High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformations

Lucie Blais, PhD,[a,c,d] Marie-France Beauchesne, PharmD,[a,c,d] Catherine Lemière, MD, MSc,[b,c] and Naoual Elftouh, MSc[c] *Montreal, Quebec, Canada*

Background: Although reassuring data exist on the use of low-to-moderate doses of inhaled corticosteroids (ICSs) during pregnancy, there are inadequate data for women receiving high doses.

Objective: To investigate the association between doses of ICS during the first trimester of pregnancy and the risk of congenital malformations among women with asthma.

Methods: We conducted a cohort study of 13,280 pregnancies of women with asthma (1990-2002) by linking 3 administrative databases from Quebec (Canada). By using generalized estimation equation models, we compared women taking >0 to 1000 μg/d ICS (beclomethasone dipropionate–chlorofluorocarbone equivalent) with women taking >1000 μg/d and those not taking ICSs. The main outcome measures were all and major congenital malformations.

Results: We identified 1257 infants with a congenital malformation (9.5%) and 782 infants with a major malformation (5.9%). We found that women who used >1000 μg/d ICS (n = 154) were significantly more likely (63%) to have a baby with a malformation than the 4392 women who used >0 to 1000 μg/d (adjusted risk ratio, 1.63; 95% CI, 1.02-2.60). On the other hand, women who used >0 to 1000 μg/d were not found to be more at risk than women who did not use ICSs during the first trimester (n = 8734). Nonsignificant trends of similar magnitude were found for major malformations.

Conclusions: Our study adds evidence on the safety of low-to-moderate doses of ICS taken during the first trimester but raises concerns about high doses. However, we cannot rule out the possibility of residual confounding by severity in this association. (J Allergy Clin Immunol 2009;124:1229-34.)

Key words: *Asthma, pregnancy, inhaled corticosteroids, congenital malformations, cohort study*

Asthma is a frequent chronic disease encountered during pregnancy, affecting between 3% and 12% of all pregnant women.[1,2] Although the goals of asthma therapy in pregnant women are similar to the ones for nonpregnant women, they particularly target preventing exacerbations, which would cause a decrease in oxygen supply to the fetus.[1] Inhaled corticosteroids (ICSs) are recognized as the first-line controller therapy, and the same doses are recommended during pregnancy and under other circumstances.[1]

In a recent literature review,[3] we identified 15 studies that investigated the risk of congenital malformations in association with the use of ICSs during pregnancy.[4-18] In 6 of these studies,[4-6,15-17] ICS users were compared with women with asthma who did not use any ICS during pregnancy, whereas in the other studies, ICS users were compared with the general population, women without asthma, or users of theophylline. None of these 6 studies reported a significant increased risk of congenital malformations associated with the use of ICS, but only 1 of these considered the average daily dose of ICSs used during the first trimester of pregnancy[6] and found that high daily doses of ICSs (>1000 μg/d equivalent beclomethasone dipropionate) was associated with a nonsignificant trend toward an increased risk of major malformations (odds ratio [OR], 1.7).

To investigate further the association between the use of different doses of ICSs, and more specifically high doses, during the first trimester of pregnancy and the risk of congenital malformation, we performed a large population-based cohort study including 13,280 pregnancies of women with asthma.

METHODS

Source of data

Data for this study were retrieved from 3 administrative databases from the Canadian province of Quebec. The database of the Régie de l'assurance-maladie du Québec (RAMQ) provides information on medical services dispensed to all residents of Quebec and prescribed medications filled in community pharmacies for residents insured by the RAMQ Drug Insurance Plan, about 42% of the residents of the province.[19] These include the elderly, and the recipients of social welfare since 1980, and since January 1997, 1.7 million other adherents, mainly workers and their families who are not covered under a private drug insurance plan at their workplace. Maintenance et Exploitation des données pour l'étude de la clientèle hospitalière (MED-ECHO) contains information on all hospitalizations occurring in the province, and the Fichier des événements démographiques, administered by the Institut de la statistique du Québec (ISQ), provides information on all births and stillbirths. These databases have often been used in the past for epidemiologic research in the field of asthma.[6,20-23] Data recorded in the RAMQ Medication

From [a]the Faculty of Pharmacy and [b]the Faculty of Medicine, Université de Montréal; [c]the Hôpital du Sacré-Cœur de Montréal; and [d]the Endowment Pharmaceutical Chair AstraZeneca in Respiratory Health, Montreal.

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Reprint requests: Lucie Blais, Université de Montréal, Faculté de pharmacie, CP 6128, succursale Centre-ville, Montréal (Québec), Canada H3C 3J7. E-mail: lucie.blais@umontreal.ca.

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Abbreviations used
ED: Emergency department
ICD-9: International Classification of Diseases, Ninth Revision
ICS: Inhaled corticosteroid
ISQ: Institut de la statistique du Québec
MED-ECHO: Maintenance et Exploitation des données pour l'étude de la clientèle hospitalière
OR: Odds ratio
RAMQ: Régie de l'assurance-maladie du Québec
RR: Risk ratio

Prescriptions database and the medical diagnosis for asthma recorded in the RAMQ Medical Services database have been formally evaluated and found to be valid.[24,25] Moreover, pregnancy-related variables such as birth weight, gestational age, date of conception, and date of delivery directly recorded in or derived from the RAMQ, MED-ECHO, and ISQ databases based on our own algorithms have been formally evaluated and deemed to be highly valid.[26]

Study design

A cohort of pregnancies from women with asthma and their children was formed from the linkage of the RAMQ, MED-ECHO, and ISQ databases. The cohort inclusion criteria were (1) having at least 1 pregnancy from a woman with asthma ending in a delivery (live birth or still birth) between 1990 and 2002, (2) being 13 to 50 years old at conception, (3) having at least 1 diagnosis of asthma (International Classification of Diseases, Ninth Revision [ICD-9] code: 493) and at least 1 prescription for an asthma medication at any time in the previous 2 years or during pregnancy, and (4) being covered by the RAMQ Drug Insurance Plan for at least 1 year before and throughout the duration of the pregnancy. This cohort is an update of our previous cohort of 4561 pregnancies of women with asthma.[6] The cohort was formed of a maximum of 4 pregnancies per woman, keeping the most recent pregnancies. Using gestational age at birth and date of birth of the offspring, we retrospectively identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy.

For each pregnancy included in the cohort, we obtained data on all prescriptions filled by the mother from the RAMQ in the year preceding, during, and 1 year after pregnancy; date of filling, name, dose, dosage form, quantity, and duration of the prescription; and encrypted identification and specialty of the prescribing physician for at least 1 year before and during the pregnancy. We also obtained data from the RAMQ on all inpatient and ambulatory medical services dispensed to the mother, nature of the medical act, date, site of medical practice (outpatient clinic, emergency department [ED], hospitalization), diagnosis code, encrypted identification, and specialty of the treating physician. These data were also obtained for the baby during the first year of life. The RAMQ also provided the date of birth of the mothers and children, whether the mother was receiving social assistance, and the area of residence of the mother during her pregnancy. MED-ECHO provided data on all maternal acute care hospitalizations occurring in the year preceding, during, and after the pregnancy, including principal diagnosis, as many as 15 secondary diagnoses, date of admission, and length of hospitalization, in addition to the length of gestation and birth weight from the delivery hospitalization. With respect to the children, we received hospitalization data for the first year of life. The Fichier des événements démographiques provided data relevant to the level of education of the mother and the parity of the ongoing pregnancy.

Ethics approval

An authorization was obtained from the Commission d'accès à l'information du Québec before requesting and linking the information from the RAMQ, MED-ECHO, and ISQ databases. This research project was approved by the Ethics Committee of the Hôpital du Sacré-Coeur de Montréal.

Congenital malformations

All cases of a congenital malformation were identified within the cohort using ICD-9 diagnosis codes specific to congenital malformations (ICD-9: 152, 155, 186, 188, 190-192, 197-198, 204-205, 237, 740-759, 778) recorded in the RAMQ and MED-ECHO databases. Our list of congenital malformations was compared with the list provided by the Collaborative Perinatal Group[27] and verified by a geneticist from Montreal's Hôpital Ste-Justine for exactness and completeness. An infant was identified as a case if the infant had at least 1 diagnosis of a congenital malformation at birth or during the first year of life recorded in the databases.

The geneticist also classified the malformations as either minor or major. A congenital malformation was classified as major if it could be life-threatening or caused major cosmetic defects and if there was at least 1 hospitalization related to the malformation during the first year of life. All and major congenital malformations were the outcomes under study.

Maternal exposure to ICSs

The use of ICSs (beclomethasone dipropionate, budesonide, fluticasone propionate, flunisolide, and triamcinolone acetonide) during the first trimester of pregnancy was expressed in beclomethasone dipropionate–chlorofluorocarbone equivalent. The daily dose of ICSs was estimated with an algorithm that we developed and used in previous studies and that is based on the name of the medications and equivalences between the different ICS products as recognized by the Canadian Asthma Consensus Guidelines,[28] the dose prescribed, the date and duration of the prescription, and the rate of renewals of the prescription.[6,22] A detailed description of the algorithm can be found in this article's Table E1 in the Online Repository at www.jacionline.org.

The average daily dose of ICSs used during the first trimester was categorized as 0, >0 to 1000, and >1000 μg/d beclomethasone dipropionate–chlorofluorocarbone equivalent (1000 μg beclomethasone dipropionate–chlorofluorocarbone is equivalent to 500 μg fluticasone propionate-hydrofluoro-alcane), with >1000 μg/d recognized as a high daily dose by the Canadian Asthma Consensus Guidelines.[28]

Potential confounding variables

Four categories of variables were considered potential confounding variables. Maternal sociodemographic characteristics included age at conception (13-18, 19-34, 35-45 years), receipt of social assistance during or in the year before pregnancy (yes/no), education ($\leq$11, 12-15, $\geq$16 years, missing), and area of residence at delivery (rural/urban). Pregnancy-related variables included parity (first/second pregnancy or more) and multiple pregnancies (twins or more/singleton). Maternal chronic conditions included chronic hypertension (yes/no), diabetes mellitus (yes/no), epilepsy (yes/no), and use of recognized teratogenic medications during the first trimester of pregnancy (yes/no).[29] Chronic hypertension, diabetes mellitus, and epilepsy were identified from diagnoses or filled prescriptions of related medications 1 year before or during pregnancy by using specific algorithms that we developed for each condition and used in other studies,[6,22] details of which are available on request. Asthma-related variables included the use of inhaled or oral short-acting β_2-agonists (0, >0-3, >3 doses per week), use of long-acting inhaled β_2-agonists (yes/no), use of theophylline (yes/no), use of intranasal corticosteroids (yes/no), and asthma exacerbation (yes/no) in the first trimester of pregnancy. An asthma exacerbation was defined as a filled prescription of oral corticosteroids, an ED visit for asthma, or a hospitalization for asthma. Two or more markers of exacerbation occurring with 15 days were counted as only 1 exacerbation. The severity of asthma before pregnancy was also considered a potential confounding variable and measured with a validated index (mild, moderate, or severe asthma) on the basis of the use of asthma medications and acute care for asthma.[30]

Statistical analysis

We first calculated descriptive statistics for the characteristics of the pregnancies as a function of the daily dose of ICSs during the first trimester. We also estimated the overall prevalence of all and major congenital malformations, and the distribution of specific malformations. In addition to