ORIGINAL ARTICLE

Impact of maternal use of asthma-controller therapy on perinatal outcomes

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ABSTRACT

Background Asthma during pregnancy usually requires treatment with controller medications about which more safety information is needed. The objectives are to assess the impact of the use of long-acting β_2-agonists (LABAs) and the dose of inhaled corticosteroids (ICSs) during pregnancy on the prevalence of low birth weight (LBW), preterm birth (PB) and small for gestational age (SGA).

Methods A cohort of women with asthma giving birth from 1998 to 2008 was constructed from Québec (Canada) administrative databases. LBW was defined as weight <2500 g, PB as delivery before 37 weeks' gestation and SGA as a birth weight below the 10th percentile. The impact of the use of LABAs and the dose of ICSs during pregnancy on the outcomes was determined with generalised-estimating-equation models.

Results The cohort included 7376 pregnancies: 8.8% exposed to LABAs and 56.9% exposed to ICSs. All LABA users also received ICSs. The prevalence of LBW, PB and SGA was 7.7%, 9.5% and 13.5%, respectively. LABA use was not found to be associated with increased prevalence of LBW (OR 0.81; 95% CI 0.58 to 1.12), PB (OR 0.84; 95% CI 0.61 to 1.15) or SGA (OR 0.92; 95% CI 0.70 to 1.20). Mean ICSs doses >125 μg/day (fluticasone-equivalent) were associated with a non-significant trend of increased LBW, PB and SGA.

Conclusions Despite the possibility of residual confounding due to uncontrolled or more severe asthma or smoking status, the use of LABA and low to moderate doses of ICSs were not associated with increased prevalence of perinatal outcomes. Additional research on higher ICSs doses is required to better evaluate their safety during pregnancy.

Key messages

What is the key question?

- What is the impact of the use of long-acting β_2-agonists (LABAs) and the dose of inhaled corticosteroids (ICSs) during pregnancy on the prevalence of low birth weight, preterm birth, and small for gestational age?

What is the bottom line?

- The use of LABA and low to moderate doses of ICSs were not associated with increased prevalence of perinatal outcomes.

Why read on?

- Asthma during pregnancy usually requires treatment with controller medications for which this study provides new safety information on perinatal outcomes.

INTRODUCTION

Asthma is one of the most common potentially serious medical conditions encountered during pregnancy, affecting 3.7–8.4% of pregnancies in the USA.[1] Current asthma treatment guidelines emphasise the importance and safety of the use of several asthma medications during pregnancy compared with the risk of poorly controlled asthma for the fetus, since uncontrolled asthma during pregnancy has been found to be associated with increased prevalence of low birth weight (LBW), preterm birth (PB) and small for gestational age (SGA).[2–6] Pregnancy-specific guidelines recommend inhaled corticosteroids (ICSs) as the first-line asthma-controller medication and long-acting β_2-agonists (LABAs) as an add-on therapy to treat moderate to severe asthma.[5]

Safety data on the use of LABAs during pregnancy are scarce despite their increasing use due to the evidence regarding the benefits of the LABA–ICS association, the fact that a lower dose of ICS can sometimes be used to achieve asthma control with the LABA-ICS association rather than ICS monotherapy at a higher dose, and the availability of combination products (LABA-ICS association in the same inhaler). Bracken *et al*[7] found no significant increased prevalence of PB or SGA with the use of LABAs and Clifton *et al*[8] found no difference in SGA in a group receiving a combination of ICSs and LABAs compared with ICSs alone. These studies had a limited number of women exposed to LABAs during pregnancy (n=64 and 9), with the possibility of an undetected increased risk (OR=1.69 for prematurity) in the Bracken *et al*[7] study.

The impact of the use of ICSs by pregnant women with asthma on LBW, PB and SGA has been evaluated in several studies, with all of them reporting non-significant results.[7–16] Some of the relative risks reported, however, were as high as 1.8,[10 12 16] indicating the possibility of an undetected increased prevalence, with only two[14 15] of these studies having sufficient power to detect an increase in prevalence of adverse perinatal outcomes of 50% or more. Moreover, only two of these studies considered the dose of ICS taken during pregnancy. Namazy *et al*[14] found a non-significant trend between the increasing doses of ICSs and the increasing prevalence of SGA. On the other hand,

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Bakhireva *et al*[2] found no differences in the prevalence of SGA across quartiles of ICS doses.

Our study further investigated the safety of the use of LABAs and different dose categories of ICSs during pregnancy on LBW, PB and SGA in a large cohort of women with asthma who gave birth between 1998 and 2008 in Québec, Canada.

METHODS

Data source

Data on medication prescriptions filled in community pharmacies, outpatient medical visits, emergency-department visits, medical procedures and hospitalisations were retrieved from two administrative databases in Québec: the Régie de l'assurance-maladie du Québec and the MED-ECHO databases. Additional information on these databases can be found in the online data supplement.

Study design

A cohort of pregnancies from women with asthma and their newborns was formed from the linkage of these databases. This new cohort includes pregnancies in the years 2002–2008 not comprised in previous cohorts from our group. The cohort inclusion criteria were (1) singleton delivery (live or stillbirth) between 1998 and 2008, (2) women aged ≤45 years, (3) women with ≥one diagnosis of asthma (International Classification of Diseases (ICD), ICD-9 code: 493 (except 493.2) or ICD-10 code: J45) and ≥one prescription for an asthma medication filled in the year before or during pregnancy, and (4) women covered by the Régie de l'assurance-maladie du Québec drug-insurance plan for at least 1 year before and throughout pregnancy. If a woman contributed several pregnancies, we kept only the two most recent. Exclusion criteria included use of theophylline, cromoglycate, nedocromil or ketotifen (45 pregnancies). Pregnancies with LABA use without ICSs (20 pregnancies) were also excluded to better reflect guideline-driven therapy.

Perinatal outcomes

LBW was defined as birth weight <2500 g, SGA as birth weight below the 10th percentile for gestational age and gender using Canadian standards,[17 18] and PB as delivery before 37 weeks' gestation.

Medication exposure during pregnancy

LABA use was categorised as (1) use or no use during pregnancy, and (2) duration of exposure: exposed during one, two or three trimesters; both measures based on data related to prescription renewals recorded in the RAMQ databases. Average daily dose of ICS (in fluticasone-propionate equivalent[3]) was measured with an algorithm based on prescription renewals that we developed and used in previous studies,[19 20] and categorised as none, low: >0–62.5, >62.5–125, >125–250; moderate: >250–500; and high doses: >500 μg/day, according to the Global Initiative for Asthma guidelines.[3] The low-dose category was broken down in three groups: >0–62.5 likely to represent sporadic use, 62.5–125 representing very low dose and >125–250, representing low dose as recommended in guidelines.

Potential confounders

Twenty risk factors of LBW, PB and SGA identified in the literature were considered as potential confounders. The severity of asthma in the year before conception was measured with an algorithm that we developed and validated, and that categorises asthma on three levels: mild, moderate or severe.[21] This algorithm is mainly based on the daily ICS dose and the use of add-on therapy: LABAs, leukotriene-receptor antagonists or theophylline (not applicable for this study) over a 1 year period. The control of asthma was assessed by weekly short-acting B_2-agonists use, use of oral corticosteroids and whether the women had a hospitalisation or an emergency department visit for asthma, all measured during pregnancy. Complete information on all confounding variables is available in the online data supplement. To account for the absence of smoking status in the databases, we used a method described by Schneeweiss *et al*[22] to estimate the impact of this unmeasured confounder on the observed ORs.

Statistical analysis

Descriptive statistics were used to report the characteristics of the pregnancies and the prevalence of perinatal outcomes as a function of LABA use and the ICS dose. In the main analysis, we estimated crude and adjusted ORs for LBW, PB and SGA, comparing LABA use to no use and categories of ICS doses to no use using one generalised-estimation-equation model for each outcome. A secondary analysis was done on the association between the number of trimesters (1, 2 or 3) with LABA use and perinatal outcomes. More information on generalised-estimation-equation models is available in the online data supplement.

Ethics approval

We obtained approval from the Commission d'accès à l'information du Québec prior to requesting and linking the information from the MED-ECHO and RAMQ databases. This study was approved by the ethics committees of Hôpital du Sacré-Coeur de Montréal and the Centre hospitalier universitaire de Sherbrooke.

RESULTS

The cohort includes 7376 pregnancies from 6199 women with asthma, aged 27.5 years on average, 80.5% living in an urban area and 56.1% receiving social assistance. In the year preceding pregnancy, 20% had moderate or severe asthma.[21] Overall, the prevalence of LBW, PB and SGA were 7.7%, 9.5% and 13.5%, respectively. Use of LABAs was documented in 8.8% of pregnancies (salmeterol as the only LABA 69.7%; formoterol as the only LABA 29.2%; or both 1.1%), with use increasing from 3.5% in 1999 to 13.4% in 2008. All LABA users also received ICSs. ICSs were used in 56.9% of pregnancies (fluticasone alone 76.0%; budesonide alone 14.5%; other ICSs or more than one ICS during pregnancy 9.5%). Table 1 presents the characteristics of the pregnancies per LABA use and category of ICS dose.

A higher proportion of women exposed to LABA during pregnancy had diabetes, gestational diabetes, eclampsia/pre-eclampsia. Also, a higher proportion of women exposed to high doses of ICS were recipients of social assistance, had chronic hypertension, diabetes, gestational diabetes, eclampsia/pre-eclampsia and cystic fibrosis than women exposed to low doses. Women using LABA and high-dose ICS were more likely to have moderate or severe asthma prior to pregnancy and asthma exacerbations (emergency department visit or hospitalisation for asthma, use of oral corticosteroids) during pregnancy.

Tables 2 and 3 provide the crude and adjusted ORs for the associations between asthma medications and perinatal outcomes.

The adjusted analysis indicates that LABA use was not found to be associated with an increased prevalence of any of the outcomes under study. A non-significant increasing trend in the prevalence of the three outcomes was seen with increasing doses of ICSs over 125 μg/day. On the other hand, we observed no

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Table 1 Women's characteristics according to LABA use and average daily ICS* dose during pregnancy

	LABA		ICS*					
	No	Yes	None	0–62.5	>62.5–125	>125–250	>250–500	>500
Number of pregnancies	6726	650	3178	1652	1303	686	409	148
n (%)								
Maternal characteristics								
Age (years)								
<18	127 (1.9)	4 (0.6)	50 (1.6)	36 (2.2)	28 (2.1)	13 (1.9)	1 (0.2)	3 (2.0)
18–34	5747 (85.4)	538 (82.8)	2756 (86.7)	1423 (86.1)	1092 (83.8)	575 (83.8)	325 (79.5)	114 (77.0)
>34	852 (12.7)	108 (16.6)	372 (11.7)	193 (11.7)	183 (14.0)	98 (14.3)	83 (20.3)	31 (20.9)
Receipt of social assistance	3741 (55.6)	394 (60.6)	1636 (51.5)	979 (59.3)	741 (56.9)	416 (60.6)	256 (62.6)	107 (72.3)
Urban residence	5415 (80.5)	525 (80.8)	2581 (81.2)	1306 (79.1)	1043 (80.0)	561 (81.8)	335 (81.9)	114 (77.0)
Maternal chronic conditions								
Chronic hypertension	194 (2.9)	21 (3.2)	86 (2.7)	50 (3.0)	38 (2.9)	17 (2.5)	15 (3.7)	9 (6.1)
Diabetes mellitus	239 (3.6)	31 (4.8)	102 (3.2)	66 (4.0)	38 (2.9)	34 (5.0)	18 (4.4)	12 (8.1)
Cystic fibrosis of the pancreas	32 (0.5)	5 (0.8)	14 (0.4)	4 (0.2)	9 (0.7)	2 (0.3)	4 (1.0)	4 (2.7)
Antiphospholipid syndrome	39 (0.6)	2 (0.3)	17 (0.5)	8 (0.5)	9 (0.7)	4 (0.6)	3 (0.7)	0
Pregnancy-related variables								
Gestational diabetes	638 (9.5)	94 (14.5)	288 (9.1)	157 (9.5)	131 (10.1)	76 (11.1)	55 (13.4)	25 (16.9)
Eclampsia/pre-eclampsia	195 (2.9)	27 (4.2)	86 (2.7)	54 (3.3)	41 (3.1)	20 (2.9)	13 (3.2)	8 (5.4)
Anaemia	979 (14.6)	96 (14.8)	443 (13.9)	240 (14.5)	189 (14.5)	110 (16.0)	72 (17.6)	21 (14.2)
Vaginal bleeding	893 (13.3)	80 (12.3)	439 (13.8)	219 (13.3)	169 (13.0)	78 (11.4)	54 (13.2)	14 (9.5)
Placental conditions	264 (3.9)	26 (4.0)	129 (4.1)	67 (4.1)	42 (3.2)	26 (3.8)	20 (4.9)	6 (4.1)
Placenta abruption	239 (3.6)	27 (4.2)	113 (3.6)	74 (4.5)	39 (3.0)	20 (2.9)	18 (4.4)	2 (1.4)
Asthma-related variables								
Severity of asthma prior to pregnancy								
Mild	5621 (83.6)	278 (42.8)	2888 (90.9)	1427 (86.4)	1045 (80.2)	404 (58.9)	122 (29.8)	13 (8.8)
Moderate	816 (12.1)	205 (31.5)	254 (8.0)	163 (9.9)	191 (14.7)	192 (28.0)	178 (43.5)	43 (29.1)
Severe	289 (4.3)	167 (25.7)	36 (1.1)	62 (3.8)	67 (5.1)	90 (13.1)	109 (26.7)	92 (62.2)
During pregnancy								
LABA	0	650 (100)	0	85 (5.1)	127 (9.7)	178 (25.9)	175 (42.8)	85 (57.4)
ICS*								
None	3178 (47.3)	0	3178 (100)	0	0	0	0	0
0–62.5	1567 (23.3)	85 (13.1)	0	1652 (100)	0	0	0	0
>62.5–125	1176 (17.5)	127 (19.5)	0	0	1303 (100)	0	0	0
>125–250	508 (7.6)	178 (27.4)	0	0	0	686 (100)	0	0
>250–500	234 (3.5)	175 (26.9)	0	0	0	0	409 (100)	0
>500	63 (0.9)	85 (13.1)	0	0	0	0	0	148 (100)
SABA (doses/week)								
0	2166 (32.2)	115 (17.7)	1776 (55.9)	267 (16.2)	167 (12.8)	41 (6.0)	27 (6.6)	3 (2.0)
>0–3	2408 (35.8)	120 (18.5)	896 (28.2)	972 (58.8)	526 (40.4)	93 (13.6)	32 (7.8)	9 (6.1)
>3	2152 (32.0)	415 (63.8)	506 (15.9)	413 (25.0)	610 (46.8)	552 (80.5)	350 (85.6)	136 (91.9)
Leukoteriene-receptor antagonists	48 (0.7)	67 (10.3)	12 (0.4)	8 (0.5)	16 (1.2)	17 (2.5)	38 (9.3)	24 (16.2)
Oral corticosteroids	599 (8.9)	165 (25.4)	107 (3.4)	162 (9.8)	212 (16.3)	138 (20.1)	94 (23.0)	51 (34.5)
Intranasal corticosteroids	769 (11.4)	160 (24.6)	228 (7.2)	202 (12.2)	206 (15.8)	146 (21.3)	103 (25.2)	44 (29.7)
≥1 ED visit for asthma	869 (12.9)	137 (21.1)	201 (6.3)	248 (15.0)	275 (21.1)	145 (21.1)	104 (25.4)	33 (22.3)
≥1 hospitalisation for asthma	65 (1.0)	24 (3.7)	9 (0.3)	20 (1.2)	23 (1.8)	17 (2.5)	12 (2.9)	8 (5.4)

*Fluticasone equivalent, μg/day.
ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting B_2-agonist; SABA, short-acting B_2-agonists.

significant increased prevalence of the outcomes among women exposed to doses <125 μg/day.

The secondary analysis presented in table E1 in the online data supplement showed that a greater number of trimesters with LABA exposure during pregnancy was not associated with increased prevalence of the perinatal outcomes.

The sensitivity analysis indicates that the impact of smoking (an unmeasured confounder) on the association between ICS doses and LABA use and LBW, PB and SGA leads to an underestimation of the true OR by a factor of 6% at the most because of the small differences in smoking prevalence between medication users and non-users. The complete results can be found in table E2 in the online data supplement.

DISCUSSION

In this cohort of pregnant women with asthma, for LABA use and ICS doses <125 μg/day we found no increased prevalence of LBW, PB and SGA, while a trend for an increased prevalence of the outcomes was seen for ICS doses above 125 μg/day. The prevalence of LBW, PB and SGA, found in the present study, were higher than those observed in the general population of Québec for the year 2008 (LBW 7.6%; PB 5.6%; SGA 10%).[23]

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Table 2 Prevalence and crude ORs of LBW, PB and SGA according to the average daily dose of ICS* and LABA use during pregnancy

	LBW		PB		SGA	
	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
LABA						
None	515 (7.7)	Reference	641 (9.5)	Reference	895 (13.3)	Reference
LABA	55 (8.5)	1.05 (0.79 to 1.41)	63 (9.7)	0.99 (0.75 to 1.31)	98 (15.1)	1.13 (0.90 to 1.42)
Daily ICS dose (µg/day)						
None	239 (7.5)	Reference	305 (9.6)	Reference	404 (12.7)	Reference
>0–62.5	102 (6.2)	0.80 (0.63 to 1.02)	133 (8.1)	0.81 (0.66 to 1.00)	201 (12.2)	0.95 (0.79 to 1.13)
>62.5–125	106 (8.1)	1.10 (0.87 to 1.40)	130 (10.0)	1.06 (0.86 to 1.32)	190 (14.6)	1.18 (0.98 to 1.42)
>125–250	64 (9.3)	1.24 (0.93 to 1.65)	73 (10.6)	1.14 (0.87 to 1.49)	99 (14.4)	1.17 (0.92 to 1.48)
>250–500	41 (10.0)	1.34 (0.95 to 1.89)	45 (11.0)	1.20 (0.87 to 1.66)	68 (16.6)	1.35 (1.01 to 1.79)
>500	18 (12.2)	1.66 (1.01 to 2.73)	18 (12.2)	1.13 (0.65 to 1.97)	31 (20.9)	1.80 (1.19 to 2.71)

*Fluticasone equivalent, µg/day.
ICS, inhaled corticosteroid; LABA, long-acting B_2-agonist; LBW, low birth weight; PB, preterm birth; SGA, small for gestational age.

These results are consistent with a meta-analysis including 40 cohort studies comparing women with and without asthma, that showed significant increased risks of LBW (RR 1.46), PB (RR 1.41) and SGA (1.22).[24]

Our results are reassuring for the use of LABAs during pregnancy with no increase in the prevalence of the perinatal outcomes studied. The published data on LABA and LBW, PB and SGA are limited to the studies of Clifton *et al*[8] with nine exposed women and Bracken *et al*[7] with 64 exposed women. Clifton *et al* found decreases in birthweight centiles in women with asthma taking fluticasone and salmeterol compared with women with asthma taking budesonide.[8] Bracken *et al*[7] found an adjusted OR of 0.99 (95% CI 0.97 to 1.02) for PB and an OR of 1.00 (95% CI 0.99 to 1.02) for intrauterine growth restriction for each additional dose of LABA taken per month during pregnancy (OR of 0.74 if women taking 30 doses per month are compared with non-users). These results are concordant with our results found in the main analysis, in which LABAs were categorised as use/no use, and in the secondary analysis, in which we considered the number of trimesters with LABA use during pregnancy. Despite the possibility of residual confounding by uncontrolled or more severe asthma that would underestimate the beneficial effect of LABA, both of our analyses revealed a trend towards a protective effect of LABA on perinatal outcomes. No protective pharmacodynamic effect of LABA on pregnancy outcomes have been demonstrated in humans, consequently, we hypothesise that the trend for a beneficial effect of LABA could possibly come from improved maternal asthma control.

The observed effects of ICS use during pregnancy on the fetus are potentially coming from different sources, and the independent impact of these sources can be difficult to disentangle. First, ICS is likely to have a positive impact on the fetus by improving maternal asthma control (and fetal oxygenation) through a reduction in lung inflammation. Similarly to the results found in our study for doses <125 µg/day, Murphy *et al*[25] observed that women with asthma not taking an ICS had a 17% reduction in birthweight centile compared with women with asthma taking low-dose ICSs. Murphy *et al* postulated that the inflammatory process present in asthma reduces the activity of the placental enzyme 11β-hydroxysteroid dehydrogenase, which metabolises corticosteroids. This resulted in significant increases in cortisol reaching the fetus and a trend for reduced fetal oestriol (a marker of fetal adrenal activity), possibly leading to impaired fetal growth. The use of low-dose ICSs, by controlling maternal asthma and inflammation, would restore normal 11β-hydroxysteroid dehydrogenase activity and thus reduce the impact of cortisol on growth impairment.[25] However, a further study by the same group did not show that ICS treatment in pregnant women with asthma results in changes in fetal oestriol concentrations, leading them to conclude that the fetal adrenal function is not susceptible to exogenous glucocorticoid inhibition.[12] The ideal measure of ICS exposure would be at the fetal level, but no published reports look at the presence of fluticasone or budesonide taken by inhalation in cord blood.

Second, as shown in table 1, the use of high ICS doses could be seen as a marker of more severe and/or difficult-to-control asthma, and this may confound the association between ICS doses and perinatal outcomes, since asthma severity and uncontrolled asthma have been found to be associated with an increased prevalence of adverse perinatal outcomes in some studies.[2 4 7 26–28] Although we adjusted for asthma severity in the year preceding pregnancy and for control of asthma during pregnancy the possibility of residual confounding persists due to the imperfect measurement of severity and control of asthma.

Finally, a dose of corticosteroids above a certain threshold may have a negative impact on the fetal adrenal function, leading to impaired fetal development.[29] For ICS doses >125 µg/day, we observed a non-significant trend showing increasing prevalence of the perinatal outcomes with increasing doses. The associations observed for the highest-ICS-dose, although not statistically significant, need further attention since the ORs from the adjusted analysis range from 1.45 to 1.57 and the number of events (18 for LBW and PB, 31 for SGA) is low, possibly indicating an increased risk not detected. Similarly, Namazy *et al*[14] found a non-significant increase in SGA from 5.1% in the lowest to 10.3% in the highest quartile of ICS dose. They did not, however, find a trend between ICS dose and the mean birth weight. Bakhireva *et al*[2] observed no difference in the incidence of SGA or mean birth weight between quartiles of ICS doses.[2] Hodyl *et al*,[12] using a cut-off of 1000 µg/day in beclomethasone-chlorofluorocarbon equivalent (or 500 µg/day fluticasone-proprionate equivalent) found no difference in abdominal circumference, umbilical-artery blood flow, or birthweight centiles between low-dose and high-dose groups. The number of ICS-exposed women in their cohort was, however, limited to 76.

Additional information on the search for the best controller-medication regimen during pregnancy is available in a recently

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Table 3 Adjusted ORs of LBW, PB and SGA related to the average daily dose of ICS and LABA use during pregnancy

	LBW	PB	SGA
	Adjusted OR* (95% CI)		
LABA	0.81 (0.58 to 1.12)	0.84 (0.61 to 1.15)	0.92 (0.70 to 1.20)
Daily ICS dose†			
None	Reference	Reference	Reference
>0–62.5	0.70 (0.53 to 0.90)	0.77 (0.61 to 0.95)	0.91 (0.76 to 1.09)
>62.5–125	1.03 (0.79 to 1.34)	1.08 (0.87 to 1.35)	1.15 (0.95 to 1.39)
>125–250	1.18 (0.83 to 1.67)	1.23 (0.91 to 1.66)	1.12 (0.87 to 1.45)
>250–500	1.20 (0.81 to 1.78)	1.28 (0.90 to 1.82)	1.26 (0.91 to 1.76)
>500	1.57 (0.86 to 2.87)	1.45 (0.76 to 2.80)	1.50 (0.92 to 2.44)
Maternal characteristics			
Age (years)			
<18	1.24 (0.67 to 2.29)	1.44 (0.84 to 2.46)c	1.58 (1.01 to 2.46)
18–34	Reference	Reference	Reference
>34	1.40 (1.09 to 1.79)	1.34 (1.07 to 1.67)c	1.18 (0.97 to 1.44)
Receipt of social assistance	1.80 (1.49 to 2.18)	1.49 (1.26 to 1.76)c	1.45 (1.25 to 1.67)
Rural residence	1.35 (1.08 to 1.69)	Not retained	1.21 (1.02 to 1.44)
Maternal chronic conditions			
Antiphospholipid syndrome	Not retained	2.99 (1.18 to 7.55)	Not retained
Pregnancy-related variables			
Gestational diabetes	0.70 (0.50 to 0.97)c	Not retained	0.63 (0.49 to 0.81)
Eclampsia/pre-eclampsia	3.75 (2.65 to 5.32)	3.34 (2.38 to 4.68)c	1.68 (1.19 to 2.37)
Anaemia	Not retained	Not retained	0.60 (0.48 to 0.75)
Fetal-maternal haemorrhage	3.83 (1.30 to 11.3)c	3.59 (1.10 to 11.75)	Not retained
Vaginal bleeding	1.65 (1.26 to 2.16)	1.98 (1.56 to 2.51)	Not retained
Placental conditions	1.70 (1.19 to 2.43)	1.65 (1.21 to 2.25)	1.39 (1.02 to 1.90)
Placenta abruption	3.14 (2.15 to 4.57)	2.66 (1.91 to 3.72)	Not retained
Asthma-related variables			
SABA (doses/week)		Not retained	Not retained
0	Reference		
>0–3	1.15 (0.90 to 1.47)c		
>3	1.18 (0.90 to 1.55)c		
Severity of asthma prior to pregnancy	Not retained		
Mild		Reference	Reference
Moderate		0.88 (0.68 to 1.13)c	1.05 (0.85 to 1.29)c
Severe		0.71 (0.47 to 1.08)c	1.29 (0.96 to 1.74)c

Not retained: variable not acting as a confounder or determinant of the outcome.
*The adjusted models, specific to each outcome, include LABA, ICS and all variables acting as confounders or determinants of the outcome.
†Fluticasone equivalent, μg/day.
c, confounder; ICS, inhaled corticosteroid; LABA, long-acting B_2-agonist; LBW, low birth weight; PB, preterm birth; SABA, short-acting B_2-agonist; SGA, small for gestational age.

published randomised controlled trial.[30] Powell *et al*[30] looked at the fraction of exhaled nitric oxide (FeNO) versus symptom-guided treatment of pregnant women with asthma in which the algorithms resulted in a greater frequency of exposure to ICSs (but lower dose) and LABAs in the FeNO group. In addition to the primary endpoint of moderate or severe exacerbations (reduced in the FeNO group), the authors also looked at fetal complications between the FeNO and symptom groups: intrauterine-growth restriction (2.8% vs 0.95%), PB (8.3% vs 5.7%) and LBW (5% vs 5%). These differences were not statistically significant, as expected with groups of 105 and 109 women. The use of low-dose ICSs with an earlier introduction of LABAs is consistent with recently published guidelines.[3 31]

Our study has some limitations that should be taken into account in interpreting the results. LABA exposure has some limits with an important number of women receiving only a month's supply of medication during the entire pregnancy, leading to an underestimation of the effect of these medications. There is some imprecision in the calculation of ICS exposure, especially for the 0–62.5 μg/day category, which included varying patterns of use such as a single short course of high-dose ICSs or even a single day of exposition. The higher ICS-dose categories are more accurate indicators of a continuous exposure. Prescriptions filled in community pharmacy, although not a direct measure of a woman's exposure, is considered a relevant proxy. Also, this possible misclassification of the exposure, if present, is likely to be non-differential and would usually lead to an underestimation of the true association. Women in the highest-ICS-dose categories were also more likely to be exposed to oral and nasal corticosteroids, resulting in a higher total exposure to corticosteroids. Some risk factors could not be controlled because of incomplete coding (ie, poor maternal nutrition, obesity, alcohol abuse and others) or complete absence (folic-acid deficiency) of the condition in the database. Information on smoking status would have been preferable to the indirect adjustment method. This method indicates that the measured OR could be an underestimation of the true OR by a factor of 6% at the most, a small difference due mainly to the

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similar smoking prevalences observed between users and non-users of ICSs in a similar previous cohort from our group.[19] Assuming greater smoking in medication non-users[9 19] the observed OR, for all three outcomes, would be an overestimation of the potential benefit for LABA and an underestimation of the true risk for ICSs. The possibility of residual confounding by uncontrolled or more severe asthma as described above cannot be ruled out completely. Measures of symptoms or pulmonary function could have permitted a better adjustment for asthma control. Finally, there is a high proportion (>50%) of women receiving social assistance in our cohort, limiting the generalisability of our results. The study's strengths are the large number of women exposed to ICSs and LABAs during pregnancy, medication-exposure assessment from data prospectively collected independently of the outcomes and recorded in pharmacy records (avoidance of recall bias), the inclusion of multiple potential confounders, and the use of previously validated algorithms to measure ICS and short-acting B_2-agonists exposure, and control and severity of asthma. The retrospective study design is more reflective of standard medical care than a more intense prospective follow-up possibly resulting in fewer exacerbations, particularly in the more susceptible highest-ICS-dose groups.[24]

In summary, the data on LABA use is reassuring, especially in light of the possibility of residual confounding by uncontrolled or severe asthma or smoking status. Moreover, ICS doses <125 µg/day were not associated with increased prevalence of the perinatal outcomes. However, additional work is needed before we can rule on the safety of higher doses of ICSs. Despite the fact that it is scientifically relevant to disentangle the pharmacological effect of higher doses of ICS from the effect of residual confounding, in clinical practice, women treated with higher doses of ICSs may be at increased risk of having a small baby or a preterm delivery, and need more intense follow-up during pregnancy. The available data at the moment suggests that the benefits of LABAs or higher doses of ICSs to maintain asthma control would outweigh their potential risks of adverse maternal and fetal effects.

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