Cite this article as: BMJ, doi:10.1136/bmj.38313.624352.8F (published 19 January 2005)

# 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 preeclampsia 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

Asthma is one of the most common chronic conditions in pregnant women, with 4% to 7% of women taking drugs for asthma during pregnancy.[1–3] Pregnancy induced hypertension affects 6% to 8% of pregnant women and has serious consequences for the mother and child.[4] An association between asthma and pregnancy induced hypertension has been reported,[2 5–10] but it is still unclear whether this was due to the drugs used to treat asthma or to the asthma itself.[6 11]

Oral corticosteroids during pregnancy have been linked to an increased risk of pre-eclampsia,[3 5] but two studies showing a non-significant risk with use of inhaled corticosteroids were underpowered.[3 12] Although inhaled corticosteroids are the cornerstone of asthma treatment,[13] even during pregnancy,[14] evidence of any effect on risk of pregnancy induced hypertension or pre-eclampsia is lacking. We carried out a large population based study among pregnant asthmatic women to investigate the association between inhaled corticosteroids and the risk of pregnancy induced hypertension, including gestational hypertension, pre-eclampsia, and eclampsia. We also studied the effect of inhaled corticosteroids on the risk of pre-eclampsia.

### Methods

The data for our study came from three administrative databases in Quebec, Canada. The Régie de l'assurance-maladie du Québec (RAMQ) database provides information on medical services distributed to all residents of Quebec and on prescribed drugs dispensed by community pharmacies for residents insured by the Régie de l'assurance-maladie du Québec. Residents include elderly people and recipients of social welfare since 1980 and 1.7 million adherents (mainly workers and their families who have no collective drug insurance provided at work) since January 1997; those covered comprise about 50% of the residents of Quebec.[15] The MED-ECHO database contains information on all admissions to hospital in Quebec, and the Fichier des événements démographiques, administered by the Institut de la statistique du Québec, provides information on all births and still births. The RAMQ and MED-ECHO databases have often been used for epidemiological research.[16–18] Data on drugs recorded in the RAMQ database and medical diagnoses recorded in the MED-ECHO database are comprehensive and valid.[19 20]

Firstly, 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 by the Régie de l'assurance-maladie du Québec 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 (ICD-9 (international classification of diseases, 9th revision; code 493) and one or more prescriptions for an asthma drug in the previous two years or during pregnancy. Women were excluded if they had ischaemic heart disease, pericarditis, myocarditis, cardiac dysrhythmia, conduction disorders, heart failure, cerebrovascular disease, nephritis, nephrotic syndrome and nephrosis, migraine, and hyperthyroidism, or if they were taking a

*Definition of maternal chronic disease is on bmj.com*

cardiovascular drug that could have been used for these disorders, one year before conception. We included women with chronic hypertension or other comorbidities. Each woman was matched with her children through the RAMQ database. This mother-child cohort 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

*Primary objective*

To study whether the use of inhaled corticosteroids during pregnancy increases the risk of pregnancy induced hypertension, we identified all cases of pregnancy induced hypertension and selected up to 10 controls for each case using density sampling.[21] Using this method, we selected controls among women that were at risk of developing the outcome at the time a case was identified. In this way women could serve as controls for more than one case occurring at different times, and cases could serve as controls before they became cases. Controls were matched to cases for year of conception and gestational age at the time pregnancy induced hypertension was diagnosed. For example, if diagnosis occurred at 30 weeks' gestation and the conception date was in 1993, then controls were randomly selected among pregnancies of at least 30 weeks' duration, in which there had been no diagnosis of pregnancy induced hypertension within the first 30 weeks, and which had a conception date in 1993. We selected up to 10 controls on the basis of this criteria. The index date for cases was the date of the occurrence of pregnancy induced hypertension and for controls it was the date of selection.

*Secondary objective*

To study the effect of inhaled corticosteroids on the risk of pre-eclampsia we selected cases of pre-eclampsia only. Using the density sampling method, we selected up to 10 controls per case matched for year of conception and gestational age at the time pre-eclampsia was diagnosed. The index date for cases was the date of the occurrence of pre-eclampsia and for controls it was the date of selection. Cases of pre-eclampsia were also included among cases of pregnancy induced hypertension. In focusing on pre-eclampsia, we aimed to include the more severe form of pregnancy induced hypertension, which has a particular pathophysiological process.

### Cases

We considered women as cases of pregnancy induced hypertension if they had recorded in the RAMQ or MED-ECHO databases a diagnosis of gestational hypertension (ICD-9 codes 642.3 or 642.9), pre-eclampsia (642.4 or 642.5), or eclampsia (642.6) after the 20th week of gestation; or they had a prescription for an antihypertensive drug (amlodipine, felodipine, hydralazine, hydrochlorothiazide, labetalol, methyldopa, metoprolol, nifedipine, oxprenolol, or pindolol) that was prescribed after 20 weeks' gestation and no such prescription before or during the 20th week. Women who had a diagnosis of chronic hypertension recorded between four and 12 months after delivery were not considered as cases but were classified as having chronic hypertension. The date of the occurrence of pregnancy induced hypertension (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 date of the occurrence of pre-eclampsia (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

For each case and control we assessed the exposure to inhaled corticosteroids by calculating the mean daily dose from conception to index date. Using data from the RAMQ database we developed an algorithm to calculate each woman's consumption on the basis of renewals of prescriptions for inhaled corticosteroids and time between renewals. Using the equivalency table published in the Canadian Asthma Consensus report, we converted the mean daily dose of inhaled corticosteroids into beclomethasone-chlorofluorocarbon equivalents.[14] We used two definitions of exposure: exposed compared with not exposed to inhaled corticosteroids from conception to index date, and mean daily dose of inhaled corticosteroids (0 μg, >0-200 μg, >200-500 μg, and >500 μg of beclomethasone-chlorofluorocarbon equivalent) from conception to index date.

### Confounding variables

Potential confounders included maternal age at delivery, socioeconomic status based on receipt of social welfare one year before or during pregnancy, and area of residence at delivery (rural or urban).

Asthma related variables included visiting a respiratory specialist during pregnancy and the use of 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 $\beta_2$ agonists (on average, three or less doses weekly *v* more than three doses weekly),[13] 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. We grouped leukotriene receptor antagonists, theophylline, and long acting $\beta_2$ agonists under "additional asthma therapy" because of their low prevalence. Their use was measured one year before and during pregnancy until the index date. To serve as a proxy for severity of asthma, as perceived by the doctor, we calculated the mean daily dose of inhaled corticosteroids in the prescription dispensed before conception: 0 μg, >0-500 μg, >500-1000 μg, and >1000 μg of beclomethasone-chlorofluorocarbon equivalent.[14]

Pregnancy related variables were parity (first *v* any subsequent delivery), visiting a gynaecologist or obstetrician during pregnancy, number of prenatal visits during pregnancy (continuous variable), multiple pregnancy, 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 inhaled corticosteroids), we estimated crude and adjusted odds ratios of pregnancy induced hypertension taking into consideration potential confounders. We carried out backward selection of variables to identify those variables to be retained in the final model.[22]

Using two other conditional logistic regression models, we also estimated the crude and adjusted odds ratios for use of inhaled corticosteroids and risk of pre-eclampsia. Analyses were carried out in SAS version 8.02.

## 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. For each case of pregnancy induced hypertension we selected 10 controls, except for one case that occurred at 41 weeks' gestation, restricting the pool of controls to the three other women who delivered at 41 weeks. We thus selected 3013 controls matched to the cases of pregnancy induced hypertension. Independently, we selected 10 controls for each of the 165 cases of pre-eclampsia except for one, giving 1643 matched controls.

Sociodemographic characteristics were similar between cases of pregnancy induced hypertension and controls (table 1). A higher proportion of cases than 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 $\beta_2$ agonists a week and had more visits to an emergency department and admissions for asthma than did controls. Cases 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 cases had more prenatal visits. A greater proportion of cases than controls had diabetes mellitus and chronic hypertension.

The cases of pre-eclampsia and their controls had similar characteristics to those of cases of pregnancy induced hypertension and their controls (table 2).

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 3). Young women (18 years or less) were at a significantly reduced risk. Markers of uncontrolled asthma were significantly associated with an increased risk of pregnancy induced hypertension. Patients were more likely to have pregnancy induced hypertension if they used more than three doses of short acting $\beta_2$ 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 $\beta_2$ 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, with a 7% increased risk of pregnancy induced hypertension for each additional visit. Chronic hypertension, diabetes, and parity were the strongest predictors of pregnancy induced hypertension.

Using 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 pregnancy induced hypertension model also remained in the pre-eclampsia model, except for maternal age at delivery and the use of short acting $\beta_2$ 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. The dose of inhaled corticosteroids prescribed before conception was kept in the pre-eclampsia model but not in the pregnancy induced hypertension model.

**Table 1** Characteristics of women with pregnancy induced hypertension and their matched controls. Values are numbers (percentages) unless stated otherwise

| Variables | Cases of pregnancy induced hypertension (n=302) | Controls (n=3013) |
|---|---|---|
| Used inhaled corticosteroids during pregnancy | 150 (50) | 1403 (47) |
| Daily dosage (μg) of corticosteroids: | | |
| 0 | 152 (50) | 1610 (53) |
| 1-200 | 106 (35) | 981 (33) |
| 201-500 | 30 (10) | 284 (9) |
| >500 | 14 (5) | 138 (5) |
| Mean age at delivery: | | |
| ≤18 | 46 (15) | 533 (18) |
| 19-34 | 230 (76) | 2298 (76) |
| ≥35 | 26 (9) | 182 (6) |
| Lives in rural area | 48 (16) | 535 (18) |
| Receives social welfare | 263 (87) | 2684 (89) |
| **Asthma related** | | |
| Visited respiratory specialist at least once during pregnancy | 35 (12) | 242 (8) |
| Drugs used during pregnancy: | | |
| Intranasal corticosteroids | 40 (13) | 302 (10) |
| Additional asthma therapy | 45 (15) | 347 (12) |
| Oral corticosteroids | 33 (11) | 200 (7) |
| >3 doses of short acting $\beta_2$ agonists weekly | 109 (36) | 1119 (37) |
| Visited emergency department or admitted for asthma | 40 (13) | 390 (13) |
| Drugs used in year before pregnancy: | | |
| Intranasal corticosteroids | 43 (14) | 377 (13) |
| Additional asthma therapy | 59 (20) | 485 (16) |
| Oral corticosteroids | 51 (17) | 343 (11) |
| >3 doses of short acting $\beta_2$ agonists weekly | 141 (47) | 1170 (39) |
| Visited emergency department or admitted for asthma | 65 (22) | 425 (14) |
| Daily dosage (μg) of inhaled corticosteroids prescribed before conception: | | |
| 0 | 156 (52) | 1761 (59) |
| 1-500 | 47 (16) | 346 (12) |
| 501-1000 | 30 (10) | 303 (10) |
| >1000 | 69 (23) | 603 (20) |
| **Pregnancy related** | | |
| First delivery | 174 (58) | 1328 (44) |
| Visited gynaecologist or obstetrician at least once | 267 (88) | 2332 (77) |
| Mean No (SD) of prenatal visits | 10 (6) | 8 (5) |
| Multiple pregnancy | 4 (1) | 11 (<1) |
| Previous pregnancy in past year | 121 (40) | 1495 (50) |
| **Chronic disease** | | |
| Diabetes mellitus | 17 (6) | 32 (1) |
| Hypertension | 33 (11) | 61 (2) |

When another set of conditional logistic regression models was used we found no dose-response relation between inhaled corticosteroids and the risk of pregnancy induced hypertension and pre-eclampsia. The covariates for both conditions in the final models also remained in these models and to the same magnitude. In table 4 we therefore only present the crude and adjusted odds ratios associated with the different dosages of inhaled corticosteroids.

Because 25% of women contributed more than one pregnancy to our analyses, we carried out supplementary analyses to investigate the potential correlation between pregnancies,

**Table 2** Characteristics of women with pre-eclampsia and their matched controls. Values are numbers (percentages) unless stated otherwise

| Variables | Cases of pre-eclampsia (n=165) | Controls (n=1643) |
|---|---|---|
| Used inhaled corticosteroids during pregnancy | 85 (52) | 719 (44) |
| Daily dosage (μg) of corticosteroids: | | |
| 0 | 80 (49) | 924 (56) |
| 1-200 | 57 (35) | 498 (30) |
| 201-500 | 19 (12) | 142 (9) |
| >500 | 9 (5) | 79 (5) |
| Mean age at delivery: | | |
| ≤18 | 29 (18) | 291 (18) |
| 19-34 | 127 (77) | 1261 (77) |
| ≥35 | 9 (6) | 91 (6) |
| Lives in rural area | 29 (18) | 302 (18) |
| Receives social welfare | 143 (87) | 1448 (88) |
| **Asthma related** | | |
| Visited respiratory specialist at least once during pregnancy | 21 (13) | 145 (9) |
| Drugs used during pregnancy: | | |
| Intranasal corticosteroids | 24 (15) | 183 (11) |
| Additional asthma therapy | 27 (16) | 194 (12) |
| Oral corticosteroids | 20 (12) | 99 (6) |
| >3 doses of short acting $\beta_2$ agonists weekly | 65 (40) | 576 (35) |
| Visited emergency department or admitted for asthma | 23 (14) | 221 (14) |
| Drugs used in year before pregnancy: | | |
| Intranasal corticosteroids | 26 (16) | 200 (12) |
| Additional asthma therapy | 38 (23) | 283 (17) |
| Oral corticosteroids | 27 (16) | 193 (12) |
| >3 doses of short acting $\beta_2$ agonists weekly | 81 (49) | 621 (38) |
| Visited emergency department or admitted for asthma | 40 (24) | 273 (17) |
| Daily dosage (μg) of inhaled corticosteroids prescribed before conception: | | |
| 0 | 78 (47) | 991 (60) |
| 1-500 | 42 (26) | 243 (15) |
| 501-1000 | 12 (7) | 147 (9) |
| >1000 | 33 (20) | 262 (16) |
| **Pregnancy related** | | |
| First delivery | 106 (64) | 715 (44) |
| Visited gynaecologist or obstetrician at least once during pregnancy | 146 (89) | 1272 (77) |
| Mean (SD) No of prenatal visits | 10 (6) | 8 (5) |
| Multiple pregnancy | 3 (2) | 8 (1) |
| Previous pregnancy in past year | 62 (38) | 811 (49) |
| **Chronic disease** | | |
| Diabetes mellitus | 10 (6) | 24 (2) |
| Hypertension | 21 (13) | 35 (2) |

including one in which only one pregnancy per woman was kept (data not shown). The results were similar to those in tables 3 and 4. The correlation therefore did not have a sizeable impact on the results obtained from the conditional logistic regression models, which are the most appropriate analyses to use with a nested case-control design.

## 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.

The association between inhaled corticosteroids and pre-eclampsia has been studied.[3 12] One study showed a significant crude association between use of inhaled corticosteroids (with or without oral corticosteroids) and pre-eclampsia, but this relation became non-significant in a multivariate model.[3] Furthermore, results were non-significant when users of inhaled corticosteroids (without using any oral corticosteroids) were compared with non-users, probably because the group using inhaled corticosteroids included only seven cases of pre-eclampsia.[3] 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.[12] 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 the use of oral corticosteroids.[2 5] 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 $\beta_2$ agonists before conception were 37% more at risk of pregnancy induced hypertension. We considered these markers of asthma control and severity in the final analyses, which addresses the concern that it is difficult to distinguish between the effects of asthma drugs and the control and severity of asthma.[2 5] We found that inhaled corticosteroids were not associated with an increased risk of pregnancy induced hypertension and 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 is associated with an increased risk of pregnancy induced hypertension and pre-eclampsia.

The high intake of short acting $\beta_2$ agonists before conception, a marker of uncontrolled asthma, was associated with an increased 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. Further evidence is needed before drawing any conclusions.

Our final models show that known risk factors for pregnancy induced hypertension and pre-eclampsia—chronic hypertension, parity, and diabetes—clearly stand out and are coherent with our knowledge of these conditions.[23] The opportunity for diagnosing pregnancy induced hypertension or pre-eclampsia is probably greater when women consult an obstetrician or gynaecologist and receive intensive follow up.

### 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. The sample size gave us enough power to isolate any clinically significant effect from inhaled corticosteroids. Little information is available from clinical trials on the safety of taking drugs for asthma during

**Table 3** Multivariate analyses for use of inhaled corticosteroids (dichotomous) and risk of pregnancy induced hypertension or pre-eclampsia

| | Pregnancy induced hypertension | | Pre-eclampsia | |
|---|---|---|---|---|
| **Variable** | **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 $\beta_2$ 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) |

pregnancy, and administrative databases are a key means of obtaining such data. Databases have the advantage of avoiding recall bias. They provide full details on name, dose, and amount of drugs dispensed—information that is almost impossible to obtain by questionnaire after time has elapsed.[24–28]

Our study does, however, have 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. The ethnicity of women may be a risk factor for pregnancy induced hypertension, but because the healthcare system in Quebec enables citizens to become insured for prescribed drugs, users and non-users of inhaled corticosteroids are likely to have had a similar distribution for ethnicity. Consequently, ethnicity may not have been a confounder. Thirdly, some coding errors may be present. Non-differential misclassification of the outcome, if present, 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 a primary outcome that combined several codes related to gestational hypertension. Fourthly, drug use was calculated on the basis of the patterns for dispensed prescribed drugs and not on the intake of the drugs. However, only 6% of drugs dispensed to pregnant women are not used.[29] 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 since 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.

## Conclusions

This study did not detect a significant association or dose-response relationship between the use of inhaled corticosteroids and the risk of pregnancy induced hypertension or pre-

**Table 4** Multivariate analyses for dose of inhaled corticosteroids and risk of pregnancy induced hypertension or pre-eclampsia

| | Pregnancy induced hypertension | | Pre-eclampsia | |
|---|---|---|---|---|
| **Variable** | **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 $\beta_2$ agonists weekly during pregnancy, dose of short acting $\beta_2$ 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 visits, diabetes mellitus, chronic hypertension.

## 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

eclampsia among asthmatic women, although markers of uncontrolled and severe asthma were found to significantly increase the risks of pregnancy induced hypertension and pre-eclampsia. These results provide healthcare professionals with more evidence with which to reassure asthmatic women and encourage them to continue their inhaled corticosteroids treatment during pregnancy to control asthma.

We thank Danielle Labrie-Pelletier (Régie de l'assurance maladie du Québec), Chantal Girard (Institut de la statistique du Québec), and Louise Légaré (Ministère de la santé et des services sociaux du Québec) for assistance with the data; James A Hanley for his valuable input; and Lori Schubert for reviewing the manuscript.

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.

Funding: This research was funded by the Association pulmonaire du Québec and the Fondation Canadienne pour l'innovation.

Competing interests: LB and M-FB are cochairs 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.

Ethical approval: This study was authorised by the Commission d'accès à l'information du Québec.

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*(Accepted 11 November 2004)*

doi 10.1136/bmj.38313.624352.8F

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