

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 al³ and the Allergic Rhinitis and its Impact on Asthma guidelines⁶ 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

pregnancies ending with a newborn without major or minor congenital malformations or chromosomal abnormalities diagnosed during the first year of life. For analyses of SGA, control subjects were defined as infants of greater than the 10th percentile of the gestational age-specific birth weight, according to the population-based Canadian references.¹⁹ For both analyses of major congenital malformations and SGA, the index date was the date of delivery. Given that no control sampling was done (all cohort pregnancies were analyzed), case-control and survival analyses produced similar findings.²⁰

For analyses of spontaneous abortions, a nested case-control approach, which matched on gestational age at the time of the event (spontaneous abortion or matched index date for selected control subjects) per design, was used. Up to 5 control subjects per case were selected from the study cohort. This design allows for a more comparable measure of exposure between cases and control subjects. The nested case-control design compares groups of exposed and nonexposed subjects at similar risk of having the event of interest, hence producing valid estimates of risk ratios; it also allows for the adjustment on gestational age at the time of the event, which is essential when an outcome occurs at varying time periods in each study subject, such as spontaneous abortion. The Cox proportional hazard and conditional logistic regression models produce similar results in this instance.²¹

Potential confounders considered for all analyses were known risk factors or associated with risk factors for the 3 studied outcomes (all these variables were either risk factors or determinants for adverse pregnancy outcomes). First were sociodemographic variables on the 1DG, including maternal age, maternal marital status (living alone or cohabiting), receipt of social assistance during pregnancy or 1 year before (yes/no), educational level in years (≤ 12 or > 12), and area of residence (urban/rural).

Second were maternal chronic comorbidities during the 12 months before pregnancy, including hypertension (yes/no), diabetes (type I or type II; yes/no), asthma (yes/no), epilepsy (yes/no), and depression (yes/no). The previous conditions were identified from either diagnoses or filled prescriptions of related medications. To further adjust for potential indication bias, we also considered maternal chronic rhinitis (chronic and allergic; yes/no) using related diagnostic codes before pregnancy.

Third was health care use during the 12 months before the 1DG, including hospitalizations or emergency department visits (yes/no) and visits to an allergist or a pulmonologist (yes/no) to control for the presence and severity of the disease (asthma and AR).

Fourth were pregnancy-related variables, including previous pregnancy, abortion or miscarriage in the year before the 1DG (yes/no). We also took into account whether pregnant women were followed by a gynecologist (yes/no) and whether other medications, including oral, topical, intramuscular, or inhaled corticosteroids, were used during pregnancy.

Finally, in the analyses for major congenital malformations and spontaneous abortions, adjustment on the seasonal allergy season (April–August) period in Quebec was made if it overlapped the first trimester.

We present means and proportions for continuous and dichotomous variables, respectively. Crude and adjusted odds ratios (ORs) with 95% CIs were calculated for each outcome separately by using logistic regression models based on the methods of generalized estimating equations. Generalized estimating equations multivariate logistic regression was used to estimate the association between exposure to intranasal triamcinolone or other intranasal corticosteroids during pregnancy and the risk of major congenital malformations and SGA separately, accounting for clustering by family (mother). In addition, conditional logistic regression models were performed for analyses for spontaneous abortions to take into account the matching on gestational age per design. Statistical analyses were done with SAS software (version 9.2; SAS Institute, Cary, NC). Differences were considered statistically significant when the 95% CIs did not overlap 1.0 and when *P* values (2-tailed) were less than .05.

RESULTS

Cohort

From a total of 289,723 potentially eligible pregnancies, 143,152 were included in the analyses for major congenital

malformations (318 [0.2%] were exposed to intranasal triamcinolone, and 2,202 [1.5%] were exposed to other intranasal corticosteroids during the first trimester), and 153,324 were included in the analyses for SGA (492 [0.3%] were exposed to intranasal triamcinolone, and 3,915 [2.6%] were exposed to other intranasal corticosteroids during the second or third trimesters, see Fig E1). Reasons for exclusions included spontaneous/planned abortions (89.7%), impossibility to link babies to mothers, and multiple pregnancies; exposure to known teratogens during the first trimester of pregnancy, having less than 12 months of follow-up after delivery (for analyses for major congenital malformations), and chromosomal malformations or minor malformations only (for analyses for major congenital malformations) were other reasons for exclusion. Overall, only 3.3% of missing links between mothers and babies occurred.

All potentially eligible pregnancies were considered for analyses on spontaneous abortions.

The rate of intranasal triamcinolone use and other intranasal corticosteroid use during pregnancy has increased over the course of the study, as did the rate of major congenital malformations in our study population (see Fig E2 in this article's Online Repository at www.jacionline.org).

Major congenital malformations

Table I presents the baseline characteristics between cases of major congenital malformations and control subjects. Cases were more likely to be urban dwellers and have a lower education level than control subjects. Cases were comparable with control subjects in terms of maternal age, welfare status, marital status, and first-trimester seasonal allergy overlap. However, they were more likely to have maternal chronic comorbidities, such as rhinitis, asthma, hypertension, diabetes, epilepsy, and depression ($P < .01$); more likely to have had a visit to an allergist or pulmonologist before delivery (increased severity of maternal respiratory diseases/conditions, $P < .01$); and more likely to have higher maternal health care use in the year preceding and during pregnancy than control subjects. After adjustment for potential confounders, including a history of rhinitis, asthma, and other maternal comorbidities, use of intranasal triamcinolone during the first trimester of pregnancy was not statistically significantly associated with an increased risk of overall major congenital malformation (adjusted OR, 0.88; 95% CI, 0.60–1.28; 31 exposed cases) compared with nonexposure to any intranasal corticosteroids (see Table E1 for the description of the specific malformations). No statistically significant association was found between the use of other intranasal corticosteroid exposure during the first trimester of pregnancy and the risk of major congenital malformations (adjusted OR, 0.99; 95% CI, 0.87–1.14; 239 exposed cases).

In the analyses of individual malformation categories (organ systems, Table II), intranasal triamcinolone increased the risk of respiratory system defects (adjusted OR, 2.71; 95% CI, 1.11–6.64; 5 exposed cases). Respiratory system defects identified in the intranasal triamcinolone group were malformations of the larynx, trachea, and bronchus and choanal atresia (see Table E2 in this article's Online Repository at www.jacionline.org for the list of specific respiratory defects for intranasal triamcinolone users and other intranasal corticosteroids users and see Table E3 in this article's Online Repository at www.jacionline.org for the use and quantity of medication exposure among the 5 cases

TABLE I. Intranasal triamcinolone and other intranasal corticosteroid use during the first trimester of pregnancy and the risk of major congenital malformations

	Cases (n = 14,007), no. (%)	Control subjects (n = 129,145), no. (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Nonexposure	13,738 (98.08)	126,916 (98.27)	Reference	Reference
Intranasal triamcinolone	31 (0.22)	287 (0.22)	0.99 (0.68-1.44)	0.88 (0.60-1.28)
Other intranasal corticosteroids†	239 (1.71)	1,963 (1.52)	1.12 (0.98-1.29)	0.99 (0.87-1.14)
Maternal characteristics (at the beginning of pregnancy)				
Age (y), mean ± SD	27.73 ± 5.49	27.72 ± 5.54	1.00 (1.00-1.00)	1.00 (0.99-1.00)
Living alone	2,032 (14.51)	19,518 (15.11)	0.95 (0.91-1.00)	0.95 (0.91-1.00)
Welfare recipient	4,679 (33.40)	42,421 (32.85)	1.02 (0.99-1.06)	0.98 (0.94-1.02)
Postsecondary education (>12 y)‡	6,020 (42.98)	56,829 (44.00)	0.96 (0.93-0.99)	0.98 (0.94-1.02)
Urban dweller (vs rural dweller)‡	12,607 (90.00)	110,769 (85.77)	1.49 (1.41-1.58)	1.42 (1.33-1.50)
Maternal comorbidities (in the year before or during pregnancy)				
Rhinitis (chronic or allergic)‡	226 (1.61)	1,809 (1.40)	1.15 (1.00-1.32)	1.06 (0.92-1.22)
Hypertension (chronic or gestational)‡	1,444 (10.31)	9,786 (7.58)	1.40 (1.32-1.48)	1.33 (1.26-1.41)
Diabetes (chronic or gestational)‡	929 (6.63)	7,124 (5.52)	1.21 (1.13-1.30)	1.04 (0.96-1.12)
Asthma‡	2,634 (18.80)	21,373 (16.55)	1.17 (1.11-1.22)	1.09 (1.04-1.51)
Epilepsy‡	136 (0.97)	838 (0.65)	1.49 (1.24-1.79)	1.25 (1.04-1.51)
Depression‡	1,694 (12.09)	13,004 (10.07)	1.22 (1.16-1.29)	1.14 (1.08-1.20)
Health services use (in the year before or during pregnancy)				
Hospitalizations or emergency department visits (yes)‡	13,925 (99.41)	127,640 (98.83)	1.99 (1.59-2.48)	1.67 (1.34-2.08)
Visit to an allergist (yes)‡	216 (1.54)	1,559 (1.21)	1.28 (1.11-1.48)	1.16 (1.00-1.34)
Visit to a pulmonologist (yes)‡	289 (2.06)	2,116 (1.64)	1.26 (1.11-1.43)	1.07 (0.94-1.22)
Pregnancy-related variables				
Prenatal follow-up by an obstetrician (yes)‡	9,338 (66.67)	77,068 (59.68)	1.35 (1.30-1.40)	1.30 (1.25-1.35)
Comedications,§ mean ± SD‡	1.68 ± 1.92	1.50 ± 1.71	1.06 (1.05-1.07)	1.04 (1.03-1.05)
Pregnancy or abortions or miscarriage in the year before pregnancy‡	1 275 (9.10)	10,652 (8.25)	1.11 (1.05-1.18)	1.09 (1.03-1.16)
First trimester of pregnancy during pollen season (yes)	10,665 (76.14)	98,770 (76.48)	0.98 (0.94-1.02)	0.99 (0.95-1.03)

*Adjusted for all variables included in the table.

†Beclomethasone dipropionate, budesonide, flunisolide, fluticasone furoate, fluticasone propionate, and mometasone furoate.

‡ $P < .01$, t test for continuous variables and χ^2 test for categorical variables.

§Dispensing of other comedications during pregnancy (number of different comedications), excluding intranasal corticosteroids, antihypertensive drugs, antidiabetic drugs, asthma medications, medications for epilepsy, and antidepressants.

of respiratory defects exposed *in utero* to intranasal triamcinolone). Only 1 case of respiratory defect occurred in combination with a musculoskeletal defect; the other 4 cases occurred with no other defect. Only considering the 4 isolated cases of respiratory defects in the analysis increased the estimate (adjusted OR, 3.61; 95% CI, 1.31-10.00).

The rate of respiratory defects increased over time in our study population and coincided with the increase in the rate of intranasal triamcinolone use during pregnancy (see Fig E2).

No statistically significant associations were found for the remaining organ systems studied (Table II). Of note, no orofacial clefts were identified.

To determine whether intranasal triamcinolone was different from other specific intranasal corticosteroids, sensitivity analyses were performed to quantify the association between specific intranasal corticosteroids and intranasal triamcinolone and the risk of major malformations overall, as well as the risk of specific organ system defects (see Table E4 in this article's Online Repository at www.jacionline.org). In unadjusted analyses intranasal budesonide and mometasone were associated with the risk of musculoskeletal defects (see Table E4). However, adjusting for potential confounders, as done in the previous analyses, rendered the estimate statistically nonsignificant (adjusted OR, 1.91; 95% CI, 0.95-3.84; 9 exposed cases; see Table E5 in this article's Online Repository at www.jacionline.org).

SGA

Table III presents characteristics of newborn SGA. Newborns with SGA were more likely to have an older mother on welfare with less education than control babies (Table III). SGA cases were comparable with control subjects in terms of maternal marital status, place of residence, maternal rhinitis diagnosed before or during pregnancy, hospitalization/emergency department visits, allergist visits, and with a pregnancy in the year before the 1DG (Table III). However, cases were more likely to have maternal chronic comorbidities, such as hypertension, diabetes, asthma, epilepsy, and depression ($P < .01$). After adjustment for potential confounders, including maternal rhinitis, intranasal triamcinolone use during the second/third trimesters was not statistically significantly associated with an increased risk of SGA (OR, 1.06; 95% CI, 0.79-1.43; 50 exposed cases) compared with nonexposure of any intranasal corticosteroids. No statistically significant association was found between the use of other intranasal corticosteroids during the second/third trimesters and the risk of SGA (OR, 0.88; 95% CI, 0.78-1.01; 339 exposed cases).

Spontaneous abortions

Among the 289,723 pregnancies included in the study cohort, 17,558 (6.1%) ended with a clinically detected spontaneous abortion. Mean gestational age at the time of the spontaneous

TABLE II. Intranasal triamcinolone and other intranasal corticosteroids use during pregnancy and the risk of categories of malformations

Organ system defects	Exposed (n = 2,498)			Nonexposed (n = 140,654), no. (%)		Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
	Intranasal triamcinolone (n = 296), no. (%)	Other INC (n = 2,180), no. (%)	Both (n = 22), no. (%)				
Major congenital malformations overall	30 (10.14)	238 (10.92)	1 (4.55)	13,738 (9.77)	Triamcinolone Other INC	0.99 (0.68-1.44) 1.12 (0.98-1.29)	0.88 (0.60-1.28) 0.99 (0.87-1.14)
Nervous system	0 (0.0)	11 (0.50)	0 (0.0)	811 (0.58)	Triamcinolone Other INC	NA NA	NA NA
Eye, ear, face, and neck	2 (0.68)	7 (0.32)	0 (0.0)	812 (0.58)	Triamcinolone Other INC	1.12 (0.28-4.53) 0.55 (0.26-1.16)	1.01 (0.25-4.03) 0.50 (0.24-1.02)
Circulatory (including heart) system	5 (1.69)	47 (2.16)	0 (0.0)	3,108 (2.21)	Triamcinolone Other INC	0.70 (0.29-1.71) 0.97 (0.73-1.30)	0.61 (0.25-1.48) 0.83 (0.62-1.11)
Respiratory system	5 (1.69)	11 (0.50)	0 (0.0)	632 (0.45)	Triamcinolone Other INC	3.56 (1.48-8.59) [†] 1.10 (0.61-1.99)	2.71 (1.11-6.64) [‡] 0.85 (0.47-1.56)
Digestive system	3 (1.01)	21 (0.96)	0 (0.0)	1,236 (0.88)	Triamcinolone Other INC	1.07 (0.34-3.34) 1.09 (0.70-1.67)	0.84 (0.27-2.63) 0.88 (0.56-1.37)
Genital organs	4 (1.35)	22 (1.01)	0 (0.0)	1,290 (0.92)	Triamcinolone Other INC	1.37 (0.51-3.68) 1.08 (0.71-1.65)	1.29 (0.48-3.48) 1.01 (0.66-1.56)
Urinary system	2 (0.68)	13 (0.60)	0 (0.0)	1,080 (0.77)	Triamcinolone Other INC	0.83 (0.21-3.35) 0.76 (0.44-1.32)	0.76 (0.19-3.06) 0.68 (0.39-1.19)
Musculoskeletal system	12 (4.05)	105 (4.82)	1 (4.55)	5,432 (3.86)	Triamcinolone Other INC	1.03 (0.59-1.81) 1.26 (1.03-1.53) [‡]	0.94 (0.54-1.65) 1.13 (0.93-1.38)
Other anomalies	1 (0.34)	32 (1.47)	0 (0.0)	1,613 (1.15)	Triamcinolone Other INC	0.26 (0.04-1.92) 1.29 (0.91-1.83)	0.24 (0.03-1.73) 1.16 (0.81-1.66)

INC, Intranasal corticosteroids; NA, not applicable because no defects were identified.

*Adjusted for maternal characteristics (age, living alone, welfare status, postsecondary education level, and place of living), maternal comorbidities in the year before or during pregnancy (rhinitis, hypertension, diabetes, asthma, epilepsy, and depression), health services use in the year before and during pregnancy (hospitalization or emergency department visits, visits to an allergist, and visits to a pulmonologist), and pregnancy-related variables (prenatal follow-up by an obstetrician, comedications, history of pregnancy, abortion or miscarriage in the year before the pregnancy, and first-trimester occurrence during Quebec's pollen season).

[†]P < .005.

[‡]P < .03.

abortion was 14.4 weeks (SD, 2.6 weeks). Cases of spontaneous abortion were matched to a total of 86,336 control subjects; 5 control subjects were found for 93.6% of the cases, 4 control subjects for 6.2% of the cases, 3 control subjects for 0.2% of the cases, and 2 control subjects for 2 cases. Spontaneous abortion cases were similar to control subjects with regard to the prevalence of maternal rhinitis in the year before the 1DG and for first-trimester seasonal allergy overlap (Table IV). Mothers with pregnancy ending with a spontaneous abortion were older, more likely to be on welfare, and urban dwellers; they also had more chronic comorbidities in the year before or during pregnancy (up to the index date) than control subjects. Cases were more likely than control subjects to have hospitalization/emergency department visits and allergist and pulmonologist visits (increased severity of maternal respiratory diseases/conditions, $P < .01$) and had prenatal follow-up by an obstetrician, more comedications, and more pregnancies in the year before the 1DG. Adjusting for all potential confounding variables, including maternal rhinitis, intranasal triamcinolone use between the 1DG and the index date was not statistically significantly associated with an increased risk of spontaneous abortion compared with nonuse (OR, 1.04; 95% CI, 0.76-1.43; 50 exposed cases); the same was found for other intranasal corticosteroids (OR, 0.99; 95% CI, 0.89-1.11; 410 exposed cases; Table IV).

DISCUSSION

Main findings

To our knowledge, our study is the first to investigate the risk of adverse pregnancy outcomes associated with intranasal triamcinolone exposure during pregnancy. We did not find a statistically significant association between the use of intranasal triamcinolone in pregnancy and the risk of overall major malformations, SGA, and spontaneous abortion. However, we did find an increased risk of respiratory system defects with first-trimester exposure to intranasal triamcinolone, taking into account maternal respiratory diseases/conditions and severity. In sensitivity analyses we found that even if intranasal budesonide has a pregnancy category B, it was associated with the highest risk of major malformation; however, this was not statistically significant. Furthermore, intranasal budesonide was associated with some of the highest risk of organ-specific defects, including respiratory defects. Lack of statistical power could partly explain the nonstatistical findings, although these could also be due to chance.

In August 2004, the FDA upgraded intranasal budesonide's pregnancy rating from category C to category B based on a review of 3 Swedish Birth Register studies, which included pregnancy and neonatal data on the majority of births in Sweden from 1995 to 2001.⁸⁻¹⁰ Our study is somewhat consistent with these, which did not find a statistically significant association between

TABLE III. Intranasal triamcinolone and other intranasal corticosteroid use during the second/third trimesters of pregnancy and the risk of SGA

	Cases (n = 14,648), no. (%)	Control subjects (n = 138,676), no. (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Second/third trimester of pregnancy				
Nonexposure	14,266 (97.39)	134,679 (99.69)	Reference	Reference
Intranasal triamcinolone	50 (0.34)	442 (0.32)	1.09 (0.81-1.45)	1.06 (0.79-1.43)
Other intranasal corticosteroids†	339 (2.31)	1,576 (2.58)	0.89 (0.80-1.01)	0.88 (0.78-1.01)
First trimester of pregnancy				
Nonexposure	14,408 (98.36)	136,223 (98.23)	Reference	Reference
Intranasal triamcinolone	34 (0.23)	304 (0.22)	1.07 (0.76-1.50)	0.98 (0.69-1.40)
Other intranasal corticosteroids†	206 (1.41)	2,173 (1.57)	0.89 (0.78-1.03)	0.88 (0.76-1.02)
Maternal characteristics (at the beginning of pregnancy)				
Age (y), mean $\pm$ SD‡	27.40 $\pm$ 5.78	27.81 $\pm$ 5.51	0.99 (0.98-0.99)	0.99 (0.99-1.00)
Living alone	2,186 (14.92)	20,883 (15.06)	0.99 (0.95-1.04)	0.99 (0.95-1.04)
Welfare recipient‡	5,448 (37.19)	44,821 (32.32)	1.22 (1.18-1.26)	1.14 (1.10-1.18)
Postsecondary education (>12 y)‡	5,293 (36.13)	62,308 (44.93)	0.71 (0.68-0.73)	0.74 (0.71-0.77)
Urban dweller (vs rural dweller)	12,697 (86.68)	120,516 (86.90)	0.98 (0.93-1.03)	0.99 (0.94-1.04)
Maternal comorbidities (in the year before or during pregnancy)				
Rhinitis (chronic or allergic)	214 (1.46)	1,972 (1.42)	1.03 (0.89-1.19)	1.03 (0.89-1.19)
Hypertension (chronic or gestational)‡	1,647 (11.24)	10,427 (7.52)	1.56 (1.47-1.64)	1.56 (1.48-1.65)
Diabetes (chronic or gestational)‡	674 (4.60)	8,213 (5.92)	0.78 (0.72-0.84)	0.72 (0.66-0.78)
Asthma‡	2,829 (19.31)	22,818 (16.45)	1.20 (1.15-1.26)	1.13 (1.08-1.18)
Epilepsy‡	142 (0.97)	947 (0.68)	1.43 (1.19-1.70)	1.26 (1.05-1.51)
Depression‡	1,797 (12.27)	14,026 (10.11)	1.24 (1.17-1.30)	1.16 (1.10-1.22)
Health services use (in the year before or during pregnancy)				
Hospitalizations or emergency department visits (yes)	14,514 (99.09)	137,213 (98.95)	1.15 (0.97-1.38)	1.02 (0.85-1.22)
Visit to an allergist (yes)	181 (1.24)	1,742 (1.26)	1.00 (0.86-1.16)	1.00 (0.86-1.16)
Visit to a pulmonologist (yes)‡	276 (1.88)	2,303 (1.66)	1.14 (1.01-1.29)	1.05 (0.93-1.20)
Pregnancy-related variables				
Prenatal follow-up by an obstetrician (yes)‡	8,995 (61.41)	83,651 (60.32)	1.05 (1.01-1.09)	1.08 (1.04-1.12)
Comedications,§ mean $\pm$ SD‡	1.61 $\pm$ 1.90	1.53 $\pm$ 1.74	1.03 (1.02-1.04)	1.00 (0.99-1.01)
Pregnancy or abortions or miscarriage in the year before pregnancy	1,141 (7.79)	11,417 (8.23)	0.93 (0.87-0.99)	0.91 (0.86-0.97)

*Adjusted for all variables included in the table.

†Beclomethasone dipropionate, budesonide, flunisolide, fluticasone furoate, fluticasone propionate, and mometasone furoate.

‡ $P < .01$, t test for continuous variables and χ^2 test for categorical variables.

§Dispensing of other medications during pregnancy (number of different medications), excluding intranasal corticosteroids, antihypertensive drugs, antidiabetic drugs, asthma medications, medications for epilepsy, and antidepressants.

maternal exposure to intranasal budesonide and the risk of cardiovascular defects or other organ system defects, including musculoskeletal defects. Indeed, we did not find an increase in the risk of cardiac defects or other organ system defects (other than respiratory defects) associated with intranasal corticosteroids (including intranasal budesonide) or the use of intranasal triamcinolone during the first trimester of pregnancy. However, we observed a statistically significantly increased risk of respiratory system defects associated with first-trimester use of intranasal triamcinolone, which is in contradiction with the Swedish studies.⁸⁻¹⁰ We acknowledge that this result is based on 5 exposed cases and needs to be replicated. In addition, further studies are required to rule out chance findings. Nevertheless, intramuscular triamcinolone was shown to be teratogenic in animals and has been shown to affect lung development,¹¹⁻¹³ which is consistent with our findings. Although adjustment was made on maternal AR (indication) and other known risk factors for major congenital malformations (maternal asthma and severity of maternal respiratory diseases), residual confounding cannot be excluded completely. Nevertheless, confounding by indication is unlikely given that use of other intranasal corticosteroids did not exhibit an increased risk of any major organ system defects.

Strengths

Study strengths include the use of a large pregnancy cohort put in place with administrative and clinical databases that provide population-based coverage of pregnant women in Quebec, with linkage of data on the individual level; this permitted analyses of a large number of exposed pregnancies with detailed information regarding exposure, outcomes, and potential confounders. Prescription fillings were used to determine medication exposure, similar to what is routinely done in all Danish, Norwegian, Medicaid, and Medicare studies.²²⁻²⁴ However, because we cannot be sure that pregnant women who are prescribed medications will actually take them, we have validated our prescription fillings data in the QPC by comparing the concordance between fillings and maternal reports.¹⁷ We have shown that the positive and negative predictive values for fillings in our study population were high. Because we are aware that these predictive values can vary between drugs that need to be used on a chronic basis and drugs that need to be taken for acute conditions, such as intranasal triamcinolone or other intranasal corticosteroids, we have stratified our analyses according to chronicity of use and have shown that the validity of our medication data (chronic use or not) was good in all instances.¹⁷ Major congenital malformation outcomes have also been

TABLE IV. Intranasal triamcinolone and other intranasal corticosteroid use during pregnancy and the risk of spontaneous abortions

	Cases (n = 17,558), no. (%)	Control subjects (n = 86,336), no. (%)	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
From beginning of pregnancy until index date:				
Nonexposure	17,103 (97.41)	84,421 (99.78)	Reference	Reference
Intranasal triamcinolone	50 (0.28)	205 (0.24)	1.20 (0.88-1.63)	1.04 (0.76-1.43)
Other intranasal corticosteroids†	410 (2.34)	1,731 (2.00)	1.17 (1.05-1.30)	0.99 (0.89-1.11)
Maternal characteristics (at the beginning of pregnancy)				
Age (y), mean (SD)‡	28.71 ± 6.41	27.94 ± 5.56	1.02 (1.02-1.03)	1.04 (1.03-1.04)
Welfare recipient‡	6,199 (35.31)	27,496 (31.85)	0.86 (0.83-0.89)	1.09 (1.05-1.13)
Urban dweller (vs rural dweller)‡	14,072 (80.15)	68,615 (79.47)	1.04 (1.00-1.09)	1.10 (1.05-1.14)
Maternal comorbidities (in the year before pregnancy until index date)				
Rhinitis (chronic or allergic)	236 (1.34)	1,017 (1.18)	1.14 (0.99-1.32)	1.06 (0.91-1.23)
Hypertension (chronic or gestational)‡	584 (3.33)	3,405 (3.94)	0.84 (0.77-0.91)	0.70 (0.64-0.77)
Diabetes (chronic or gestational)‡	367 (2.09)	2,579 (2.99)	0.69 (0.62-0.77)	0.63 (0.56-0.71)
Asthma‡	6,321 (36.00)	28,549 (33.07)	1.14 (1.10-1.18)	1.07 (1.03-1.11)
Epilepsy‡	197 (1.12)	658 (0.76)	1.48 (1.26-1.74)	1.04 (0.88-1.23)
Depression‡	2,824 (16.08)	8,692 (10.07)	1.72 (1.64-1.80)	1.50 (1.42-1.57)
Health services use (in the year before pregnancy until index date)				
Hospitalizations or emergency department visits (yes)‡	11,280 (64.24)	42,692 (49.45)	1.97 (1.90-2.04)	2.10 (2.02-2.18)
Visit to an allergist (yes)‡	226 (1.29)	958 (1.11)	1.16 (1.00-1.34)	1.09 (0.93-1.26)
Visit to a pulmonologist (yes)‡	310 (1.77)	1,183 (1.37)	1.30 (1.14-1.47)	1.12 (0.98-1.27)
Pregnancy-related variables				
Prenatal follow-up by an obstetrician (yes)‡	4,369 (24.88)	28,561 (33.08)	0.63 (0.60-0.65)	0.52 (0.50-0.54)
Comedications (no. of different comedications)§‡	1.25 ± 1.68	1.10 ± 1.67	1.05 (1.04-1.06)	1.03 (1.02-1.04)
Pregnancy or abortions or miscarriage in the year before pregnancy‡	1,910 (10.88)	6,776 (7.85)	1.44 (1.36-1.52)	1.17 (1.10-1.23)
First trimester of pregnancy during pollen season (yes)	13,538 (77.10)	66,191 (76.67)	1.03 (0.99-1.07)	1.06 (1.02-1.11)

*Adjusted for all variables included in the table.

†Beclomethasone dipropionate, budesonide, flunisolide, fluticasone furoate, fluticasone propionate, and mometasone furoate.

‡ $P < .01$, t test for continuous variables and χ^2 test for categorical variables.

§Dispensing of other comedications during pregnancy (number of different comedications), excluding intranasal corticosteroids, antihypertensive drugs, antidiabetic drugs, asthma medications, medications for epilepsy, and antidepressants.

validated against medical charts.¹⁸ Furthermore, gestational age has been validated,¹⁴ decreasing exposure misclassification bias for the studied time windows of interest. Although data on the specific indications for intranasal triamcinolone use were not available, it can be assumed that the majority of women are using the medication for similar indications during pregnancy, and a comparator exposure category with similar indications was also studied (other intranasal corticosteroids) to take into account indication bias. Furthermore, we adjusted for maternal comorbidities, some of which were indications for intranasal triamcinolone use during gestation and other medication use, including inhaled and oral corticosteroids. Data in our study were collected prospectively, limiting recall bias.

Limitations

The main limitation includes missing information on potentially important confounders, such as smoking, folic acid intake, and alcohol intake. Although we could not adjust for these variables, the fact that our findings are consistent with those of Kallen et al,⁹ who adjusted for these variables, suggests that the level of confounding would not have changed our conclusions. In addition, defects identified in our study have been seen in animal studies,¹¹⁻¹³ suggesting a probable mechanism of action. Although confounding by indication was reduced by the fact that exposure to other intranasal corticosteroids was not associated with the outcomes studied, confounding can still occur because of different patterns of prescribing, and hence residual

confounding cannot be completely ruled out. Even if our estimates are based on high numbers of exposed cases, we cannot eliminate increased risk in analyses on specific organ system defects caused by lower statistical power in some strata. In addition, given the number of comparisons made in this study, we cannot rule out the fact that some of our findings could have occurred by chance alone. Because we considered pregnant women insured by the Prescription Drug Insurance program, the generalizability of results to those insured by private drug insurance could be affected. However, validation studies have shown that pregnant women receiving medication insurance from Quebec's public system have similar characteristics and comorbidities as those who have private medication insurance. Although socioeconomic status might differ between the 2 groups (publicly and privately insured subjects for their medications), it does not affect internal validity given that all have similar socioeconomic status in our study population.²⁵ Furthermore, given that we could not differentiate women who terminated their pregnancy because they had a prenatal diagnosis of a major anomaly from those with an unwanted pregnancy, all women with a planned abortion were excluded, hence potentially underestimating the risk. Finally, our major malformation prevalence is higher than the routinely reported 3% to 5%. This is a known fact in the province of Quebec and is referred to as the founder's effect.^{26,27} Although our baseline prevalence of malformations is high, it does not invalidate our study findings given that the comparator groups also have the same baseline prevalence of malformations, canceling out this higher than usual

frequency. Our major malformation ICD-9 and ICD-10 codes have been validated,¹⁸ and malformations were identified during the first 12 months of life to confirm diagnoses, which further increase the validity of our outcome measures.

Interpretation

This study assessed the safety of intranasal triamcinolone use during pregnancy comparing intranasal triamcinolone-exposed women with women exposed to other intranasal corticosteroids and nonexposed pregnant women. We observed no statistically significantly increased risk of major congenital malformations overall, SGA, and spontaneous abortion associated with intranasal triamcinolone use in pregnancy. This was similar to what has been seen with other intranasal corticosteroids. However, first-trimester use of intranasal triamcinolone was associated with a significantly increased risk of respiratory system defects. Although our results are consistent with findings in animal studies, further investigations in humans are required to rule out chance findings and confirm this signal.

Conclusion

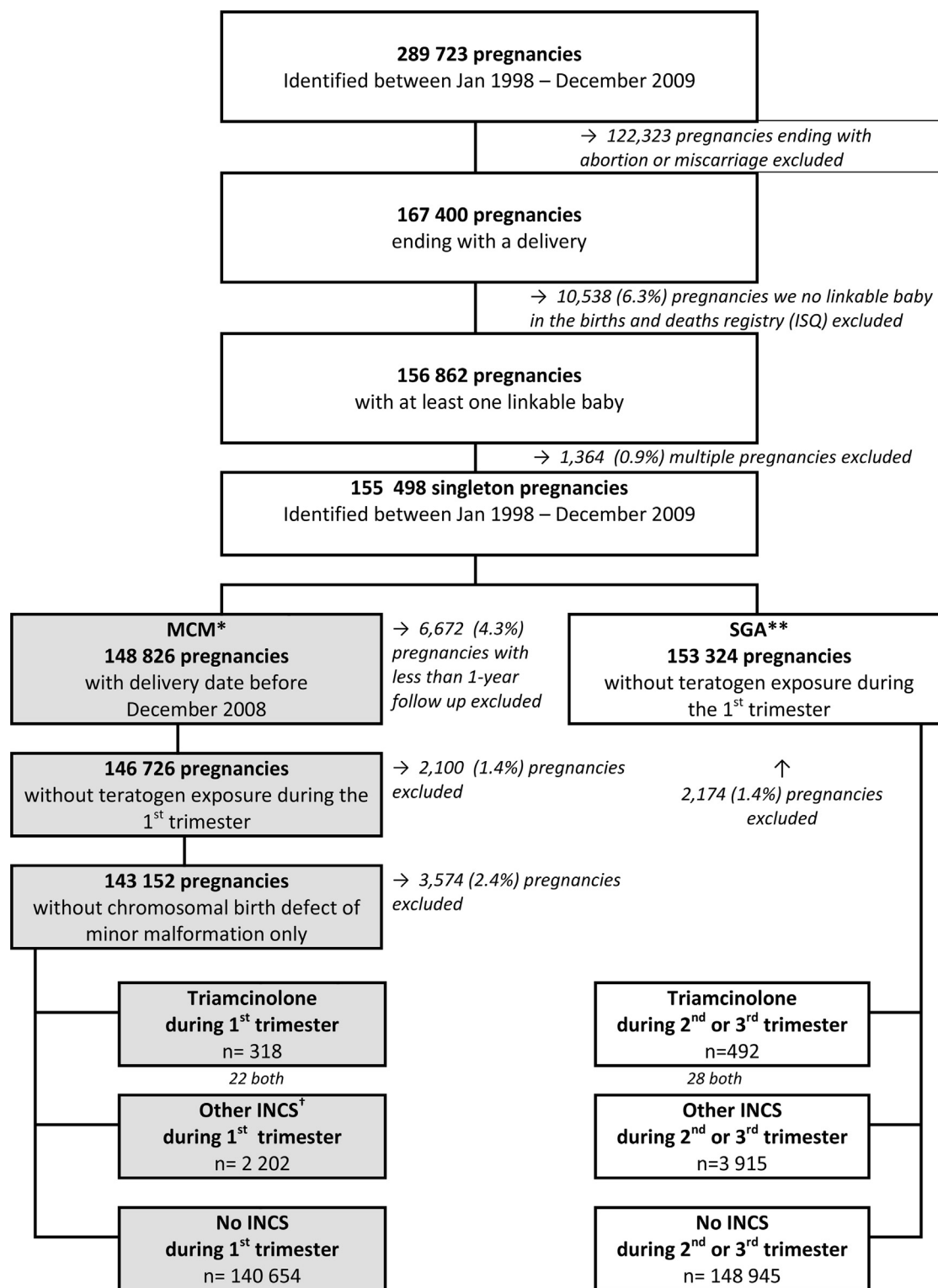
Although intranasal triamcinolone is available OTC in the United States, patients and health care providers have to be aware of the potential risk of respiratory defects when used during the first trimester of pregnancy. This study might help inform physicians and patients on the treatment of AR or seasonal allergies during gestation.

Key messages

- AR is prevalent.
- Gestational intranasal triamcinolone use increases the risk of respiratory defects but not spontaneous abortions or SGA.
- This is important given that the drug is available OTC.

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*MCM: major congenital malformations; **SGA: small-for-gestational age; †INCS: intranasal corticosteroids.

FIG E1. Study population selection. INCS, Intranasal corticosteroids; MCM, major congenital malformation.

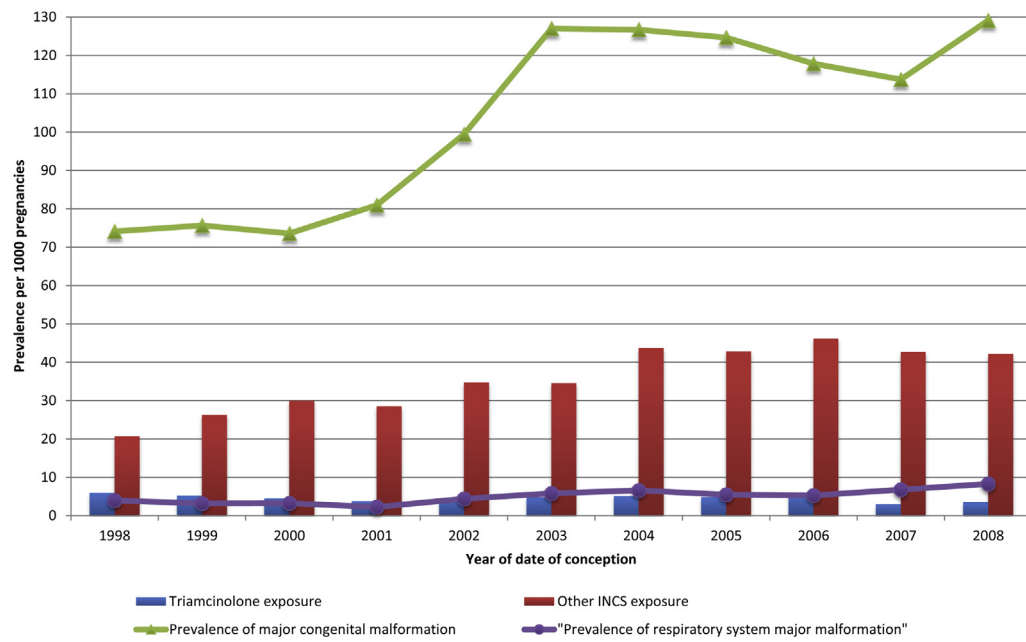


FIG E2. Prevalence of major congenital malformation, respiratory system malformations, and pregnancies exposed to triamcinolone or other intranasal corticosteroids per year of conception.

TABLE E1. List of major malformations among those taking intranasal triamcinolone during the first trimester

ICD-9/ICD-10 codes	Description of the malformation
754.5	Varus deformities of feet
753.2	Obstructive defects or renal pelvis and ureter
756.0	Other congenital musculoskeletal anomalies
756.9	Other congenital musculoskeletal anomalies
752.9	Congenital anomalies of genital organs
754.5	Varus deformities of feet
754.5	Varus deformities of feet
748.9	Congenital anomalies of respiratory system
743.9	Congenital anomalies of eye
755.2	Other congenital anomalies of limbs
748.3	Congenital anomalies of respiratory system
751.9	Other congenital anomalies of digestive system
745.4	Ventricular septal defect
746.6	Other congenital anomalies of heart
756.0	Other congenital musculoskeletal anomalies
756.9	Other congenital musculoskeletal anomalies
745.5	Atrial septal defect
754.5	Varus deformities of feet
750.5	Pyloric stenosis
759.2	Anomalies of other endocrine glands, congenital
745.5	Atrial septal defect
Q620	Congenital hydronephrosis
Q6218	Atresia and stenosis of ureter
745.5	Atrial septal defect
748.0	Choanal atresia
754.9	Certain congenital musculoskeletal deformities
743.9	Congenital anomalies of eye
754.5	Varus deformities of feet
Q658	Other congenital deformities of hip
752.6	Hypospadias and epispadias
752.9	Congenital anomalies of genital organs
748.3	Congenital anomalies of respiratory system
748.9	Congenital anomalies of respiratory system
752.9	Congenital anomalies of genital organs
Q662	Metatarsus varus
745.5	Atrial septal defect
751.9	Other congenital anomalies of digestive system

Note: A newborn can have more than 1 malformation.

TABLE E2. Types of respiratory system defects among those exposed to intranasal triamcinolone and other intranasal corticosteroids during the first trimester

Cases exposed to intranasal triamcinolone during the first trimester (n = 5)*	
Duration of use in days	Description of respiratory defect
47	748.9: Congenital malformations of respiratory, unspecified
33	748.3: Congenital malformations of larynx, trachea and bronchus
215	748.0: Choanal atresia
215	754.9: Congenital malformations of musculoskeletal system, unspecified
3	748.3: Other congenital malformations of the larynx, trachea and bronchus
21	748.9: Congenital malformations of respiratory, unspecified
Cases exposed to other intranasal corticosteroids during the first trimester (n = 11)†	
Duration of use in days	Description of respiratory defect
126	748.3: Other congenital malformations of the larynx, trachea and bronchus
233	748.9: Congenital malformations of respiratory, unspecified
151	748.3: Congenital malformations of larynx, trachea and bronchus
116	748.9: Congenital malformations of respiratory, unspecified
9	748.3: Congenital malformations of larynx, trachea and bronchus
8	748.0: Choanal atresia
11	Q315: Congenital laryngomalacia
11	Q673: Plagiocephaly
42	Q315: Congenital laryngomalacia
42	Q320: Congenital tracheomalacia
70	748.0: Choanal atresia
176	748.3: Congenital malformations of larynx, trachea and bronchus
151	748.9: Congenital malformations of respiratory, unspecified
8	748.3: Congenital malformations of larynx, trachea and bronchus
76	748.3: Congenital malformations of larynx, trachea and bronchus
9	Q332: Sequestration of lung
125	754.8: Other congenital deformities of chest

Choanal atresia is a congenital disorder in which the back of the nasal passage (choana) is blocked, usually by abnormal bony or soft tissue (membranous) because of failed recanalization of the nasal fossae during fetal development.

Laryngomalacia is a congenital softening of the tissues of the larynx (voice box) above the vocal cords. This is the most common cause of noisy breathing in infancy. The laryngeal structure is malformed and floppy, causing the tissues to fall over the airway opening and partially block it.

Plagiocephaly, also known as flat head syndrome, is a condition characterized by an asymmetric distortion (flattening of one side) of the skull. It is characterized by a flat spot on the back or one side of the head caused by remaining in a supine position for too long.

Tracheomalacia in a newborn occurs when the cartilage in the windpipe (trachea) has not developed properly. Instead of being rigid, the walls of the trachea are floppy. Because the windpipe is the main airway, breathing difficulties begin soon after birth.

*One case also has a musculoskeletal defect.

†Some cases have more than 1 malformation.

TABLE E3. Use and quantity of intranasal triamcinolone and other medications among cases with respiratory defects exposed to intranasal triamcinolone during the first trimester (n = 5)

Newborn ID	Drug name/form	Duration in days	Quantity
1	Triamcinolone/nasal spray	30	120
2	Fluticasone (propionate)/oral aerosol	40	120
2	Triamcinolone/nasal spray	30	120
3	Salbutamol/oral aerosol	20	200
3	Triamcinolone/nasal spray	30	120
3	Fusidique (acide)/eye drops	2	5
4	Triamcinolone/nasal spray	30	120
4	Doxylamine/pyridoxine/L.A. co	7	28
4	Amoxicillin/oral suspension	10	75
4	Salbutamol/oral aerosol	20	200
4	Fluticasone (propionate)/oral aerosol	20	120
5	Prednisone/co	76	95
5	Calcium (carbonate)/co	25	100
5	Triamcinolone/nasal spray	30	120
5	5-Aminosalicylique (acid)/Ent co.	13	80
5	Sulfasalazine/co	30	180
5	Rofecoxib/co	28	56

TABLE E4. Unadjusted risk of major congenital malformation overall and by organ system with respect to exposure to specific intranasal corticosteroids during the first trimester

MCM:	Pregnancies exposed to intranasal corticosteroids						Unadjusted OR (95% CI)
	Triamcinolone (n = 318)	Beclomethasone (n = 63)	Flunisolide (n = 18)	Budesonide (n = 111)	Fluticasone (n = 912)	Mometasone (n = 1127)	
Any MCM	31 (9.8)	5 (7.9)	2 (11.1)	16 (14.4)	94 (10.3)	124 (11.0)	Triamcinolone 0.98 (0.69-1.43) Beclomethasone 0.79 (0.32-1.97) Flunisolide 1.12 (0.25-4.93) Budesonide 1.55 (0.91-2.64) Fluticasone 1.06 (0.86-1.31) Mometasone 1.14 (0.95-1.37)
MCM by organ system							
Nervous system	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.6)	7 (0.6)	Fluticasone 0.96 (0.40-2.31) Mometasone 1.09 (0.52-2.27)
Eye, ear, face, and neck	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	6 (0.5)	Triamcinolone 1.09 (0.27-4.40) Budesonide 1.58 (0.22-11.24) Mometasone 0.94 (0.42-2.08)
Circulatory system	5 (1.6)	2 (3.2)	0 (0.0)	1 (0.9)	20 (2.2)	26 (2.3)	Triamcinolone 0.70 (0.29-1.71) Beclomethasone 1.50 (0.37-6.08) Budesonide 0.41 (0.06-2.86) Fluticasone 0.99 (0.64-1.54) Mometasone 1.05 (0.71-1.55)
Respiratory system	5 (1.6)	0 (0.0)	0 (0.0)	1 (0.9)	7 (0.8)	3 (0.3)	Triamcinolone 3.49 (1.44-8.45)* Budesonide 1.87 (0.26-13.38) Fluticasone 1.68 (0.79-3.57) Mometasone 0.59 (0.20-1.80)
Digestive system	3 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	8 (0.9)	12 (1.1)	Triamcinolone 1.07 (0.34-3.35) Budesonide 1.02 (0.14-7.33) Fluticasone 0.99 (0.49-2.00) Mometasone 1.21 (0.68-2.15)
Genital organs	4 (1.3)	0 (0.0)	0 (0.0)	1 (0.9)	9 (1.0)	12 (1.1)	Triamcinolone 1.37 (0.51-3.68) Budesonide 0.97 (0.14-6.89) Fluticasone 1.07 (0.55-2.06) Mometasone 1.15 (0.65-2.04)
Urinary system	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.9)	6 (0.7)	6 (0.5)	Triamcinolone 0.83 (0.21-3.32) Budesonide 1.16 (0.17-8.20) Fluticasone 0.86 (0.38-1.93) Mometasone 0.69 (0.31-1.54)
Musculoskeletal system	13 (4.1)	4 (6.4)	1 (5.6)	9 (8.1)	33 (3.6)	59 (5.2)	Triamcinolone 1.03 (0.59-1.80) Beclomethasone 1.63 (0.58-4.57) Flunisolide 1.35 (0.17-10.85) Budesonide 2.15 (1.08-4.29)† Fluticasone 0.92 (0.65-1.31) Mometasone 1.37 (1.06-1.79)‡
Other MCMs	1 (0.3)	0 (0.0)	1 (5.6)	3 (2.7)	15 (1.6)	14 (1.2)	Triamcinolone 0.26 (0.04-1.89) Flunisolide 5.10 (0.69-37.77) Budesonide 2.47 (0.79-7.73) Fluticasone 1.46 (0.87-2.42) Mometasone 1.09 (0.64-1.83)

Note: Estimates are given only when exposure occurred during the first trimester of pregnancy for the specific organ analyzed.

MCM, Major congenital malformation.

* $P = .0056$.

† $P = .0291$.

‡ $P = .0178$.

TABLE E5. Multivariate (adjusted) risk of musculoskeletal defects with respect to exposure to specific intranasal corticosteroids during the first trimester

TABLE 20. Multivariate (adjusted) risk of musculoskeletal defects with respect to exposure to specific intranasal corticosteroids during the first trimester									
Pregnancies exposed to intranasal corticosteroids							OR		
	Triamcinolone (n = 318)	Beclomethasone (n = 63)	Flunisolide (n = 18)	Budesonide (n = 111)	Fluticasone (n = 912)	Mometasone (n = 1127)		Unadjusted (95% CI)	Adjusted* (95% CI)
Musculoskeletal system	13 (4.1)	4 (6.4)	1 (5.6)	9 (8.1)	33 (3.6)	59 (5.2)	Triamcinolone	1.03 (0.59-1.80)	0.93 (0.53-1.63)
							Beclomethasone	1.63 (0.58-4.57)	1.50 (0.53-4.20)
							Flunisolide	1.35 (0.17-10.85)	1.34 (0.16-10.96)
							Budesonide	2.15 (1.08-4.29) [†]	1.91 (0.95-3.84)
							Fluticasone	0.92 (0.65-1.31)	0.83 (0.59-1.18)
							Mometasone	1.37 (1.06-1.79) [‡]	1.24 (0.95-1.61)

*Adjusted for maternal characteristics (age, living alone, welfare status, postsecondary education level, and place of living), maternal comorbidities in the year before or during pregnancy (rhinitis, hypertension, diabetes, asthma, epilepsy, and depression), health services use in the year before and during pregnancy (hospitalization or emergency department visits, visits to an allergist, and visits to a pulmonologist), and pregnancy-related variables (prenatal follow-up by an obstetrician, comedications, history of pregnancy, abortion or miscarriage in the year before the pregnancy, and first-trimester occurrence during Quebec's pollen season).

[†] $P = .0291$.

[‡] $P = .0178$.