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Original article

First-trimester nonsystemic corticosteroid use and the risk of oral clefts in Norway

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ABSTRACT

Purpose: Exposure of pregnant mice to corticosteroids can produce oral clefts in offspring. Although data in humans are more mixed, recent reports have suggested that dermatologic steroids are associated with oral clefts.
Methods: We investigated maternal first-trimester exposure to corticosteroids (focusing on dermatologic uses) and oral clefts in offspring using two population-based studies. The Norway Cleft Study (1996–2001) is a national case-control study including 377 infants with cleft lip ± palate (CLP), 196 infants with cleft palate only (CPO), and 763 controls. The Norwegian Mother and Child Cohort Study (MoBa, 1998–2008) is a national birth cohort including 123 infants with CLP, 61 infants with CPO, and 551 controls.
Results: In the case-control study, there was the suggestion of an association of dermatologic corticosteroids with both CLP (adjusted OR [aOR], 2.3; 95% confidence interval [CI], 0.71–7.7) and CPO (aOR, 3.4; CI, 0.87–13). There was no evidence of this association in the cohort data (odds ratio for CLP, 1.2; CI, 0.50–2.8 and odds ratio for CPO, 1.0; CI, 0.30–3.4), although exposure to dermatologic steroids was less specifically ascertained. There were no associations with other types of corticosteroids.
Conclusions: Our data add to the suggestive but inconsistent findings for this association.
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Introduction

Corticosteroids were the first recognized as a potential human teratogen in the 1950s, when Fraser and Fainstat [1] demonstrated that injection of cortisone in pregnant mice led to clefts in the offspring [2]. Corticosteroids reduce inflammation and modulate immune response and are used to treat a range of clinical condition. Indications include asthma, autoimmune diseases, allergies, eczema, cancer, and rheumatoid arthritis. These various diseases require different modes of administration, potency, dosage, and duration of treatment, which makes epidemiologic studies challenging. Maternal use of corticosteroids during pregnancy has been associated with cleft lip and/or palate (CLP) in some studies [3–9] but not all [10,11], and the question of causation is generally regarded as unresolved [11].

Oral corticosteroids are thought to be more of a concern than steroids applied topically because topical applications are less readily absorbed. However, a recent epidemiologic study from Denmark reported an association of dermatologic corticosteroids with clefts in offspring (adjusted odds ratio [aOR], 1.5; 95% confidence interval [CI], 1.0–2.1) [10].

We explored this hypothesis in two population-based studies. One was a case-control study of facial clefts in Norway, and the other was the Norwegian national birth cohort study. We specifically addressed the question of whether mothers' use of dermatologic corticosteroids during the first trimester increased the risk of CLP in offspring.

Materials and methods

Design

The Norway Cleft Study (case control)

In Norway, the treatment of all babies with CLP is carried out in two specialized surgical centers in Oslo and Bergen. From 1996 to

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2001, the families of all newborn infants in Norway referred for clefts surgery were invited to participate in a case-control study. Controls were randomly selected from all live births during the same period, sampling from the Medical Birth Registry of Norway. Parents of both cases and controls were recruited within the first 3 months after delivery. Details on the study design have been published [12,13]. A total of 653 infants with clefts were eligible for study, and 573 of their families (88%) agreed to participate. There were 1006 randomly selected live-born nonmalformed controls eligible for study, and 763 of their families (76%) agreed to participate.

MoBa (cohort)

From 1999 to 2008, the Norwegian Institute of Public Health conducted a prospective population-based pregnancy cohort study (the Norwegian Mother and Child Cohort Study or MoBa), inviting all pregnant women in Norway to participate. Thirty-nine percent of the expectant mothers consented, and the cohort includes 109,000 children, 91,000 mothers, and 71,700 fathers. Details of study design and demographic characteristics of the cohort have been published [14,15]. Our analysis is based on version 5 of the data files and was approved for studies on risk factors for oral clefts. Within the cohort, 123 cases with CLP and 61 with cleft palate only (CPO) were identified through the Medical Birth Registry of Norway. We randomly selected 551 mothers from the MoBa cohort to serve as controls.

Questionnaire

The Norway Cleft Study (case control)

All mothers in the case-control study completed a self-administered questionnaire after delivery covering demographic information and a wide range of exposures during pregnancy. In particular, mothers were asked detailed questions about their use of prescribed and over-the-counter medications during the first, second and third month of pregnancy. An English translation of the questionnaire is available online [16]. Information on medications was collected for only the first 3 months of pregnancy, which is the period during which exposures can potentially affect the embryologic fusion of the lip (around week 4–6 of embryonic life) and palate (around week 7–10) [17]. Medication was coded according to the Anatomical Therapeutic Chemical Classification System [18]. We included in our analysis all medications containing corticosteroids.

MoBa (cohort)

Mothers in the cohort study were asked to complete self-administered questionnaires at pregnancy week 15, 22, and 30. We used information from the 15-week questionnaire, which focuses on maternal health and use of medications 6 months before pregnancy and during the first 15 weeks of pregnancy. The mean time which the questionnaire was completed was 17.3 weeks (SD 3.0). An English translation of the questionnaire is available online [19]. Medication was again coded according to the Anatomical Therapeutic Chemical Classification System and all medications containing corticosteroids were included.

Case information

The Norway Cleft Study (case control)

Information for cases on accompanying birth defects or syndromes was obtained from three sources: (1) medical records at the hospital performing corrective surgery, (2) the Medical Birth Registry, and (3) the mothers' questionnaire. Cases with no additional malformations or known syndromes were classified as "isolated clefts."

MoBa (cohort)

Cases within the cohort were identified by linking all cohort members with the Medical Birth Registry, which includes information on all defects recorded during the newborn's hospital stay. For oral clefts, the sensitivity of the Medical Birth Registry is 94% for CLP and 57% for CPO [20].

Statistical analysis

Logistic regression models were performed in STATA version 12 (StataCorp. 2011. Stata Statistical Software: Release 12, StataCorp LP, College Station, TX) to estimate the ORs and 95% CIs.

The Norway Cleft Study (case control)

Steroid medications were categorized as any use, use of dermatologic corticosteroids, and "other" corticosteroids. Most women who reported steroid exposure during at least 1 month reported exposure for more than 1 month. Exposure during any of the first 3 months of pregnancy was therefore counted as "exposed." The outcome was total clefts and the two main cleft subtypes (CLP and CPO). We adjusted for the following potential confounders: mother's education (six categories), work status in early pregnancy (yes or no), alcohol intake (total number of drinks during the first 3 months of pregnancy; none, 1–3, 4–6, and 7+), smoking (none, passive only, 1–5 cigarettes/day, 6–10 cigarettes/d, and 11+ cigarettes/d), folic acid supplementation (none, <400 μg/d, and 400+ μg/d), dietary folates (quartiles with cutoffs at 171, 214, and 264 μg/d), multivitamin supplementation (yes or no), and calendar year of baby's birth. The main analyses were performed for all cases regardless of the presence of other defects; in a sensitivity analysis, we restricted the outcome to isolated cases.

MoBa (cohort)

In the questionnaire, mothers were asked for specific symptoms and/or conditions before and during pregnancy and asked to list the medication(s) they used. The timing of exposure (spanning from 6 month before pregnancy to the 15th week) is reported for each condition and/or symptom and not for each medication. This provides difficulties in determining the timing of the exposure when the mother reports using more than one medication for a given symptom/condition. For dermatologic conditions, this was not a big concern as the women who reported using more than one medication, in all cases, reported using another dermatologic corticosteroid. However, the majority of women who were using corticosteroids for other conditions, such as asthma and allergies, also reported using noncorticosteroid medication. Given the small numbers and uncertainty of the timing of exposure, only the dermatologic corticosteroids were analyzed in this study. Exposure during the first 15 weeks of pregnancy counted as "exposed." We adjusted for folic acid use (400 μg/d or none), smoking (none, passive only, and active smoker), mother's education (<high school and high school or more) and alcohol consumption (none or any).

Ethical approval for the Norwegian Cleft Study was granted by the Norwegian Data Inspectorate and the Regional Medical Ethics Committee of Western Norway. The Norwegian Mother and Child Cohort Study was approved by the Regional Committee for Medical Research Ethics in South-Eastern Norway.

Results

The Norway Cleft Study (case control)

Table 1 describes demographic information for mothers of cases and controls. Overall, 4.2% of case mothers (24/573) and 2.5% of

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