medications (ATC code N03), benzodiazepines (ATC code N05BA), β-blockers (ATC code C07A), oral contraceptives (ATC code G03A) and analgesic agents (ATC code N02).

The history of birth defects among siblings dating from the end of the study period back to 1977 was obtained from the discharge registry.

Finally, the year in which pregnancy began was also included in our analysis.

Statistical analysis

We used logistic regression analysis (SAS procedure PROC GENMOD) to estimate prevalence odds ratios (ORs) with 95% confidence intervals (CIs) to compare the prevalence odds of clefts among births with and without exposure to corticosteroids during pregnancy. In our main analysis, we estimated the effects of using corticosteroids during the first trimester (defined as the first 12

weeks after the start of pregnancy), the period including primary organogenesis during which exposure is most likely to cause structural defects.

Covariables that were potential confounders were included in the regression models if they were significant (likelihood ratio test $p < 0.05$) risk factors for clefts in univariable analyses. In univariable analyses, p values were estimated with missing values excluded. The covariables were evaluated separately for cleft lip with or without cleft palate and cleft palate alone, yielding two sets of variables included in all further regression models of the two outcomes. Since the proportions of missing values were all less than 5%, we used mode imputation for missing values in adjusted models.

Table 1: Frequency distributions of exposure to corticosteroids among 832 636 live births in Denmark (part 1 of 2)

Characteristic	No. (%) exposed			No. (%) not exposed	Total no. (%)
	1–4 wk before pregnancy *n = 21 859*	First trimester *n = 51 973*	Second and third trimesters *n =121 690*	*n = 669 142*	
Year of birth					
1996–1998	5 474 (25.0)	12 400 (23.9)	26 894 (22.1)	162 483 (24.3)	199 863 (24.0)
1999–2001	5 257 (24.1)	12 508 (24.1)	28 419 (23.4)	159 424 (23.8)	197 823 (23.8)
2002–2004	5 039 (23.1)	11 943 (23.0)	28 234 (23.2)	154 843 (23.1)	192 674 (23.1)
2005–2008	6 089 (27.9)	15 122 (29.1)	38 143 (31.3)	192 392 (28.8)	242 276 (29.1)
Maternal age at start of pregnancy, yr					
< 18	49 (0.2)	104 (0.2)	186 (0.2)	1 944 (0.3)	2 232 (0.3)
18–24	2 567 (11.7)	6 127 (11.8)	12 670 (10.4)	93 620 (14.0)	111 814 (13.4)
25–29	7 399 (33.9)	17 882 (34.4)	39 959 (32.8)	235 779 (35.2)	290 506 (34.9)
30–34	8 062 (36.9)	18 805 (36.2)	45 840 (37.7)	233 550 (34.9)	294 103 (35.3)
35–39	3 228 (14.8)	7 729 (14.9)	19 818 (16.3)	90 051 (13.5)	115 617 (13.9)
40–44	541 (2.5)	1 284 (2.5)	3 113 (2.6)	13 755 (2.1)	17 787 (2.1)
≥ 45	13 (0.1)	42 (0.1)	104 (0.1)	443 (0.1)	577 (0.1)
Maternal parity					
0	8 655 (39.6)	21 308 (41.0)	48 906 (40.2)	288 720 (43.2)	354 451 (42.6)
1	8 272 (37.8)	19 299 (37.1)	46 192 (38.0)	239 526 (35.8)	301 448 (36.2)
2	3 138 (14.4)	7 373 (14.2)	17 683 (14.5)	91 970 (13.7)	115 647 (13.9)
≥ 3	1 311 (6.0)	2 906 (5.6)	6 623 (5.4)	34 281 (5.1)	43 208 (5.2)
Unknown	483 (2.2)	1 087 (2.1)	2 286 (1.9)	14 645 (2.2)	17 882 (2.2)
Maternal place of residence at start of pregnancy					
Capital region	7 023 (32.1)	16 609 (32.0)	39 430 (32.4)	215 766 (32.3)	268 558 (32.3)
Sealand	2 805 (12.8)	6 470 (12.5)	15 197 (12.5)	85 641 (12.8)	106 128 (12.8)
Southern Denmark	4 764 (21.8)	10 828 (20.8)	24 858 (20.4)	138 892 (20.8)	172 595 (20.7)
Middle Jutland	5 140 (23.5)	12 693 (24.4)	29 206 (24.0)	151 616 (22.7)	190 832 (22.9)
Northern Jutland	2 084 (9.5)	5 228 (10.1)	12 075 (9.9)	66 495 (9.9)	82 736 (9.9)
Unknown	43 (0.2)	145 (0.3)	924 (0.8)	10 732 (1.6)	11 787 (1.4)
Maternal place of origin					
Denmark	18 764 (85.8)	44 414 (85.5)	105 673 (86.8)	572 403 (85.5)	713 522 (85.7)
Europe or North America	886 (4.1)	2 332 (4.5)	5 573 (4.6)	34 463 (5.2)	41 858 (5.0)
Other	2 110 (9.7)	5 036 (9.7)	10 047 (8.3)	59 472 (8.9)	73 876 (8.9)
Unknown	99 (0.5)	191 (0.4)	397 (0.3)	2 804 (0.4)	3 380 (0.4)
Maternal level of education					
Compulsory school	4 801 (22.0)	11 179 (21.5)	24 386 (20.0)	143 542 (21.5)	177 363 (21.3)
Secondary school	2 747 (12.6)	6 510 (12.5)	14 954 (12.3)	87 367 (13.1)	107 553 (12.9)
Vocational training or some postsecondary education	7 941 (36.3)	19 007 (36.6)	44 853 (36.9)	234 366 (35.0)	294 629 (35.4)

Results

A total of 832 636 live births with known gestational age and no chromosomal abnormalities were included in the study cohort. Of these, 798 003 (95.8%) were singleton births and 34 633 (4.2%) were multiple births.

We identified 1232 isolated orofacial clefts diagnosed during the first year of life (305 cleft lips, 570 cleft lips with cleft palates and 357 cleft palates alone). The corresponding rates of isolated clefts diagnosed during the first year of life were 1.48, 1.05 and 0.43 per 1000 births.

In our cohort, 163 494 women (19.6%) used corticosteroids at least once during the period from four weeks before pregnancy to birth. Use

Table 1: Frequency distributions of exposure to corticosteroids among 832 636 live births in Denmark (part 2 of 2)

Characteristic	No. (%) exposed			No. (%) not exposed	Total no. (%)
	1–4 wk before pregnancy *n = 21 859*	First trimester *n = 51 973*	Second and third trimesters *n =121 690*	*n = 669 142*	
Maternal level of education (continued)					
Postsecondary education	5 817 (26.6)	13 830 (26.6)	33 883 (27.8)	175 648 (26.3)	220 046 (26.4)
Unknown	553 (2.5)	1 447 (2.8)	3 614 (3.0)	28 219 (4.2)	33 045 (4.0)
Maternal socioeconomic status					
Unemployed	5 584 (25.6)	13 220 (25.4)	28 606 (23.5)	167 977 (25.1)	207 363 (24.9)
Employment with minimal qualifications	7 640 (35.0)	18 054 (34.7)	42 031 (34.5)	230 945 (34.5)	287 883 (34.6)
Employment with midlevel qualifications	4 422 (20.3)	10 420 (20.1)	25 396 (20.9)	130 737 (19.5)	164 146 (19.7)
Employment with unknown qualifications	1 212 (5.5)	3 040 (5.9)	7 225 (5.9)	41 693 (6.2)	51 414 (6.2)
Self-employed or employed by spouse	488 (2.2)	1 219 (2.4)	3 067 (2.5)	16 387 (2.5)	20 416 (2.5)
Managerial position	2 496 (11.4)	5 966 (11.5)	15 127 (12.4)	78 413 (11.7)	98 146 (11.8)
Unknown	17 (0.1)	54 (0.1)	238 (0.2)	2 990 (0.5)	3 268 (0.4)
Smoking status during pregnancy*					
Did smoke	4 010 (18.3)	9 454 (18.2)	23 013 (18.9)	130 607 (19.5)	161 498 (19.4)
Unknown	832 (3.8)	1 912 (3.7)	4 137 (3.4)	23 179 (3.5)	28 855 (3.5)
History of orofacial clefts among offspring*	48 (0.2)	83 (0.2)	180 (0.2)	1 161 (0.2)	1 422 (0.2)
History of birth defects among offspring*	1 134 (5.2)	2 696 (5.2)	6 347 (5.2)	31 170 (4.7)	39 652 (4.8)
Maternal diseases*					
Infectious disease during first trimester	72 (0.3)	198 (0.4)	382 (0.3)	1 613 (0.2)	2 134 (0.3)
Infection of the genitourinary tract during first trimester	128 (0.6)	291 (0.6)	694 (0.6)	3 092 (0.5)	4 016 (0.5)
History of diabetes	305 (1.4)	717 (1.4)	1 540 (1.3)	7 108 (1.1)	9 193 (1.1)
History of epilepsy	142 (0.7)	317 (0.6)	740 (0.6)	3 663 (0.5)	4 663 (0.6)
Maternal drug use during first trimester*					
Antiepileptic agent	82 (0.4)	213 (0.4)	458 (0.4)	2 165 (0.3)	2 779 (0.3)
Benzodiazepine	137 (0.6)	333 (0.6)	671 (0.6)	2 355 (0.4)	3 245 (0.4)
β-Blocker	98 (0.5)	243 (0.5)	561 (0.5)	2 029 (0.3)	2 741 (0.3)
Oral contraceptive	221 (1.0)	708 (1.4)	1 387 (1.1)	8 012 (1.2)	9 938 (1.2)
Analgesic agent	410 (1.9)	988 (1.9)	1 924 (1.6)	6 251 (0.9)	8 842 (1.1)

*Numbers not shown for women who did not smoke during pregnancy, who did not have previous children with birth defects, who did not have the specified diseases or who did not use the specified drugs.

Table 2: Risk factors associated with isolated orofacial clefts among 832 636 live births in univariable analysis

Risk factor	*N*	*n* (prevalence per 1000 births)	OR (95% CI)	*p* value*
Cleft lip with or without cleft palate				
Year of birth				
1996–1998	199 863	233 (1.17)	1.00	
1999–2001	197 823	218 (1.10)	0.95 (0.79–1.14)	
2002–2004	192 674	215 (1.11)	0.96 (0.80–1.15)	
2005–2008	242 276	209 (0.09)	0.74 (0.61–0.89)	0.006
Maternal residence at start of pregnancy†				
Capital region	268 558	272 (1.01)	1.00	
Sealand	106 128	141 (1.33)	1.31 (1.07–1.61)	
Southern Denmark	172 595	181 (1.05)	1.04 (0.86–1.25)	
Middle Jutland	190 832	202 (1.06)	1.05 (0.87–1.25)	
Northern Jutland	82 736	71 (0.86)	0.85 (0.65–1.10)	0.030
Maternal place of origin‡				
Denmark	713 522	779 (1.09)	1.00	
Europe and North America	41 858	42 (1.00)	0.92 (0.67–1.25)	
Rest of the world	73 876	52 (0.70)	0.64 (0.49–0.85)	0.004
Smoking status during pregnancy§				
Did not smoke	642 283	648 (1.01)	1.00	
Did smoke	161 498	198 (1.23)	1.22 (1.04–1.43)	0.018
History of orofacial clefts among offspring				
No	831 214	864 (1.04)	1.00	
Yes	1 422	11 (7.74)	7.49 (4.12–13.61)	< 0.001
History of birth defects among offspring				
No	795 984	819 (1.03)	1.00	
Yes	36 652	56 (1.53)	1.37 (1.04–1.79)	0.030
Cleft palate alone				
Year of birth				
1996–1998	199 863	104 (0.52)	1.00	
1999–2001	197 823	84 (0.42)	0.82 (0.61–1.09)	
2002–2004	192 674	88 (0.46)	0.88 (0.66–1.17)	
2005–2008	242 276	81 (0.33)	0.64 (0.48–0.86)	0.024
Maternal residence at start of pregnancy†				
Capital region	268 558	91 (0.34)	1.00	
Sealand	106 128	62 (0.58)	1.72 (1.25–2.38)	
Southern Denmark	172 595	97 (0.56)	1.66 (1.25–2.21)	
Middle Jutland	190 832	70 (0.37)	1.08 (0.79–1.48)	
Northern Jutland	82 736	33 (0.40)	1.18 (0.79–1.75)	< 0.001
History of orofacial clefts in offspring				
No	831 214	352 (0.42)	1.00	< 0.001
Yes	1 422	5 (3.52)	8.33 (3.44–20.17)	

Note: CI = confidence interval, OR = odds ratio.
*Likelihood ratio test.
†Women whose place of residence was not known (1.4%) were excluded from the analysis.
‡Women whose country of origin was not known (0.4%) were excluded from the analysis.
§Women for whom smoking status was not known (3.5%) were excluded from the analysis.

of corticosteroids during the first trimester occurred among 51 973 women (6.2%). During this period, dermatologic corticosteroids were the most common form of the drug used (43.3%), followed by other topical forms (23.3%), nasal sprays (21.6%), inhalants (14.3%) and drugs taken orally (4.2%).

Table 1 shows the pattern of corticosteroid use according to the potential confounders that we assessed.

To identify potential confounders for the association between corticosteroid use and risk of orofacial clefts, we first evaluated the univariable associations between the covariables identified as potential confounders and cleft lip with or without cleft palate and cleft palate alone. Table 2 shows the statistically significant (likelihood ratio test $p < 0.05$) risk factors for clefts from the univariable analyses.

Women who used any corticosteroid during the first trimester were not significantly more likely to bear offspring with a cleft lip with or without a cleft palate (crude OR 1.05 [95% CI 0.80–1.37]) or a cleft palate alone (crude OR 1.23 [95% CI 0.83–1.82]) than women who did not use any corticosteroid during the first trimester. Table 3 shows the adjusted ORs for the association between corticosteroid use during the first trimester of pregnancy and clefts. Testing the homogeneity of effects between any use and all possible forms of use yielded a likelihood ratio p value of 0.3174 for cleft lip with or without cleft palate and a likelihood ratio p value of 0.8907 for cleft palate alone. However, the use of dermatologic corticosteroids was associated with an increased risk of cleft lip with or without cleft palate (OR 1.45 [95% CI 1.03–2.05]). Corticosteroids in the form of inhalants, nasal sprays and other topicals were not associated with an increased risk of clefts. None of the infants with clefts had been exposed to oral corticosteroids during the first trimester.

Table 4 shows the results of the exploratory analyses of the effects of exposure to dermatologic corticosteroids. Our classification of use according to the daily defined doses during the first trimester and the potency of the corticosteroid did not reveal clear dose–response or potency–response relations.

Table 3: Association between corticosteroid use during first trimester of pregnancy and isolated orofacial clefts among 832 636 live births

		Cleft lip with or without cleft palate		Cleft palate alone	
Corticosteroid use	No. of live births	No. (prevalence*)	Adjusted OR† (95% CI)	No. (prevalence*)	Adjusted OR‡ (95% CI)
Any use	51 973	57 (1.10)	1.05 (0.80–1.38)	27 (0.52)	1.23 (0.83–1.82)
No use	780 663	818 (1.05)	1.00	330 (0.42)	1.00
Route of administration					
Oral					
Yes	2 195	0 (0.00)	NA	0 (0.00)	NA
No	830 441	875 (1.05)	1.00	357 (0.43)	1.00
Inhalant					
Yes	7 421	6 (0.81)	0.75 (0.34–1.68)	3 (0.40)	0.94 (0.30–2.92)
No	825 215	869 (1.05)	1.00	354 (0.43)	1.00
Nasal spray					
Yes	11 245	6 (0.53)	0.52 (0.23–1.16)	5 (0.44)	1.07 (0.44–2.58)
No	821 391	869 (1.06)	1.00	352 (0.43)	1.00
Dermatologic					
Yes	22 480	34 (1.51)	1.45 (1.03–2.05)	14 (0.62)	1.45 (0.85–2.48)
No	810 156	841 (1.04)	1.00	343 (0.42)	1.00
Other topical form					
Yes	12 091	13 (1.08)	1.04 (0.60–1.79)	5 (0.41)	0.97 (0.40–2.34)
No	820 545	862 (1.05)	1.00	352 (0.43)	1.00

Note: CI = confidence interval, NA = not applicable, OR = odds ratio.
*Per 1000 live births.
†Odds ratio adjusted for year of birth, maternal place of residence at start of pregnancy, maternal place of origin, smoking status during pregnancy, history of orofacial clefts among offspring and history of any birth defects among offspring.
‡Odds ratio adjusted for year of birth, maternal place of residence at start of pregnancy and history of orofacial clefts among offspring.

(Note that the daily defined doses for dermatologic corticosteroids were based on the sizes of the packaging and not on the World Health Organization standards, which do not provide such values for creams and ointments.)

We also compared the use of dermatologic corticosteroids during the first trimester of pregnancy with no use of any corticosteroids during pregnancy and with the use of corticosteroids during other periods of pregnancy. The results of the sensitivity analyses support the results of our main analysis and are summarized in Appendix 1 (available at www.cmaj.ca/cgi/content/full/cmaj.101063/DC1). Also included in Appendix 1 are the fully adjusted models including all variables identified as potential confounders, singleton children alone and alternative definitions of the main period of exposure.

Table 4: Association between use of dermatologic corticosteroid agents during first trimester of pregnancy and isolated orofacial clefts among 832 636 live births

Characteristics of use	Cleft lip with or without cleft palate: first trimester use		Cleft palate alone: first trimester use	
	No.	Adjusted OR* (95% CI)	No.	Adjusted OR† (95% CI)
Medication‡				
Triamcinolone	2	1.36 (0.34–5.47)	0	NA
Hydrocortisone	3	1.28 (0.41–3.98)	1	1.02 (0.14 –7.23)
Betamethasone	8	1.25 (0.62–2.51)	6	2.30 (1.02–5.15)
Hydrocortisone butyrate	15	1.82 (1.09–3.04)	4	1.17 (0.43–3.12)
Fluocinonide	0	NA	1	21.27 (2.95–153.13)
Mometasone furoate	3	0.73 (0.23–2.27)	2	1.21 (0.30–4.86)
Clobetasol	3	1.81 (0.58–5.65)	0	NA
No. of daily defined doses				
5–20	15	1.68 (1.01–2.80)	7	1.87 (0.89–3.97)
25–30	17	1.98 (1.23–3.21)	5	1.42 (0.59–3.44)
35–50	1	0.47 (0.07–3.31)	1	1.13 (0.16–8.07)
> 50	1	0.27 (0.04–1.90)	1	0.66 (0.09–4.71)
Potency§				
Group I: weak	3	1.28 (0.41–3.98)	1	1.02 (0.14–7.23)
Group II: moderately potent	17	1.70 (1.05–2.75)	4	0.96 (0.36–2.57)
Group III: potent	11	0.99 (0.54–1.79)	9	2.00 (1.03–3.87)
Group IV: very potent	3	1.81 (0.58–5.63)	0	NA

Note: CI = confidence interval, NA = not applicable, OR = odds ratio.
*Adjusted for year of birth, maternal place of residence at start of pregnancy, maternal place of origin, smoking status during pregnancy, history of orofacial clefts among offspring and history of any birth defects among offspring.
†Adjusted for year of birth, maternal place of residence at start of pregnancy and history of orofacial clefts among offspring.
‡Budesonide, fluocortolone, clobetasone, fluoprednidene, alclometasone, hydrocortisone buteprate, desoximetasone, fluocinolone acetonide, diflucortolone, diflorasone, fluticasone, halcinonide and flumetasone were also used, but no orofacial clefts were seen among the offspring of women taking these medications.
§See Appendix 1 for definition of potency and categorization.

Interpretation

In a large nationwide cohort of live births, general use of corticosteroids during pregnancy was not significantly associated with an increased risk of orofacial clefts. However, the use of dermatologic corticosteroids was associated with an increased risk of cleft lip with or without cleft palate. In contrast, the use of oral corticosteroids, nasal sprays, inhalants or other topical forms was not associated with an increased risk of clefts.

Systemic corticosteroids have been associated with cleft palate and other adverse events in the fetus in rodents.[1,25–28] Topical corticosteroids are assumed to be safer than systemic corticosteroids. However, corticosteroids have been detected in the fetal blood of some animals after topical application,[29] and topical use of diflorasone diacetate has been associated with cleft palate in rabbits.[30]

Preparations that contain corticosteroids are among the most frequently prescribed dermatologic treatments. They are commonly used during pregnancy for various skin conditions such as eczema and psoriasis. In humans, topical corticosteroids cross the skin barrier. In a study involving young adults with atopic dermatitis, percutaneous application of 1.0% hydrocortisone cream yielded median serum cortisol levels of 125 nmol/L during the acute phase of the condition and 16 nmol/L during remission.[31] Furthermore, it has been shown that even for a low-potency corticosteroid such as hydrocortisone, 15.0% of the dose crosses the placenta unmetabolized.[32] These studies suggest fetal serum cortisol levels in the range of 2.4–18.75 nmol/L after the application of 1.0% hydrocortisone cream to the mother's skin.

Many previous epidemiologic studies, though not all,[7] have reported increased risks of orofacial clefts primarily after the use of oral corticosteroids.[3–6,8–10] However, many of the previous studies were limited by a lack of statistical power. The largest study to date, an American case–control study, included 39 instances of orofacial clefts associated with exposure to corticosteroids,[4] whereas our study included 84 instances associated with exposure during the first trimester. In addition, many of the previous studies determined corticosteroid use through postnatal interviews, which introduced the potential for recall bias.

Studies specifically evaluating topical corticosteroids and orofacial clefts are uncommon.[4–6,8,9] A recent Cochrane review of the safety of topical corticosteroids during pregnancy concluded that the current studies were limited and inconclusive and that cohort studies with very large samples were needed.[33]

Limitations

We relied on national health registers to find infants with orofacial clefts as defined by ICD-10 codes. The predictive value of the diagnosis of birth defects in the National Hospital Discharge Registry has previously been evaluated as being high (88.0%).[34] We would expect these numbers to be higher for clefts alone, and any misclassification would likely bias our results toward no effect.

Our study did not include abortions. This could introduce bias in a study of drug use during pregnancy and the risk of birth defects, if the birth defect itself increases the risk of planned or spontaneous abortion. It is unlikely that such a bias played a role in a study of birth defects such as isolated orofacial clefts.

We relied on a national prescription drug registry to determine corticosteroid use with the assumption that a filled prescription would lead to use of the drug. However, some divergence with respect to use and timing of use is to be expected, and this divergence would bias our results toward no effect. We were not able to include information on over-the-counter use or hospital use of corticosteroids in this study. Again, we expect that any misclassification would bias our results toward no effect.

Confounding by indication is not obvious in our study; the indications for corticosteroid use are many, and none has been associated with orofacial clefts. That no association was seen between corticosteroid use during late pregnancy and risk of orofacial clefts, despite the apparent increase in risk seen with the use of dermatologic corticosteroids during early pregnancy, also supports the minimal impact of confounding by indication.

The absence of risk associated with corticosteroids taken orally or as inhalants seen in our study should be evaluated in the context of the study's statistical power, which was limited, particularly for oral forms of the drug. However, moderate to high risks can be excluded. For example, for inhalants, we can exclude an increase in the risk of cleft lip with or without cleft palate that is higher than 68%.

The observed association between dermatologic corticosteroids and orofacial clefts in our study may be a result of multiple statistical comparisons. Given that exploratory analyses of the dose–response and potency–response relations between the use of dermatologic corticosteroids and cleft lip with or without cleft palate did not support a causal association, we cannot exclude that the observed results are non-causal random effects. The overall association between dermatologic corticosteroids and orofacial clefts appeared to be carried by hydrocortisone butyrate alone, a corticosteroid on the lower end of the potency scale.

Conclusion

Our results add to the safety information for a class of drugs commonly used during pregnancy. Our study did not show an adverse effect of corticosteroid use during pregnancy on the risk of orofacial clefts. However, the absence of risk associated with corticosteroids taken orally or as inhalants seen in our study does not necessarily show that these products are safe for use during pregnancy.

If the observed association between dermatologic corticosteroids and orofacial clefts seen in our study is causal, it is in contrast to the lack of association seen for corticosteroids taken orally or as inhalants. Since indepth investigation of the pattern of association between orofacial clefts and use of dermatologic corticosteroids during pregnancy indicated that this result did not signify a causal connection, it is likely that this association arose from multiple statistical comparisons.

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