Human Reproduction, Vol.28, No.4 pp. 908–915, 2013
Advanced Access publication on February 20, 2013 doi:10.1093/humrep/det024

human reproduction

ORIGINAL ARTICLE *Early pregnancy*

Relationship between maternal asthma, its severity and control and abortion

Lucie Blais[1,2,3,*], Fatima-Zohra Kettani[1,2], and Amélie Forget[1,2]

[1]Faculté de pharmacie, Université de Montréal, C.P. 6128, succursale Centre-ville, Montréal, QC, Canada H3C 3J7 [2]Hôpital du Sacré-Cœur de Montréal, 5400, boul. Gouin Ouest, Montréal, QC, Canada H4J 1C5 [3]Endowment pharmaceutical Chair AstraZeneca in Respiratory Health, Montréal, QC, Canada

*Correspondence address. Tel: +1-514-343-6111 ext. 3786; +1-Fax: +514-343-6120; E-mail: lucie.blais@umontreal.ca

Submitted on September 20, 2012; resubmitted on January 10, 2013; accepted on January 16, 2013

STUDY QUESTION: Are women with asthma, and more specifically those with severe or uncontrolled asthma, at higher risk of spontaneous and induced abortions?

SUMMARY ANSWER: Pregnant women with asthma, notably when uncontrolled, are at higher risk of spontaneous abortion.

WHAT IS KNOWN ALREADY: Only one study has examined the association between asthma and spontaneous and induced abortions and revealed a modest increase in the risk of spontaneous abortions, particularly in women with more severe asthma and those with previous exacerbations, and a marginal decrease in the risk of induced abortions.

STUDY DESIGN, SIZE, DURATION: A cohort of pregnancies from asthmatic ($n = 15\,107$) and non-asthmatic ($n = 34\,331$) women was reconstructed by linking three administrative databases from Quebec (Canada), between 1992 and 2002. The cohort included 7870 spontaneous abortions, 14 596 induced abortions and 26 972 live births.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Pregnant women with and without asthma were analyzed. Asthma was defined by at least one asthma diagnosis and one dispensed prescription for an asthma medication in the 2 years prior to or during pregnancy. Asthma severity and control were assessed using validated indexes in the year before the 20th week of pregnancy or the termination of the pregnancy. Logistic polytomous regression models were used to estimate the relationship between asthma and asthma severity and control on the risk of abortion, while adjusting for potential confounders.

MAIN RESULTS AND THE ROLE OF CHANCE: The prevalence of spontaneous and induced abortions was 15.9 and 29.5%, respectively. Maternal asthma was associated with an increased risk of a spontaneous abortion [odds ratio (OR) = 1.41; 95% confidence interval (CI): 1.33–1.49] and a decreased risk of induced abortions (OR = 0.92; 0.88–0.97). No association was observed between asthma severity and abortion, while uncontrolled asthma increased the risk of a spontaneous abortion by 26% (95% CI: 14–41%) and the risk of induced abortions by 11% (95% CI: 1–21%).

LIMITATIONS, REASONS FOR CAUTION: It is possible that the study results were confounded by imbalances between groups in variables that are not recorded in the databases, but that are known to be associated with spontaneous abortions, such as alcohol consumption, obesity or maternal smoking. However, we performed sensitivity analyses which revealed that these factors are unlikely to explain the observed increased risk for a spontaneous abortion. It is also possible that women with asthma are more likely to have abortions recorded in the databases, because subjects with a chronic disease tend to visit a physician more often than those without asthma. Therefore, our odds estimates for these outcomes may be overestimated when asthmatic women were compared with non-asthmatic women. A further limitation of the study is that it would have been more appropriate to measure the severity and control of asthma only during the pregnancy.

WIDER IMPLICATIONS OF THE FINDINGS: Our cohort is less representative of women in the upper socio-economic level. This is not a threat to internal validity, but it could limit the external validity if the impact of asthma on the risk of abortion differed according to the socio-economic status of the mother. Despite the absence of supporting data, this possibility cannot be completely excluded.

STUDY FUNDING/COMPETING INTEREST(S): This study was funded by the Canadian Institutes of Health Research and Genentech. L.B. received research grants from Astra-Zeneca, Pfizer, sanofi-aventis, Novartis and Merck for research projects and co-chairs the Astra-Zeneca Endowment Pharmaceutical Chair in Respiratory Health. F.Z.K and A.F. have no competing interests to declare.

Key words: Asthma / pregnancy / spontaneous abortions / induced abortions / asthma severity and control

Introduction

Asthma has been reported to affect up to 8.8% of pregnant women (Kwon *et al.*, 2006). In observational studies, women with asthma have higher risks of several complications of pregnancy, including pre-eclampsia, caesarean delivery, infants with low birthweight and infants with congenital malformations (Demissie *et al.*, 1998; Liu *et al.*, 2001; Enriquez *et al.*, 2007; Tata *et al.*, 2007, 2008; Blais *et al.*, 2010). Moreover, studies have shown an association between poorly controlled asthma and increased risk of adverse outcomes suggesting that good asthma management in the preconception period and during pregnancy is beneficial for both mother and fetus (Murphy *et al.*, 2006; Bakhireva *et al.*, 2008).

However, there are very little data on the impact of maternal asthma, or its severity and control, on the risk of spontaneous and induced abortions. We found four studies that examined the association between asthma and abortions (Sobande *et al.*, 2002; Tata *et al.*, 2007; Syed *et al.*, 2008; Sarkar *et al.*, 2009). One of them showed no significant differences in the proportion of spontaneous abortions between pregnant asthmatic and non-asthmatic women, but it lacked statistical power (Sarkar *et al.*, 2009). The three other studies reported a higher risk of abortions among women with asthma compared with those without asthma (Sobande *et al.*, 2002; Tata *et al.*, 2007; Syed *et al.*, 2008), yet only one of them specifically looked at each type of abortion, adjusted for potential confounders and assessed whether risks differ according to asthma severity and control (Tata *et al.*, 2007). The Tata *et al.* (2007) study revealed a modest increase in odds of a spontaneous abortion (10%), and a marginal decrease in odds of an induced abortion (5%) when comparing women with and without asthma (Tata *et al.*, 2007). The increased risk of a spontaneous abortion was particularly high in women with more severe asthma and those with previous exacerbations. However, the authors used a control group of women without asthma in their analyses instead of a control group with mild or controlled asthma (Tata *et al.*, 2007).

Therefore, we designed a cohort study to further evaluate the association between maternal asthma and abortions (spontaneous and induced) as well as to study the impact of asthma severity and control on these outcomes, using data from a large cohort of pregnancies from asthmatic and non-asthmatic women from Québec, Canada.

Materials and Methods

Data source

This study involved data from three interlinked administrative health databases from the province of Québec: the *Régie de l'assurance-maladie du Québec* (RAMQ), the *Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière* (MED-ECHO) and the *Fichier des événements démographiques du Québec* managed by the *Institut de la statistique du Québec*. The RAMQ databases provide information on medical services dispensed to all residents of Québec and on prescribed medications filled in community pharmacies by residents covered by the RAMQ Public Drug Insurance Plan (43% of the population). The MED-ECHO database gathers data on acute care hospitalizations and covers all residents of Québec. The *Fichier des événements démographiques* provides information on all births and stillbirths in Québec. The detailed content of these databases and their validity have been largely discussed in previous studies (Blais and Forget, 2008; Breton *et al.*, 2010).

Study design

From the three databases, a cohort of pregnancies from all asthmatic women and pregnancies from a 33% random sample of non-asthmatic women occurring between 1 January 1990 and 31 December 2002 was built. If a woman had more than one pregnancy during the study period, only the latest pregnancy was retained in the cohort. Moreover, to be included in this cohort, women had to be between 13 and 50 years of age at the beginning of their pregnancy and had to be covered by the RAMQ drug insurance plan for at least one year prior to the pregnancy and throughout its entire duration. To be considered as having asthma, a woman had to have a diagnosis of asthma recorded in the RAMQ or MED-ECHO databases (ICD-9 code 493, except 493.2) and at least one filled prescription for an asthma medication recorded in the RAMQ database in the 2 years prior to or during pregnancy. Non-asthmatic women were selected with the same inclusion criteria, except that they had no diagnosis of asthma recorded in the databases and filled no prescription for an asthma medication between 1988 and 2002.

Deliveries included in this cohort have been used in the past to study the impact of asthma and asthma medications on the health of the mother and the newborn (Breton *et al.*, 2010; Blais *et al.*, 2012). However, it is worth noting that this article is the first to report the data on abortions included in this cohort.

Outcomes

Spontaneous abortions (loss of pregnancy before the 20th week of gestation without medical or surgical termination) were defined as pregnancies terminating by (i) the ICD-9 codes 634 or 761.8; or (ii) a medical procedure coded 6900 or 6906 or (ii) pregnancies without a delivery and no code for an induced abortion.

Induced abortions (therapeutic or elective termination of pregnancy) were defined as pregnancies ending by (i) the ICD-9 codes 630–633, 635–636, 638–639, 779.6, or (ii) a medical procedure coded as 6902, 6905, 6908–6909, 6938–6939, 6941, 6947–6949, 6951, 6430.

Pregnancies ending in a live birth were identified with ICD-9 diagnosis codes or medical procedure codes related to labour and delivery; details of which are available upon request.

Exposures

The exposures under study were maternal asthma, as defined above, as well as asthma severity and asthma control in the year before the 20th week of pregnancy or the termination of the pregnancy. Asthma severity and control were measured with validated indexes that we developed and that are based on the use of asthma medications and acute care for asthma over a 12-month period and on the definition provided in the Canadian Asthma Consensus Guidelines (Boulet *et al.*, 1999; Lemiere *et al.*, 2004; Firoozi *et al.*, 2007). Asthma severity is categorized under three levels (mild, moderate and severe), which are mainly based upon the doses of inhaled corticosteroids (ICSs) and the use of long-acting beta2-agonists (LABA) as add-on therapy. Asthma control is either categorized as controlled or uncontrolled based upon emergency visits and hospitalizations

for asthma, a filled prescription for a short-course of oral corticosteroids and high weekly doses of short-acting beta-agonists (SABA).

Potential confounders

Several variables were considered as potential confounders in this study. Maternal characteristics included age at conception (<18, 18–34, >34 years), a well-established risk factor of a spontaneous abortion and receipt of social assistance 1 year prior to or during pregnancy (yes/no). Maternal chronic conditions consisted of chronic hypertension (yes/no) and diabetes mellitus (yes/no)—two other potential risk factors of spontaneous abortion—which were identified from diagnoses or filled prescriptions of related medications recorded in the RAMQ or MED-ECHO databases 1 year prior to pregnancy using specific algorithms that we developed for each condition and used in other studies (Blais *et al.*, 2007; Breton *et al.*, 2009); details of which will be provided upon request. We also assessed the use of teratogenic medications (e.g. angiotensin-converting-enzyme inhibitors, anticholinergic drugs, antithyroid drugs, carbamazepine, cyclophosphamide, lithium, misoprostol, phenythoin, tetracycline, warfarin) (yes/no) in the first trimester of pregnancy (Koren *et al.*, 1998) and whether or not the women had a history of undergoing at least one abortion in the 2 years prior to pregnancy, as this is a well-known risk factor for spontaneous abortion. Finally, the use of intranasal corticosteroids (yes/no) and a visit to a respiratory physician in the year before the 20th week of pregnancy or the termination of the pregnancy (yes/no) were assessed as potential asthma-related confounding variables in the analyses performed among pregnancies of asthmatic women.

Use of asthma medications and health-care services for asthma

We described the use of asthma medications and health-care services for asthma in the year before the 20th week of pregnancy or the termination of the pregnancy. We reported the use and mean daily dose of ICS, the average weekly use of SABA (0, >0–3, >3 doses per week), the use of LABA or leukotriene receptor antagonists or theophylline (yes/no), and the use of oral corticosteroids (yes/no). We also assessed whether a woman had a hospitalization or an emergency department visit for asthma in the year before the 20th week of pregnancy or the termination of the pregnancy (yes/no). The average daily dose of ICS and weekly use of SABA were measured with algorithms that we developed and used in previous studies (Blais *et al.*, 2007; Martel *et al.*, 2007). A detailed description of the algorithms can be obtained upon request. Of note, since all these asthma-related variables are included in the algorithms measuring asthma severity and control (i.e. our secondary exposures), they were not considered as potential confounders in the analyses.

Statistical analyses

The prevalence of spontaneous and induced abortions was estimated among pregnancies from women with and without asthma. Descriptive statistics were used to compare the characteristics of women who had a spontaneous or an induced abortion with the characteristics of women who had a live birth, which were considered as the reference group.

Two polytomous logistic regression models were used to obtain crude and adjusted odds ratios (OR) and their 95% confidence interval (CI) for spontaneous and induced abortions in association with maternal asthma in the entire cohort (model 1), and with asthma severity and control among asthmatic women only (model 2), adjusting for all potential confounders listed above. In both models, live births were used as the reference category.

Since data on smoking, BMI and alcohol consumption, which are recognized as risk factors for a spontaneous abortion, are not available in the databases, we used a sensitivity analysis proposed by Schneeweiss *et al.* (2006) (the 'Array approach') to assess the impact of these potential confounders on our main analysis; for example, the association between asthma and a spontaneous abortion. This method allows evaluation of how the strength of the association between an unmeasured confounder and the outcome, and the imbalance of the confounder among exposure categories, affect the observed OR. A detailed description of this method is available in the Supplementary data.

All analyses were performed with the SAS 9.2 software package (SAS Institute, Cary, NC, USA) except the sensitivity analysis, which was performed using Microsoft Excel 2007 (Schneeweiss, 2006). A $P < 0.05$ was considered significant.

Ethical considerations

An authorization was obtained from the *Commission d'accès à l'information du Québec* prior to requesting and linking the information from the three databases. This study was approved by the Ethics Committee of the Hôpital du Sacré-Coeur de Montréal.

Results

A total of 49 438 pregnancies from asthmatic ($n = 15\,107$) and non-asthmatic women ($n = 34\,331$) formed the cohort under study. Overall, 15.9% of pregnancies resulted in a spontaneous abortion, while 29.5% resulted in an induced abortion.

As observed in Table I, a higher proportion of women who had an abortion (any type) were aged >34 years, were recipients of social assistance, used teratogenic drugs during the first trimester of pregnancy and had a history of abortions in the 2 years before pregnancy than women who had a live birth (all $P < 0.001$). Women who had a spontaneous abortion were also more likely to have asthma, chronic hypertension and diabetes mellitus than women who had a live birth, while the opposite was seen with for women who had an induced abortion ($P < 0.001$).

Among asthmatic women, those who had an abortion (any type) had more severe asthma and more uncontrolled asthma than women who had a live birth (Table II). A greater proportion of women who had a spontaneous abortion used ICS in the year before pregnancy, took more doses of SABA per week and used other anti-asthmatic medications than women who had a live birth. In addition, women who had a spontaneous abortion were more likely to have an emergency department visit for asthma in the year prior to pregnancy than women who had a live birth. There were no differences between the groups for asthma hospitalizations (Table II).

As seen in Table III, having asthma was associated with increased odds of spontaneous abortions, while it was associated with decreased odds of induced abortions. Young and old maternal age, receipt of social assistance, previous abortions and use of teratogenic medications were important risk factors for both types of abortion. It is worth noting that all potential confounders were kept in the model since they were all significantly associated with the outcomes.

In the subgroup of pregnancies of asthmatic women, asthma severity was not significantly associated with either type of abortion. On the other hand, uncontrolled asthma was associated with increased odds of spontaneous abortions and induced abortions (Table IV).

Table I Characteristics of pregnant women included in the cohort (*N* = 49 438).

	Spontaneous abortions (*N* = 7870), *n* (%)	Induced abortions (*N* = 14 596), *n* (%)	Live births (*N* = 26 972), *n* (%)	*P*-value
Maternal socio-demographic variables				
Age at conception (years)				
<18	407 (5.2)	837 (5.7)	664 (2.5)	
18–34	4803 (61.0)	11 333 (77.6)	23 429 (86.9)	
>34	2660 (33.8)	2426 (16.7)	2879 (10.7)	<0.001
Receipt of social assistance during or in the year before pregnancy	4659 (59.2)	8699 (59.6)	14 610 (54.2)	<0.001
Maternal chronic conditions				
Asthma	2946 (37.4)	4170 (28.6)	7991 (29.6)	<0.001
Chronic hypertension	340 (4.3)	210 (1.4)	485 (1.8)	<0.001
Diabetes mellitus	275 (3.5)	197 (1.3)	503 (1.9)	<0.001
Use of teratogenic medications during the first trimester of pregnancy	402 (5.1)	338 (2.3)	243 (0.9)	<0.001
≥1 Spontaneous abortion in the 2 years before the current pregnancy	647 (8.2)	505 (3.5)	1724 (6.4)	<0.001
≥1 Induced abortion in the 2 years before the current pregnancy	479 (6.1)	2566 (17.6)	1725 (6.4)	<0.001

Chi-square tests were used to compare categorical variables.

Table II Use of medications and health-care services for asthma in the year before the 20th week of pregnancy or the termination of the pregnancy among the 15 107 asthmatic women.

In the year preceding the 20th week of pregnancy or the termination of the pregnancy	Spontaneous abortions (*N* = 2946), *n* (%)	Induced abortions (*N* = 4170), *n* (%)	Live births (*N* = 7991), *n* (%)	*P*-value
Use of ICSs	1616 (54.9)	2000 (48.0)	3636 (45.5)	<0.001
Mean ± sd daily dose (μg) of ICSs among users	234.6 ± 329.6	186.6 ± 289.1	183.5 ± 280.8	<0.001
Use of short-acting beta2-agonists (doses/week)				
0	862 (29.3)	1431 (34.3)	2920 (36.5)	<0.001
>0–3	999 (33.9)	1393 (33.4)	2677 (33.5)	
>3	1085 (36.8)	1346 (32.3)	2394 (30.0)	
Use of long-acting beta-agonists, leukotriene receptor antagonists or theophylline	348 (11.8)	342 (8.2)	521 (6.5)	<0.001
Use of oral corticosteroids (prescriptions <14 days)	472 (16.0)	548 (13.1)	868 (10.9)	<0.001
Use of intranasal corticosteroids	428 (14.5)	408 (9.8)	861 (10.8)	<0.001
≥1 visit to a respiratory physician	272 (9.2)	256 (6.1)	547 (6.8)	<0.001
Hospitalizations for asthma	40 (1.4)	61 (1.4)	100 (1.3)	0.621
Emergency department visits for asthma	474 (16.1)	606 (14.5)	1090 (13.6)	0.005
Asthma severity				
Mild	2261 (76.7)	3345 (80.2)	6552 (82.0)	<0.001
Moderate	454 (15.4)	564 (13.5)	971 (12.2)	
Severe	231 (7.8)	261 (6.3)	468 (5.9)	
Uncontrolled asthma	1381 (46.9)	1704 (40.9)	3064 (38.3.)	<0.001

ICS, inhaled corticosteroids.
χ^2 tests were used to compare categorical variables. ANOVA tests were use used to compare continuous variables.

Table III Association between maternal asthma and the risk of abortion ($N = 49\,438$).

	Spontaneous abortions versus live births, adjusted OR[a] (95% CI)	Induced abortions versus live births, adjusted OR[a] (95% CI)
Maternal asthma (yes versus no)	1.41 (1.33–1.49)	0.92 (0.88–0.97)
Age		
>18–34	Reference	Reference
<18	2.93 (2.58–3.33)	2.73 (2.46–3.04)
>34	4.39 (4.12–4.67)	1.83 (1.72–1.94)
Social assistance (yes versus no)	1.12 (1.06–1.18)	1.18 (1.13–1.23)
Previous spontaneous abortion (yes versus no)	1.21 (1.09–1.33)	0.59 (0.53–0.65)
Previous induced abortion (yes versus no)	1.07 (0.96–1.19)	3.10 (2.90–3.31)
Use of teratogenic medications in first trimester (yes versus no)	4.39 (3.71–5.21)	2.60 (2.19–3.07)
Chronic hypertension (yes versus no)	1.50 (1.28–1.75)	0.75 (0.63–0.88)
Diabetes mellitus (yes versus no)	1.35 (1.15–1.58)	0.72 (0.61–0.85)

OR, odds ratio; CI, confidence interval.
[a]All ORs were obtained from polytomous regression model 1.

Table IV Association between abortion and asthma severity and control, measured in the year before the 20th week of pregnancy or the termination of the pregnancy among asthmatic women ($N = 15\,107$).

	Spontaneous abortions versus live births, adjusted OR[a] (95% CI)	Induced abortions versus live births, adjusted OR[a] (95% CI)
Severity of asthma		
Mild	Reference	Reference
Moderate	1.02 (0.89–1.18)	1.07 (0.94–1.22)
Severe	1.05 (0.86–1.26)	1.03 (0.86–1.23)
Uncontrolled asthma (yes versus no)	1.26 (1.14–1.41)	1.11 (1.01–1.21)
Age		
>18–34	Reference	Reference
<18	2.34 (1.93–2.85)	2.34 (1.98–2.78)
>34	4.67 (4.16–5.24)	1.86 (1.65–2.11)
Social assistance (yes versus no)	1.10 (0.99–1.21)	0.97 (0.89–1.06)
Previous spontaneous abortion (yes versus no)	1.45 (1.25–1.69)	0.76 (0.65–0.90)
Previous induced abortion (yes versus no)	1.06 (0.88–1.26)	3.12 (2.77–3.52)
Use of teratogenic medications in first trimester (yes versus no)	4.15 (3.21–5.37)	2.45 (1.87–3.22)
Chronic hypertension (yes versus no)	1.28 (1.02–1.62)	0.64 (0.49–0.85)
Diabetes mellitus (yes versus no)	1.51 (1.20–1.91)	0.76 (0.58–0.99)
Use of intranasal corticosteroids (yes versus no)	1.17 (1.03–1.34)	0.89 (0.78–1.01)
≥1 visit to a respiratory physician	1.03 (0.87–1.22)	0.89 (0.75–1.04)

OR, odds ratio; CI, confidence interval.
[a]All ORs were obtained from polytomous regression model 2.

The sensitivity analyses were performed assuming an absolute difference of 14% in the prevalence of smoking, of 13% in the prevalence of high BMI and of 0.8% in the prevalence of alcohol consumption between asthmatic and non-asthmatic women, and assuming an OR of 3.4 (Dominguez-Rojas *et al.*, 1994), 1.7 (Metwally *et al.*, 2008) and 2.3 (Windham *et al.*, 1997), respectively, for the associations between these variables and spontaneous abortions. Based upon these assumptions, the OR for spontaneous abortions in association with asthma would decrease to 1.22, 1.31 and 1.40, if adjusted for smoking, BMI and alcohol consumption, respectively (see Supplementary data, Table SE1).

Discussion

In this population-based study, maternal asthma was found to be associated with an increased risk of spontaneous abortions and with a reduced risk of induced abortions. Moreover, the level of asthma severity was not associated with either type of abortion, while uncontrolled asthma was associated with a higher risk of spontaneous and induced abortions.

To the best of our knowledge, only four studies have investigated the relationship between asthma and abortions (Sobande *et al.*, 2002; Tata *et al.*, 2007; Syed *et al.*, 2008; Sarkar *et al.*, 2009). Three of them found a higher prevalence of abortions among pregnant asthmatic women than non-asthmatic ones (Sobande *et al.*, 2002; Tata *et al.*, 2007; Syed *et al.*, 2008). However, two of these studies only reported the crude mean difference in the number of abortions between asthmatic and non-asthmatic women (0.62 versus 0.24, respectively $P < 0.0001$ in ref. Syed *et al.*, 2008: 0.70 versus 0.35, respectively, $P = 0.005$; Sobande *et al.*, 2002) and did not differentiate between spontaneous and induced abortions. The third study by Tata *et al.* (2007) separately examined spontaneous and induced abortions, did adjust for some potential confounders and evaluated the impact of asthma severity and control on the risk of spontaneous and induced abortions. Their study found an increase in odds of spontaneous abortions [adjusted OR (aOR):1.10; 95% CI: 1.06–1.13], lower than we observed here, and a marginal decrease in odds of induced abortions (aOR: 0.95; 0.92–0.99), quite close to our estimate. The small increased risk of spontaneous abortions reported was higher in women with more severe asthma, as indicated by the use of ICS with or without LABA (aOR: 1.24;1.17–132), and those with previous exacerbations (aOR: 1.28; 1.15–1.43), compared with women without asthma.(Tata *et al.*, 2007) The Tata *et al.* (2007) study also showed that induced abortions (therapeutic) were increased in women with previous exacerbations (aOR: 1.16; 1.04–1.30). However, more informative comparison groups for these associations would have been women with less severe asthma and asthmatic women without a previous exacerbation, to be able to estimate whether severe and uncontrolled asthma are associated with an increased risk of abortions, above and beyond the risk associated with the disease *per se*. In our study, we did not observe an association between asthma severity and the risk of abortion, however, we found that uncontrolled asthma increased the risk of a spontaneous abortion by 26% and the risk of an induced abortion by 11%, suggesting that good asthma management in the preconception period and during pregnancy is of greater importance for the mother than her level of asthma severity. Besides, although Tata *et al.* adjusted their analyses for three important confounders (i.e. maternal age, smoking habit and BMI), they had high levels of missing data for these variables (25–45%) (Tata *et al.*, 2007). In our study, we could not adjust for smoking or BMI as these variables are not available in administrative databases. However, we performed sensitivity analyses which revealed that maternal smoking, high BMI and even alcohol consumption, another risk factor, are unlikely to explain the observed increased risk for a spontaneous abortion. Furthermore, Tata *et al.* (2007) did not adjust their analyses for socio-economic status, previous abortions, use of teratogenic medications, chronic hypertension and diabetes mellitus. These variables, along with the maternal age, were found in our study to act as risk factors for spontaneous abortions, which is consistent with the literature (Mills *et al.*, 1988; Regan *et al.*, 1989; Maconochie *et al.*, 2007; Czeizel and Banhidy, 2011).

One proposed mechanism to explain the increased risk of a spontaneous abortion in women with asthma is hypoxia, particularly during asthma exacerbations (Murphy *et al.*, 2006). Our finding that showed that women with uncontrolled asthma are more at risk of spontaneous abortions reinforces this hypothesis. One should keep in mind however, that asthma severity and control were measured in the year before the 20th week or the termination of the pregnancy, and not only during the pregnancy. A 1-year period was used since the indexes of asthma severity and control that we used were validated over that period (Firoozi *et al.*, 2007). We recognize that measuring asthma severity and control during pregnancy only would have been more appropriate, but a sensitivity analysis revealed that the results were similar whether asthma severity and control were measured over a 1-year period or during pregnancy only. Moreover, it could be the medication taken for the treatment of asthma that has direct adverse effects on the immediate viability of the fetus *in utero* (Murphy *et al.*, 2006). The possible mechanism behind the decreased risk of induced abortions is not as clear. Induced abortions could be for therapeutic or personal reasons. Therefore, it is possible that a woman with asthma who wants to have a baby would have closer medical supervision, which will reduce her risk for a therapeutic abortion, not to mention voluntary abortion in this case also. Ultimately, the results of our study underscore the importance of examining spontaneous and induced abortion separately, as the impact of asthma on these two outcomes are opposed.

Our study has some important strengths. By using administrative databases, we had access to a large number of pregnancies from asthmatic and non-asthmatic women that enabled us to obtain precise relative risk estimates for spontaneous and induced abortions separately. In addition, the validity of the medical diagnoses of asthma recorded in the RAMQ database has been formally evaluated and found to be good (Blais *et al.*, 2006). Moreover, using validated indexes and appropriate comparison groups, we were able to differentiate between the impact of the disease (asthma per se), the impact of the level of asthma severity and the impact of uncontrolled asthma on the risk of abortions. However, there are also some limitations that should be taken into account when interpreting the results. First, it is possible that the results were confounded by imbalances between groups in variables that are not recorded in the databases but that are known to be associated with spontaneous abortions, such as alcohol consumption, BMI or maternal smoking. However, our sensitivity analysis revealed that these variables are unlikely to explain the observed risk. Secondly, it is possible that women with asthma are more likely to have abortions recorded in the databases, because subjects with a chronic disease tend to visit a physician more often than those without asthma. Therefore, our odds estimates for these outcomes may be overestimated when asthmatic women were compared with non-asthmatic women. Finally, our cohort is less representative of women in the upper socioeconomic level. This is not a threat to internal validity but could reduce the external validity of the study if the impact of asthma, or its severity and control, on the risk of abortion differed according to socioeconomic status of the mother. Despite the absence of supporting data, this possibility cannot be completely excluded.

In summary, pregnant asthmatic women, and specifically those whose asthma is poorly controlled, are more likely to have a

spontaneous abortion. Our study identified a modifiable predictor (asthma) of a spontaneous abortion, which provides additional evidence regarding the importance of maintaining optimal asthma control prior to and during pregnancy.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Authors' roles

L.B. was involved in study conception and design and in the acquisition of data. A.F. was involved in data analysis. L.B., F.Z.K and A.F. contributed to data interpretation. F.Z.K drafted the manuscript. All authors provided substantial intellectual contributions and approved the final version of the manuscript.

Funding

This study was funded by the Canadian Institutes of Health Research and Genentech.

Conflict of interest

L.B. also received research grants from Astra-Zeneca, Pfizer, sanofi-aventis, Novartis and Merck for research projects and co-chairs the Astra-Zeneca Endowment Pharmaceutical Chair in Respiratory Health. F.Z.K. and A.F. have no competing interests to declare.

References

Bakhireva LN, Schatz M, Jones KL, Chambers CD. Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth. *Ann Allergy Asthma Immunol* 2008;**101**:137–143.

Blais L, Forget A. Asthma exacerbations during the first trimester of pregnancy and the risk of congenital malformations among asthmatic women. *J Allergy Clin Immunol* 2008;**121**:1379–1384, 1384.

Blais L, Lemière C, Menzies D, Berbiche D. Validity of asthma diagnoses recorded in the Medical Services database of Quebec. *Pharmacoepidemiol Drug Saf* 2006;**15**:245–252.

Blais L, Beauchesne MF, Rey E, Malo JL, Forget A. Use of inhaled corticosteroids during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. *Thorax* 2007; **62**:320–328.

Blais L, Kettani FZ, Elftouh N, Forget A. Effect of maternal asthma on the risk of specific congenital malformations: A population-based cohort study. *Birth Defects Res A Clin Mol Teratol* 2010;**88**:216–222.

Blais L, Firoozi F, Kettani FZ, Ducharme FM, Lemiere C, Beauchesne MF, Berard A. Relationship between changes in inhaled corticosteroid use and markers of uncontrolled asthma during pregnancy. *Pharmacotherapy* 2012;**32**:202–209.

Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian Asthma Consensus Report, 1999. Canadian Asthma Consensus Group. *CMAJ* 1999;**161**:S1–S61.

Breton MC, Beauchesne MF, Lemiere C, Rey E, Forget A, Blais L. Risk of perinatal mortality associated with asthma during pregnancy. *Thorax* 2009;**64**:101–106.

Breton MC, Beauchesne MF, Lemiere C, Rey E, Forget A, Blais L. Risk of perinatal mortality associated with inhaled corticosteroid use for the treatment of asthma during pregnancy. *J Allergy Clin Immunol* 2010; **126**:772–777.

Czeizel AE, Banhidy F. Chronic hypertension in pregnancy. *Curr Opin Obstet Gynecol* 2011;**23**:76–81.

Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. *Am J Respir Crit Care Med* 1998; **158**:1091–1095.

Dominguez-Rojas V, de Juanes-Pardo JR, Astasio-Arbiza P, Ortega-Molina P, Gordillo-Florencio E. Spontaneous abortion in a hospital population: are tobacco and coffee intake risk factors? *Eur J Epidemiol* 1994;**10**:665–668.

Enriquez R, Griffin MR, Carroll KN, Wu PS, Cooper WO, Gebretsadik T, Dupont WD, Mitchel EF, Hartert TV. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol* 2007;**120**:625–630.

Firoozi F, Lemiere C, Beauchesne MF, Forget A, Blais L. Development and validation of database indexes of asthma severity and control. *Thorax* 2007;**62**:581–587.

Koren G, Pastuszak A, Ito S. Drug therapy - Drugs in pregnancy. *N Engl J Med* 1998;**338**:1128–1137.

Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: Prevalence, diagnosis, and symptoms. *Immunol Allergy Clin North Am* 2006;**26**:29–62.

Lemiere C, Bai T, Balter M, Bayliff C, Becker A, Boulet LP, Bowie D, Cartier A, Cave A, Chapman K *et al.* Adult asthma consensus guidelines update 2003. *Can Respir J* 2004;**11**:9A–18A.

Liu S, Wen SW, Demissie K, Marcoux S, Kramer MS. Maternal asthma and pregnancy outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 2001;**184**:90–96.

Maconochie N, Doyle P, Prior S, Simmons R. Risk factors for first trimester miscarriage—results from a UK-population-based case-control study. *BJOG* 2007;**114**:170–186.

Martel MJ, Rey E, Beauchesne MF, Perreault S, Forget A, Maghni K, Lefebvre G, Blais L. Use of short-acting beta2-agonists during pregnancy and the risk of pregnancy-induced hypertension. *J Allergy Clin Immunol* 2007;**119**:576–582.

Metwally M, Ong KJ, Ledger WL, Li TC. Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. *Fertil Steril* 2008; **90**:714–726.

Mills JL, Simpson JL, Driscoll SG, Jovanovic-Peterson L, Van AM, Aarons JH, Metzger B, Bieber FR, Knopp RH, Holmes LB *et al.* Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. *N Engl J Med* 1988;**319**:1617–1623.

Murphy VE, Clifton VL, Gibson PG. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes. *Thorax* 2006;**61**:169–176.

Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. *BMJ* 1989;**299**: 541–545.

Sarkar M, Koren G, Kalra S, Ying A, Smorlesi C, De SM, Diav-Citrin O, Avgil M, Lavigne SV, Berkovich M *et al.* Montelukast use during pregnancy: a multicentre, prospective, comparative study of infant outcomes. *Eur J Clin Pharmacol* 2009;**65**:1259–1264.

Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf* 2006;**15**:291–303.

Sobande AA, Archibong EI, Akinola SE. Pregnancy outcome in asthmatic patients from high altitudes. *Int J Gynaecol Obstet* 2002;**77**:117–121.

Syed RZ, Zubairi AB, Zafar MA, Qureshi R. Perinatal outcomes in pregnancy with asthma. *J Pak Med Assoc* 2008;**58**:525–527.

Tata L, Lewis S, McKeever T, Smith C, Doyle P, Smeeth L, West J, Hubbard R. A comprehensive analysis of adverse obstetric and pediatric complications in women with asthma. *Am J Respir Crit Care Med* 2007;**175**:991–997.

Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, Gibson JE, Hubbard RB. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. *Thorax* 2008;**63**:981–987.

Windham GC, Von BJ, Fenster L, Schaefer C, Swan SH. Moderate maternal alcohol consumption and risk of spontaneous abortion. *Epidemiology* 1997;**8**:509–514.