

Primary care

Use of inhaled corticosteroids during pregnancy and risk of pregnancy induced hypertension: nested case-control study

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Abstract

Objective To determine whether the use of inhaled corticosteroids during pregnancy increases the risk of pregnancy induced hypertension and pre-eclampsia among asthmatic women.

Design Nested case-control study.

Setting Three administrative health databases from Quebec: RAMQ, MED-ECHO, and Fichier des événements démographiques.

Participants 3505 women with asthma, totalling 4593 pregnancies, between 1990 and 2000.

Main outcome measures Pregnancy induced hypertension and pre-eclampsia.

Results 302 cases of pregnancy induced hypertension and 165 cases of pre-eclampsia were identified. Use of inhaled corticosteroids from conception until date of outcome was not associated with an increased risk of pregnancy induced hypertension (adjusted odds ratio 1.02, 95% confidence interval 0.77 to 1.34) or pre-eclampsia (1.06, 0.74 to 1.53). No significant dose-response relation was observed between inhaled corticosteroids and pregnancy induced hypertension or pre-eclampsia. Oral corticosteroids were significantly associated with the risk of pregnancy induced hypertension (adjusted odds ratio 1.57, 1.02 to 2.41), and a trend was seen for pre-eclampsia (1.72, 0.98 to 3.02).

Conclusion No significant increase of the risk of pregnancy induced hypertension or pre-eclampsia was detected among users of inhaled corticosteroids during pregnancy, while markers of uncontrolled and severe asthma were found to significantly increase the risks of pregnancy induced hypertension and pre-eclampsia.

Introduction

Around 8% of pregnant women take drugs for asthma.¹ An association has been reported between asthma and pregnancy induced hypertension,²⁻⁵ but it is still unclear whether this was due to the drugs used to treat asthma or the asthma itself.⁴⁻⁹ Oral corticosteroids have been linked to an increased risk of pre-eclampsia.^{3,10} Although inhaled corticosteroids are the cornerstone of asthma treatment,¹¹ even during pregnancy,¹² evidence is lacking on any effect on risk of pregnancy induced hyper-

tension or pre-eclampsia. We carried out a large population based study among pregnant asthmatic women to investigate the association between pregnancy induced hypertension and use of inhaled corticosteroids. We also studied the drugs' effect on the risk of pre-eclampsia.

Methods

Our data came from three administrative databases for residents of Quebec, Canada: the Régie de l'assurance-maladie du Québec (RAMQ), which has information on medical services and prescribed drugs dispensed by pharmacies for insureds of RAMQ¹³; MED-ECHO, which has information on admissions to hospital; and the Fichier des événements démographiques, with information on births and still births.


We selected a cohort of asthmatic pregnant women aged 14 to 44 years from the RAMQ database. The women had to have been insured for their drugs at least a year before conception and during their pregnancy. They also had to have had at least one pregnancy ending in a delivery between 1 January 1990 and 31 December 2000, as well as one or more diagnoses of asthma and one or more prescriptions for an asthma drug in the previous two years or during pregnancy. The mother-child cohort obtained from the RAMQ database was then linked with the MED-ECHO and Fichier des événements démographiques databases to obtain information on hospital and sociodemographic variables for each woman.


Study design

We identified all cases of pregnancy induced hypertension and used density sampling to select up to 10 controls for each case.¹⁴ Using this method, we selected controls among women who were at risk of developing pregnancy induced hypertension at the time a case was identified. Controls were matched to cases for year of conception and gestational age at the time pregnancy induced hypertension was diagnosed.

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To investigate the effect of inhaled corticosteroids on the risk of pre-eclampsia, we selected cases of pre-eclampsia only. Using density sampling we selected up to 10 controls per case, matched for year of conception and gestational age at the time pre-eclampsia was diagnosed. Cases of pre-eclampsia were also included among cases of pregnancy induced hypertension.

The index date for cases of pregnancy induced hypertension and pre-eclampsia was the date of the occurrence of the condition and for their matched controls it was the date of selection.

Cases

We considered women as cases of pregnancy induced hypertension if they had a recorded diagnosis of gestational hypertension, pre-eclampsia, or eclampsia after 20 weeks' gestation or a prescription for an antihypertensive drug that was prescribed after 20 weeks' gestation and no such prescription before or during the 20th week. The index date was defined as the earliest date between the diagnosis of pregnancy induced hypertension and the first prescription of an antihypertensive drug dispensed after 20 weeks' gestation.

Cases of pre-eclampsia had to have had at least one diagnosis of pre-eclampsia after 20 weeks' gestation. The index date was defined as the date of the diagnosis of pre-eclampsia recorded after 20 weeks' gestation. For multiple pregnancies the time limit was 15 weeks.

Assessment of exposure

We assessed the exposure of cases and controls to inhaled corticosteroids by calculating the mean daily dose from conception to index date. We developed an algorithm to calculate each woman's consumption by looking at renewals of prescriptions for inhaled corticosteroids and time between renewals. We converted the daily dose into beclomethasone-chlorofluorocarbon equivalents.¹² Definitions of exposure were: exposed compared with not exposed to inhaled corticosteroids from conception to index date; and mean daily dose (0 µg, >0-200 µg, >200-500 µg, and >500 µg beclomethasone-chlorofluorocarbon equivalent) of inhaled corticosteroids from conception to index date.

Confounding variables

Potential confounders included maternal age at delivery, socioeconomic status, and area of residence at delivery.

Asthma related variables included visiting a respiratory specialist during pregnancy and using intranasal corticosteroids in the year before pregnancy and during pregnancy until the index date. We assessed the control of asthma through the frequency of use of short acting β_2 agonists (on average, three or fewer doses weekly *v* more than three doses weekly),¹¹ the use of oral corticosteroids, and visits to an emergency department or admissions for asthma, one year before and during pregnancy until the index date. To serve as a proxy for doctor perceived severity of asthma, we calculated the mean daily dose of inhaled corticosteroids in the prescription dispensed before conception.¹²

Pregnancy related variables were parity, visiting a gynaecologist or obstetrician during pregnancy, number of prenatal visits during pregnancy, multiple pregnancies, and a pregnancy in the preceding year. Maternal chronic diseases considered were diabetes mellitus and chronic hypertension (see bmj.com).

Statistical analyses

Using two conditional logistic regression models (users compared with non-users of inhaled corticosteroids and dose of drug), we estimated crude and adjusted odds ratios of pregnancy induced hypertension. We carried out backward selection of variables to identify those variables to be retained in the final model.¹⁵

We also used two other conditional logistic regression models to estimate the crude and adjusted odds ratios for use of inhaled corticosteroids and risk of pre-eclampsia.

Results

We identified 3505 asthmatic women, totalling 4593 pregnancies between 1990 and 2000. This cohort comprised 302 cases of pregnancy induced hypertension (rate 6.58%, 95% confidence interval 5.88% to 7.32%), including 128 cases of gestational hypertension, 165 cases of pre-eclampsia, and nine cases of eclampsia. We selected 3013 controls matched to the cases of pregnancy induced hypertension and 1643 controls matched to the cases of pre-eclampsia. Most women were aged between 19 and 34 years (76%) and, between conception and the index date, about half of the cases did not use inhaled corticosteroids, about 45% used daily doses of or below 500 µg, and 5% used daily doses of inhaled corticosteroids above 500 µg. Numbers were similar among controls (see bmj.com).

A higher proportion of cases with pregnancy induced hypertension than their controls were prescribed inhaled corticosteroids in the year before pregnancy, were taking oral corticosteroids before and during pregnancy, and saw a respiratory specialist during pregnancy. Cases took more doses of short acting β_2 agonists a week and had more visits to an emergency department and admissions for asthma one year before pregnancy. They were more likely to be in a first pregnancy that led to a delivery and to have multiple pregnancies. More cases than controls saw a gynaecologist or an obstetrician and had more prenatal visits.

The use of inhaled corticosteroids was not associated with an increased risk of pregnancy induced hypertension (adjusted odds ratio 1.02, 95% confidence interval, 0.77 to 1.34; table 1). Young women (18 years or less) were at a significantly reduced risk. Patients were more likely to have pregnancy induced hypertension if they used more than three doses of short acting β_2 agonists per week before pregnancy (37%), visited an emergency department or were admitted for asthma before pregnancy (59%), and used oral corticosteroids during pregnancy until the index date (57%). Using more than three doses of short acting β_2 agonists per week during pregnancy, however, significantly reduced the risk of pregnancy induced hypertension by 33%. Being seen by at least one gynaecologist or obstetrician increased the risk of having a diagnosis of pregnancy induced hypertension by 76%, as did a higher number of prenatal visits. Chronic hypertension, diabetes, and parity were the strongest predictors of pregnancy induced hypertension.

Use of inhaled corticosteroids during pregnancy was also not associated with a risk of pre-eclampsia (adjusted odds ratio 1.06, 95% confidence interval 0.74 to 1.53). All the predictors remaining in the model for pregnancy induced hypertension also remained in the

Table 1 Multivariate analyses for use of inhaled corticosteroids (dichotomous) and risk of pregnancy induced hypertension or pre-eclampsia

Variable	Pregnancy induced hypertension		Pre-eclampsia	
	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Used inhaled corticosteroids during pregnancy until index date (yes or no)	1.13 (0.89 to 1.44)	1.02 (0.77 to 1.34)	1.36 (0.99 to 1.88)	1.06 (0.74 to 1.53)
Mean age at delivery:				
≤18	0.87 (0.62 to 1.21)	0.67 (0.47 to 0.96)	1.00 (0.65 to 1.52)	—
19-34	1.0	1.0	1.0	—
≥35	1.43 (0.93 to 2.21)	1.52 (0.95 to 2.43)	0.99 (0.49 to 2.00)	—
Used oral corticosteroids during pregnancy (yes or no)	1.72 (1.17 to 2.54)	1.57 (1.02 to 2.41)	2.16 (1.30 to 3.59)	1.72 (0.98 to 3.02)
>3 v ≤3 doses β ₂ agonists weekly:				
During pregnancy	0.95 (0.74 to 1.22)	0.67 (0.48 to 0.93)	1.20 (0.87 to 1.67)	—
Before conception	1.38 (1.09 to 1.76)	1.37 (1.02 to 1.86)	1.58 (1.15 to 2.18)	—
Visited emergency department or admitted for asthma before pregnancy (yes or no)	1.69 (1.26 to 2.27)	1.59 (1.16 to 2.20)	1.63 (1.11 to 2.39)	1.70 (1.12 to 2.58)
Daily dosage (µg) of inhaled corticosteroids prescribed before conception:				
0	1.0	—	1.0	1.0
1-500	1.54 (1.08 to 2.18)	—	2.25 (1.50 to 3.38)	2.09 (1.36 to 3.23)
501-1000	1.12 (0.74 to 1.69)	—	1.06 (0.56 to 1.99)	1.14 (0.59 to 2.19)
> 1000	1.29 (0.96 to 1.74)	—	1.61 (1.04 to 2.47)	1.59 (1.01 to 2.50)
Parity (first v any subsequent delivery)	1.77 (1.38 to 2.52)	2.11 (1.60 to 2.78)	2.45 (1.74 to 3.45)	2.48 (1.73 to 3.57)
Visited gynaecologist or obstetrician during pregnancy (yes or no)	2.26 (1.57 to 3.25)	1.76 (1.20 to 2.57)	2.24 (1.37 to 3.65)	2.04 (1.21 to 3.44)
Prenatal visits (each additional visit)	1.09 (1.06 to 1.12)	1.07 (1.04 to 1.10)	1.08 (1.05 to 1.11)	1.06 (1.02 to 1.09)
Diabetes mellitus (yes or no)	5.64 (3.07 to 10.34)	4.21 (2.09 to 8.45)	4.45 (2.07 to 9.58)	1.95 (0.77 to 4.92)
Chronic hypertension (yes or no)	6.07 (3.88 to 9.50)	5.10 (3.12 to 8.32)	6.80 (3.82 to 12.10)	6.99 (3.64 to 13.44)

Table 2 Multivariate analyses for dose of inhaled corticosteroids and risk of pregnancy induced hypertension or pre-eclampsia

Variable	Pregnancy induced hypertension		Pre-eclampsia	
	Crude odds ratio (95% CI)	Adjusted odds ratio* (95% CI)	Crude odds ratio (95% CI)	Adjusted odds ratio† (95% CI)
Daily dosage (µg) of inhaled corticosteroids during pregnancy until index date:				
0	1.0	1.0	1.0	1.0
1-200	1.15 (0.88 to 1.49)	1.06 (0.80 to 1.41)	1.32 (0.93 to 1.89)	1.05 (0.71 to 1.55)
201-500	1.12 (0.74 to 1.69)	0.88 (0.54 to 1.44)	1.54 (0.91 to 2.62)	1.24 (0.70 to 2.22)
>500	1.06 (0.60 to 1.90)	0.75 (0.39 to 1.46)	1.29 (0.63 to 2.66)	0.77 (0.33 to 1.80)

*Adjusted for mean age at delivery, use of oral corticosteroids during pregnancy, dose of short acting β₂ agonists weekly during pregnancy, dose of short acting β₂ agonists weekly before pregnancy, visits to emergency department or admissions for asthma before pregnancy, parity, visits to gynaecologist or obstetrician during pregnancy, each additional prenatal visit, diabetes mellitus, chronic hypertension.

†Adjusted for use of oral corticosteroids during pregnancy, visits to emergency department or admissions for asthma before pregnancy, inhaled corticosteroids prescribed before conception, parity, visits to gynaecologist or obstetrician during pregnancy, each additional prenatal visit, diabetes mellitus, chronic hypertension.

pre-eclampsia model, except for maternal age at delivery and the use of short acting β₂ agonists. The magnitude of the adjusted odds ratios kept in both models was similar, with the exception of diabetes mellitus, which had a non-significant effect on pre-eclampsia.

When we used another set of conditional logistic regression models, we found no dose-response relation between inhaled corticosteroids and the risk of pregnancy induced hypertension or pre-eclampsia (table 2). The covariates for both conditions in the final models also remained in these models and to the same magnitude.

Discussion

Pregnant asthmatic women who use inhaled corticosteroids are not at increased risk of pregnancy induced hypertension or pre-eclampsia. Markers of uncontrolled and severe asthma, such as use of oral corticosteroids, were, however, associated with increased risks.

One study reported a significant crude association between use of inhaled corticosteroids (with or without

oral corticosteroids) and pre-eclampsia, but the association became non-significant in a multivariate model.¹⁰ Furthermore, results were non-significant when users of inhaled corticosteroids (without oral corticosteroids) were compared with non-users, probably because the group using inhaled corticosteroids included only seven cases of pre-eclampsia. A randomised controlled trial comparing users of beclomethasone (16 cases of pre-eclampsia) with users of theophylline (15 cases) reported a crude rate ratio of 1.0 for risk of pre-eclampsia.¹⁶ We found no significant association, although our study had increased statistical power and we compared users of inhaled corticosteroids with non-users while adjusting for the independent effect of oral corticosteroids and other potential confounders.

Two previous studies reported a twofold increased risk of pregnancy induced hypertension with use of oral corticosteroids.^{2,3} We found a 57% increased risk. We also found that markers of asthma control and severity measured before pregnancy were associated with an increased risk of pregnancy induced hypertension and pre-eclampsia. Patients who visited an

emergency department or were admitted for asthma in the year before conception were, respectively, 59% and 70% more at risk of pregnancy induced hypertension and pre-eclampsia. Moreover, patients with a high intake of short acting β_2 agonists before conception, a marker of uncontrolled asthma, were 37% more at risk of pregnancy induced hypertension. The use of the same quantity of the same drugs during pregnancy was, however, related to a reduction in the risk of pregnancy induced hypertension. We found that inhaled corticosteroids were not associated with an increased risk of pregnancy induced hypertension or pre-eclampsia, that oral corticosteroids were associated with an increased risk of pregnancy induced hypertension and may be related to an increased risk of pre-eclampsia, and that a lower level of asthma control was associated with an increased risk of pregnancy induced hypertension and pre-eclampsia.

Advantages and limitations of the study

Our study comprised a large sample size and we studied a wide variety of potential confounders, more accurately reflecting the situation of pregnant asthmatic women. Little information is available from clinical trials on the safety of asthma drugs during pregnancy, and databases are a key means of obtaining such data. Databases also avoid recall bias.

Our study has a few limitations, inherent in the use of administrative databases. Firstly, data are not available on women who failed to consult medical services during pregnancy or who did not give birth in a medical centre. Secondly, information is lacking on characteristics such as smoking, use of alcohol and over the counter drugs, and ethnicity. Owing to the healthcare system in Quebec, it is likely that users and non-users of inhaled corticosteroids had a similar distribution for ethnicity. Thirdly, some coding errors may be present. Non-differential misclassification of the outcome might bias the odds ratio towards the null. Nevertheless, this problem should be mitigated by the large number of cases and controls and the use of an outcome that combined several codes related to gestational hypertension. Fourthly, drug use was calculated from patterns for dispensed prescribed drugs and not on the intake of prescribed drugs. A recent study showed that only 6% of drugs dispensed to pregnant women were not used.¹⁷ Finally, the RAMQ database provides information on welfare recipients and adherents only and not citizens who are covered by private drug insurance. Our study population is mostly representative of the lower to middle class population of Quebec, but because we considered several confounders and the association under study was likely to have more biological than socioeconomic grounds, we believe that our results could be generalised to patients from other socioeconomic backgrounds.

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Contributors: LB, ER, SP, and M-FB designed the study. AF, GL, and M-JM generated and prepared the cohort. M-JM analysed the data. M-JM, LB, and ER interpreted the findings. All authors wrote the paper. LB will act as guarantor.

What is already known on this topic

Asthma during pregnancy is associated with serious complications, notably pregnancy induced hypertension

Few trials have studied the effect of asthma drugs in this association

No study has investigated the effect of inhaled corticosteroids

What this study adds

Use of inhaled corticosteroids during pregnancy does not significantly increase the risk of pregnancy induced hypertension and pre-eclampsia

Risks were significantly associated with markers of uncontrolled and severe asthma

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Competing interests: LB and M-FB are co-chairs of the endowment chair AstraZeneca in respiratory health. LB is the recipient of a new investigator salary support from the Canadian Institutes for Health Research. M-FB has received a fee from GlaxoSmithKline for speaking at an educational programme on asthma. SP is the recipient of a Chercheur Boursier Junior II salary support from the Fonds de la recherche en santé du Québec and is pharmaceutical advisory expert for the Quebec health ministry. M-JM is the recipient of a K M Hunter Foundation-Canadian Institutes for Health Research doctoral research scholarship. GL is the recipient of a doctoral research scholarship from the Natural Science and Engineering Research Council of Canada.

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