Risk of congenital malformations for asthmatic pregnant women using a long-acting β_2-agonist and inhaled corticosteroid combination versus higher-dose inhaled corticosteroid monotherapy

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Background: Current recommendations for managing persistent asthma during pregnancy when low-dose inhaled corticosteroids (ICSs) are insufficient include adding a long-acting β_2-agonist (LABA) or increasing the ICS dose. However, there are no data to help clinicians evaluate the safest regimen during pregnancy.

Objective: We sought to compare the risk of major congenital malformations in asthmatic women exposed to a LABA plus ICS combination and those exposed to ICS monotherapy at higher doses during the first trimester.

Methods: A cohort of asthmatic pregnant women exposed to ICSs during the first trimester who delivered between January 1990 and March 2009 was established. The primary outcome was major malformation recorded at birth or during the first year of life. Two subcohorts were established as follows: (1) users of a LABA plus low-dose ICS combination or users of a medium-dose ICS and (2) users of a LABA plus medium-dose ICS combination or users of a high-dose ICS. Generalized estimating equations were used to compare the risk of major malformations between the groups.

Results: In one subcohort there were 643 women who used a LABA plus low-dose ICS and 305 who used a medium-dose ICS; the other subcohort included 198 users of a LABA plus medium-dose ICS and 156 users of a high-dose ICS. The prevalence of major malformations was 6.9% and 7.2%, respectively. The adjusted odds ratio for major malformations was 1.1 (95% CI, 0.6-1.9) when a LABA plus low-dose ICS was used compared with a medium-dose ICS and 1.2 (95% CI, 0.5-2.7) when a LABA plus medium-dose ICS was used compared with a high-dose ICS.

Conclusion: The risk of major malformations was similar with a LABA plus ICS combination and ICS monotherapy at higher doses, suggesting that both therapeutic options can be considered during pregnancy. (J Allergy Clin Immunol 2015;135:123-30.)

Key words: *Asthma, pregnancy, congenital malformations, inhaled corticosteroid, long-acting β_2-agonist, combination therapy, high-dose inhaled corticosteroid, cohort study, comparative safety study, administrative health databases*

Asthma is one of the most common serious diseases among women of childbearing age, affecting 4% to 12% of pregnant women.[1-5] Moreover, pregnant women with severe or uncontrolled asthma are at higher risk of pregnancy complications and adverse fetal outcomes than women with controlled asthma.[4,6-8] Consequently, asthma management guidelines recommend the active treatment of asthma with appropriate medications during pregnancy to prevent asthma symptoms and exacerbation.[4,9,10]

Asthma management during pregnancy is based on a stepwise approach that requires an initial assessment of the level of severity and subsequent evaluations of its control.[4,11] When asthma cannot be controlled with a low dose of inhaled corticosteroid (ICS), the controller therapy options preferred by the guidelines are either addition of an inhaled long-acting β_2-agonist (LABA) to a low-dose ICS or increasing the ICS dose to the medium range. Similarly, for women with more severe asthma that is not controlled with a medium dose of ICS, the guidelines recommend the addition of a LABA to the medium-dose ICS or increasing the ICS dose to the high range.[4,9]

However, there has been no direct comparison of these treatment regimens to guide physicians in whether it is safer to increase the ICS dose during pregnancy or to add a LABA. The current literature reports increasing evidence of the safety of low-to-medium doses of ICSs during pregnancy (compared with no use) but also indicates a possible increased risk of congenital malformations with high ICS doses during pregnancy. There is also evidence that the ICS plus LABA combination is superior to an increased dose of ICS in nonpregnant adults.[9,12] In contrast, only limited observational data are available on the safety of LABAs during pregnancy,[13] and a recently published study by our group reported a significantly increased risk of major cardiac malformations in women exposed to LABAs during the first trimester.[14]

Patients' and physicians' perceptions of the teratogenicity of a medication could influence their decisions to continue or change the treatment regimen during pregnancy.[15-17] Among

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Abbreviations used

ICD-9: *International Classification of Diseases, ninth revision*
ICD-10: *International Classification of Diseases, tenth revision*
ICS: Inhaled corticosteroid
LABA: Long-acting β_2-agonist
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
SABA: Short-acting β_2-agonist

the important clinical decisions that physicians must make if asthma cannot be controlled with a low dose of ICS during pregnancy is whether to prescribe a LABA to supplement the current dose of an ICS or to increase the dose of an ICS. Evidence for the fetal safety of each treatment option is required if an informed decision is to be made. In this study we compared the risk of major congenital malformations in pregnant asthmatic women treated with a LABA/ICS combination and those treated with a higher dose of ICS monotherapy.

METHODS

Sources of the data

The data analyzed in this study were retrieved from the Régie de l'assurance-maladie du Québec (RAMQ) database and the Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (MED-ECHO) database. The RAMQ database contains data on the medical services provided to all residents of Quebec and data on the prescription medications dispensed in community pharmacies for residents covered by the RAMQ's Public Drug Insurance Plan (around 42% of the residents of Quebec). The MED-ECHO database contains data on acute care hospitalization and covers all the residents of Quebec. The validity of the diagnoses of asthma and congenital malformations recorded in the RAMQ and MED-ECHO databases has been formally evaluated, and the data were shown to have a positive predictive value of 75% and a negative predictive value of 96% for asthma diagnoses and values of 82% and 88%, respectively, for diagnoses of congenital malformation.[18,19] The prescription data recorded in the RAMQ database have been formally evaluated and found to be accurate and valid (83% correct identification of the patients and drugs dispensed from the prescriptions).[20]

Study design

A population-based retrospective cohort design was used to achieve our objective. The cohort was selected from the Quebec Asthma and Pregnancy Database, which includes all pregnancies in asthmatic women and a random sample of pregnancies in nonasthmatic women between January 1, 1990, and March 31, 2010, identified from the hospitalization for delivery records in the MED-ECHO database. Using gestational age at birth and date of birth of the newborns, we retrospectively identified the date of the first day of the last menstrual period and the date of delivery for each pregnancy using a validated algorithm.[21] The cohort inclusion criteria were as follows: (1) a pregnancy with a recorded singleton delivery between January 1, 1990, and March 31, 2009, so that at least 1 year of follow-up data were available for the newborn; (2) at least 1 asthma diagnosis in the 2 years preceding delivery (*International Classification of Diseases, ninth revision* [ICD-9], code 493 [except 493.2] or *International Classification of Diseases*, *tenth revision* [ICD-10], code J45); (3) use of ICSs in the first trimester of pregnancy (1-14 weeks); and (4) coverage with the RAMQ's Public Drug Insurance Plan for at least 3 months before and throughout the pregnancy. The exclusion criteria were as follows: (1) multiple births from a single pregnancy, (2) rare maternal condition affecting fetal development (rheumatic disease, Cushing disease, iodine deficiency, adrenal tumor, and folic acid deficiency)[22]; (3) fetal infection[22]; (4) at least 1 filled prescription for a teratogenic medication in the first trimester[23,24]; (5) chronic use of an oral corticosteroid in the first trimester (ie, ≥30-day supply); and (6) at least 1 filled prescription for an oral β_2-agonist, leukotriene receptor antagonist, theophylline, ipratropium, cromoglycate, or nedocromil in the first trimester. For women contributing more than 1 pregnancy during the study period, we included only the 2 most recent pregnancies to allow convergence of regression models. This article reports the first results for congenital malformations derived from the Quebec Asthma and Pregnancy Database.

Congenital malformations

Cases of major congenital malformations were identified by using the ICD-9/ICD-10 hospital-based diagnostic codes recorded in the RAMQ or MED-ECHO databases at birth or during the infant's first year of life. The codes used were specific to congenital malformations (ICD-9: 740-759; ICD-10: Q00-Q99). Our list of malformations was compared with the list provided by the Collaborative Perinatal Group, and their exactness and completeness were verified by a geneticist from le Centre Hospitalier Universitaire Sainte-Justine in Montreal.[25] A congenital malformation was defined as major if it was life-threatening or could cause major cosmetic defects. When a malformation could be classified as major or minor by the geneticist, we considered it major only if there was at least 1 hospitalization with a primary diagnosis or admission diagnosis related to this malformation that was recorded in the MED-ECHO database during the newborn's first year of life. The specific major malformation classes and their related diagnostic codes are presented in Table E1 in this article's Online Repository at www.jacionline.org. The primary outcome was any major congenital malformation.

Subcohorts and assessment of exposure

LABA (salmeterol or formoterol) use was defined as filling at least 1 prescription during the first trimester or 3 months before pregnancy, with the likelihood of its use during the first trimester based on the date and duration of the filled prescription (the algorithm used is available on request). For ICS exposure (fluticasone, beclomethasone, triamcinolone, flunisolide, budesonide, or ciclesonide), we estimated the average daily dose taken during the first trimester. The estimate was made by using an algorithm that we developed for previous studies, which is based on the name of the medication, the equivalence between the different ICS products recognized by the Canadian Asthma Consensus Guidelines (in fluticasone equivalents),[26] the dose prescribed, the date and duration of the filled prescription, and the rate of renewal of the prescription.[27,28] The daily dose of ICS was categorized as follow: low dose (>0-250 μg), medium dose (>250-500 μg), and high dose (>500 μg). These algorithms accounted for the combination therapy (LABA plus ICS) being administered with a fixed-combination inhaler (salmeterol/fluticasone or formoterol/budesonide) or with separate inhalers. Two subcohorts were established to compare the treatment regimens indicated for women with similar levels of asthma severity. In the first subcohort (hereafter referred to as the *moderate asthma subcohort*) we compared women who used a LABA plus low-dose ICS with those who used medium-dose ICS monotherapy. In the second subcohort (hereafter referred to as the *severe asthma subcohort*) we compared women who used a LABA plus medium-dose ICS with those who used high-dose ICS monotherapy.

Confounding variables

The following variables were identified in the literature as risk factors for congenital malformations and were considered potential confounders in our analysis: maternal age at the beginning of pregnancy (18-34 and <18 or ≥35 years),[29] receipt of social assistance during pregnancy (yes/no),[30] area of residence at delivery (rural/urban),[31,32] chronic hypertension (yes/no),[33] diabetes mellitus (yes/no),[22,33] exacerbation of asthma (defined as a filled prescription for an oral corticosteroid, an emergency department visit, or a hospitalization for asthma) 3 months before pregnancy (yes/no),[8] and