Intranasal triamcinolone use during pregnancy and the risk of adverse pregnancy outcomes

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Background: Intranasal corticosteroid use during pregnancy has increased over the past decade.

Objective: We aim to estimate the safety of intranasal triamcinolone use during pregnancy, which was introduced for over-the-counter use in October 2013.

Methods: We designed a population-based prospective cohort study. From a cohort of 289,723 pregnancies in Montreal, Quebec, Canada, from 1998-2008, intranasal triamcinolone–exposed, other intranasal corticosteroid–exposed, and nonexposed women during the first trimester were studied for major congenital malformations (overall and organ specific) and spontaneous abortions and during the second/third trimesters for small-for-gestational age (SGA) newborns. The first trimester is the time window of interest for malformations and spontaneous abortion (organogenesis), and the second/third trimesters are the time windows of interest for SGA (fetal growth). Logistic regression model–based generalized estimating equations were used.

Results: Adjusting for potential confounders, use of intranasal triamcinolone during the first trimester of pregnancy was not significantly associated with the risk of overall congenital malformations (odds ratio [OR], 0.88; 95% CI, 0.60-1.28; 31 exposed cases) compared with nonexposure; however, it was associated with the risk of respiratory defects (OR, 2.71; 95% CI, 1.11-6.64; 5 exposed cases). Pregnancy exposure to intranasal triamcinolone was not significantly associated with the risk of spontaneous abortion (OR, 1.04; 95% CI, 0.76-1.43; 50 exposed cases). No association was found between second- or third-trimester exposure to intranasal triamcinolone and the risk of SGA (OR, 1.06; 95% CI, 0.79-1.43; 50 exposed cases).

Conclusions: Maternal exposure to intranasal triamcinolone during pregnancy was not associated with the risk of SGA/spontaneous abortions/overall malformations. However, it has been shown to increase the risk of respiratory system defects. Chance finding cannot be ruled out. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: *Triamcinolone, rhinitis, pregnancy, major congenital malformations, small for gestational age, spontaneous abortions*

Intranasal triamcinolone was introduced on the market as a prescription drug in the United States and Canada in 1996. It was approved for over-the-counter (OTC) use in October 2013 in the United States and January 2015 in Canada. Nevertheless, the US Food and Drug Administration (FDA) and Health Canada have not changed it from pregnancy category C.

Intranasal triamcinolone is indicated for the treatment of allergic rhinitis (AR), an inflammatory disease of the nasal mucous membranes.[1,2] The introduction of an allergen into the nose produces an IgE-mediated inflammatory response, which results in symptoms ranging from sneezing and itching to severe nasal obstruction.[1,2] AR is the most common allergic disease and affects approximately 20% to 30% of women of childbearing age.[3] Previous studies suggested that for 10% to 30% of women, allergic symptoms will increase during pregnancy and will return to prepregnancy status after delivery.[4,5] This variation in symptoms depends in part on whether the pregnancy occurs during the seasonal allergy season. Uncontrolled upper airway disease during gestation leads to lower quality of life and might trigger asthma onset or aggravate comorbid asthma, which could unfavorably affect pregnancy outcome.[6]

Pharmacologic treatments for AR include antihistamines, decongestants, intranasal corticosteroids, mast cell stabilizers, and immunotherapy.[3] In their systematic review of AR drug treatment during pregnancy, Gilbert et al[3] and the Allergic Rhinitis and its Impact on Asthma guidelines[6] recommended intranasal corticosteroids as first-line treatment over oral antihistamines based on efficacy. Intranasal corticosteroids have a low risk of systemic effect because of their pharmacokinetics, and all second-generation intranasal corticosteroids are considered similar with regard to safety at the recommended starting dose during pregnancy.[7]

Nevertheless, in August 2004, the FDA upgraded intranasal budesonide, which is an intranasal corticosteroid, to pregnancy category B based on a review of 3 Swedish Birth Register studies containing pregnancy and neonatal outcomes from Sweden from 1995 to 2001.[8-10] All other intranasal corticosteroids used for the treatment of AR remained pregnancy category C because of insufficient human data. Recently, the FDA approved intranasal triamcinolone OTC sales with pregnancy category C, which could partly be explained by the fact that intramuscular triamcinolone acetonide was found to be teratogenic in animals.[11,12] Indeed, triamcinolone acetonide has the potential to have a potent teratogenic effect on various mammalian fetal tissues, as well as a steroid effect on the lung, fetal growth retardation, and cleft palate anomalies.[13] At present, no human pregnancy data are available for intranasal triamcinolone.

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Abbreviations used
AR: Allergic rhinitis
1DG: First day of gestation; first day of last menstrual period
FDA: US Food and Drug Administration
ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Classification of Diseases, Tenth Revision
OR: Odds ratio
OTC: Over the counter
QPC: Quebec Pregnancy Cohort
RAMQ: Régie de l'assurance maladie du Québec
SGA: Small for gestational age

Given the potential public health effect, the objectives of our study were to assess the safety of intranasal triamcinolone exposure during pregnancy on the occurrence of major congenital malformations, small-for-gestational-age (SGA) status, and spontaneous abortions.

METHODS

Cohort

We conducted a population-based cohort study using data from the Quebec Pregnancy Cohort (QPC), which was built with the linkage of 4 large databases in Quebec. The QPC is an ongoing population-based cohort with prospective data collection on all pregnancies that occurred between January 1997 and September 2009 in the province of Quebec. Data on mothers and children after the end of pregnancy were also collected. Individual-level information was obtained from province-wide databases and linked by using unique personal identifiers. The QPC was first constructed by identifying all pregnancies in the Régie de l'assurance maladie du Québec (RAMQ) and Quebec hospitalization archive (MedEcho) databases; subsequently, the first day of the last menstrual period (first day of gestation [1DG]) was defined by using data on gestational age, which was validated against patients' charts.[14] Prospective follow-up was available from 1 year before the 1DG, during pregnancy, and until December 2009.

Analyses of spontaneous abortions were based on all pregnancies in the cohort, whereas analyses of malformations and SGA status in newborns were based on singleton livebirths. The QPC data sources for this study included the medical service database (RAMQ: diagnoses, medical procedures, socioeconomic status of women, and prescribers), the Quebec's Public Prescription Drug Insurance database (drug name, start date, dosage, and duration), the hospitalization archive database (MedEcho: diagnoses and procedures), and the Quebec Statistics database (ISQ: patients' sociodemographics and birth weight). The QPC is further described by Bérard and Sheehy.[15]

We included pregnancies with continuous prescription drug insurance coverage of at least 12 months before the 1DG and during pregnancy; all pregnancies meeting this criterion were considered and analyzed. We excluded pregnancies exposed to known teratogens during the first trimester (0-14 completed weeks of gestation), as described by Kulaga et al.[16] For analyses of spontaneous abortion, we excluded women with planned abortions or women whose abortions occurred at a gestational age of less than 6 completed weeks of gestation (these are potentially subjected to misclassification because many early pregnancy losses are not recognized clinically). We also excluded pregnancies with spontaneous abortions after 22 weeks of gestation, which is clinically implausible. For analyses involving malformations and birth weight (SGA), we excluded pregnancies for which this information was missing (see Fig E1 in this article's Online Repository at www.jacionline.org). For analyses of malformations, we also excluded pregnancies resulting in minor malformations alone in newborns.

The study was approved by the Quebec Data Access Agency and the CHU Ste-Justine Institutional Review Board.

Study design

This is a longitudinal prospective cohort study.

Intranasal triamcinolone

We identified prescriptions for intranasal triamcinolone dispensed to women in the cohort from the Quebec Public Prescription Drug Insurance database, with the timing of exposure determined by the dispensed date and duration of prescription. The relevant exposure time window for the analyses of malformations was the first trimester (0-14 completed weeks of gestation); the relevant exposure time window was the second or third trimester of pregnancy (>14 weeks of gestation) for SGA analyses. As for analyses of spontaneous abortions, the exposure time window was from the 1DG until the index date (defined as gestational age of the spontaneous abortion or corresponding index date for matched control subjects) because of the nested case-control analysis for this specific pregnancy outcome.

Two comparator groups were defined. First, to take into account the underlying indication (to take into account potential indication bias), an active comparator group included pregnancies with exposure to other intranasal corticosteroids (ie, beclomethasone dipropionate, budesonide, flunisolide, fluticasone furoate, fluticasone propionate, or mometasone furoate) during the relevant time windows. Second, a nonexposed category was defined as pregnancies with no exposure to intranasal triamcinolone or any other intranasal corticosteroids during the time windows of interest.

Data on prescription fillings have been validated and compared with maternal reports, which is more reliable than data on medication prescribing in medical charts; the positive predictive value of prescription drug data in the cohort was found to be at least 87% (95% CI, 70% to 100%), and the negative predictive value was at least 92% (95% CI, 86% to 98%).[17]

Outcomes

Cases of major congenital malformations diagnosed in the first year of life were identified in the QPC with data from the RAMQ and MedEcho databases and defined according to International Classification of Diseases, Ninth Revision (ICD-9), codes (740-759 excluding codes of minor congenital malformations or chromosomal abnormalities: 743.6, 744.1-744.4, 744.8, 744.9, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.0, 755.1, 757.2-757.6, 757.8, 757.9, and 758.4) and International Classification of Diseases, Tenth Revision (ICD-10), codes (Q00-Q99, excluding codes of minor malformations or chromosomal abnormalities: Q08-Q10, Q162, Q17-Q19, Q250, Q270, Q381, Q515, Q516, Q20-Q53, Q664-Q666, Q689, Q70, Q81-Q84, and Q94-Q95). Minor malformations were not considered because they are likely diagnosed selectively (hence detection bias and misclassification of the outcome); chromosomal abnormalities were excluded given that they are likely not related to the drug of interest. ICD-9 and ICD-10 codes of major congenital malformations in the QPC have been validated against patients' charts.[14] The positive predictive value of major congenital malformations diagnosed in the first year of life in the QPC has been found to be at least 80%, and the negative predictive value has been found to be 93%.[18] All organ systems were considered.

SGA was used as a combined measure of prematurity and low birth weight. Cases of SGA, which were identified in the QPC with the hospital archives database (gestational age) and the Quebec Statistics database (birth weight and sex), were defined as the lowest 10th percentile of the gestational age-specific birth weight in the cohort, according to the sex-specific population-based Canadian references.[19] Gestational age and birth weight have been validated against patients' charts.[14]

Cases of spontaneous abortion were identified in the QPC by using the RAMQ database with ICD-9 codes 630-634 and ICD-10 codes O01-O03. Only cases occurring between the 6th and 22nd weeks of gestation were included. Planned or induced abortions were excluded from these analyses.

Statistical analyses

The unit of analysis was a pregnancy. Within the underlying study cohort, we conducted 3 separate case-control analyses. For analyses on major congenital malformations, control subjects were defined as those with