

Résultats des travaux de recherche de la Chaire pharmaceutique AstraZeneca en Santé respiratoire

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HSCM

HÔPITAL DU SACRÉ-CŒUR
DE MONTRÉAL

Doués pour la vie

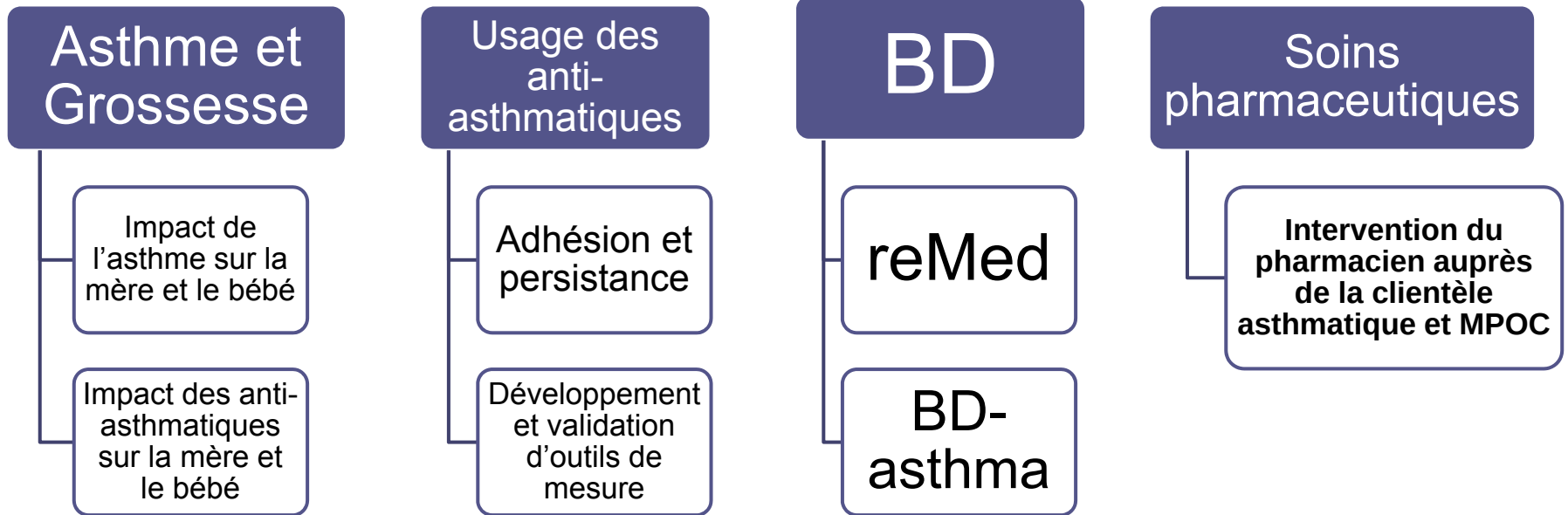
7 décembre 2012

Université 
de Montréal

Plan

- Programme de recherche de la Chaire
- Infrastructures de recherche
- Quelques résultats
- Implication de la Chaire dans la formation des étudiants

Programme de recherche



Infrastructures de recherche

- Asthma and Pregnancy Cohort
- reMed
- BD-asthma

Asthma and Pregnancy Cohort 1990-2010

MED-ECHO et RAMQ

Grossesses
femmes
asthmatiques

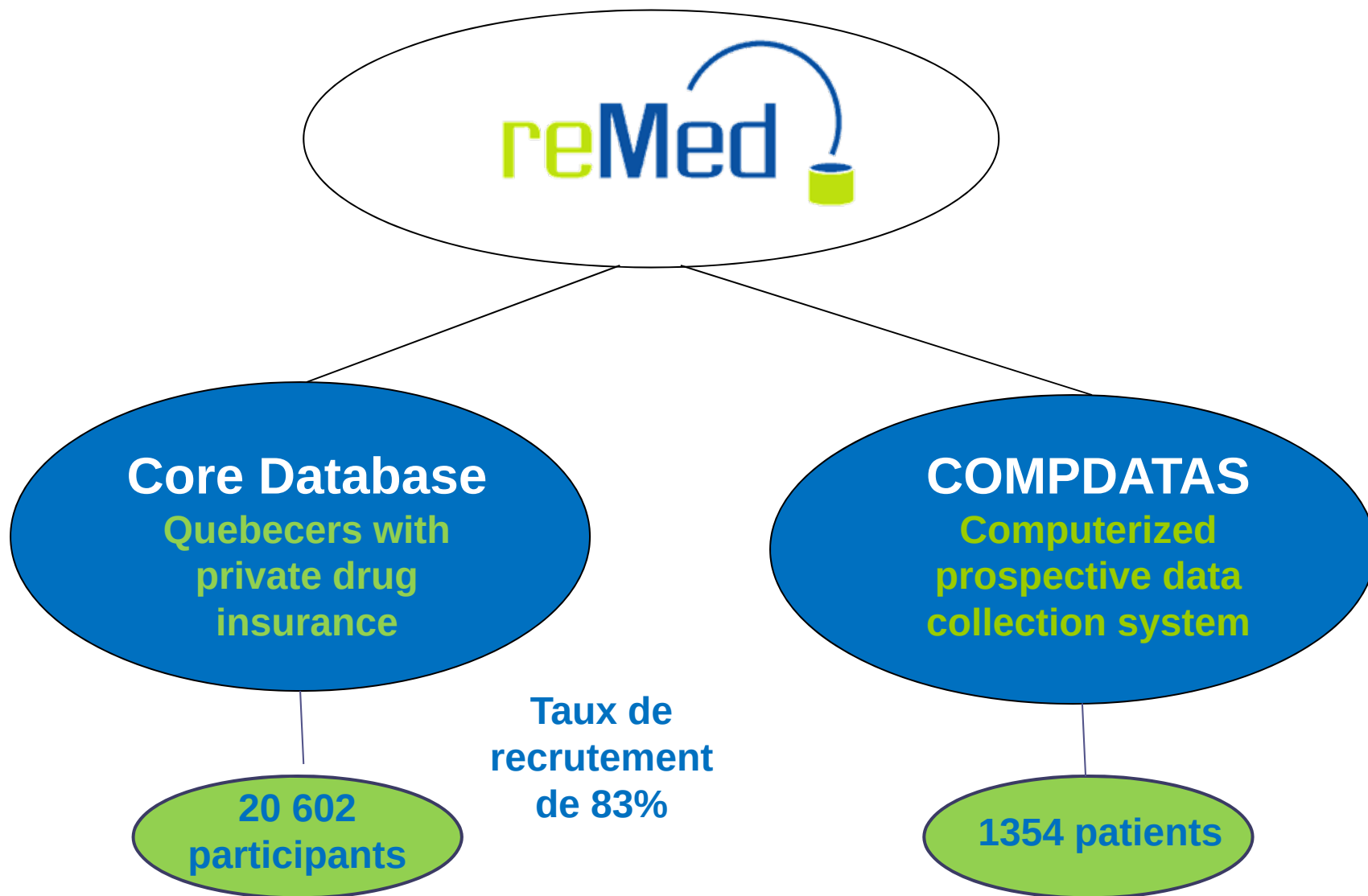
Grossesses
femmes non-
asthmatiques

Assurance
Rx RAMQ

Assurance
Rx privée

Assurance
Rx RAMQ

Assurance
Rx privée



L Blais, A Bérard, L Lalonde, J Moisan, S Perreault, E Rahme, et al.

Data storage and transfer

- Dynamic list of participants
- Medication data obtained from the pharmacies' computer services providers: Telus, Centre Rx GJC, XD3
- reMed server located at UdM
- Highly secured and confidential
- Data transferred to reMed server every **2 weeks**
- 1 year of retrospective medication data at reMed inscription
- Data transfer since March 2008

COMPDATAS

EX-ASTHMA

PI : S Bacon, U Concordia

MI and adherence to asthma medications

PI : K Lavoie, UQUAM

Pharmacogénétique de la warfarin

PI : S Perreault et M-P Dubé
UdM

TRANSIT

PI : L Lalonde, Udm

ADAIR

PI: M-F Beauchesne
USherbrooke et Udm

BD-asthma

PI: Lucie Blais Udm, Uds

BAP

PI: Francine Ducharme
CHU St-Justine

Étude des facteurs influençant l'usage des médicaments
antidiabétiques oraux chez les diabétiques de type 2

PI : L Guenette, U Laval

BD-Asthma

L Blais, MF Beauchesne, K Lavoie, S Bacon,
C Lemièrre, M Labrecque, P Larivée

Expansion
pour inclure
les patients
MPOC

Patients asthmatiques, cliniques
externes HSCM et CHUS

Entrevue

Caractéristiques socio-
démographiques
Histoire de l'asthme,
co-morbidités et Rx
Habitudes de vie
Prime MD

Questionnaire

ACQ
Morisky
BDI-II
ASI

Dossier
médical

Fonction pulmonaire
Prescription
Co-morbidité

BD

RAMQ
MED-ECHO
reMED
ISQ

Quelques résultats ...

Projets de recherche: BD-Asthma

1) Évaluation de l'adhésion aux traitements antiasthmatiques d'entretien: Élaboration et validation d'un questionnaire

- J Begin, N Dugré, F Arbour, A Fillion, MF Beauchesne, L Blais
- Objectif principal: développer et valider le contenu d'un Q auto-administré pour quantifier l'adhésion au tx.

Projets de recherche: BD-Asthma

2) Electronic assessment of patient's adherence to asthma controller medications: a proof of concept study

- L Blais, C Lemière, A Cartier
- **Objectif:** Développer un outil électronique pour mesurer l'adhésion aux traitements d'entretien en asthme et l'utilisation des traitements de secours et rendre cette information disponible aux médecins lors des cliniques externes
- Adhésion aux traitements de fonds et utilisation des traitements de secours mesurées à partir des renouvellements d'ordonnances
- Données provenant de reMed
- Information transmise aux pneumologues avant la visite médicale du patient

Projets de recherche: BD-Asthma

3) Comparaison de l'adhésion au traitement entre les patients asthmatiques recevant des corticostéroïdes inhalés et des beta2-agonistes à longue action en combinaison selon l'approche SMART et l'approche à dose-fixe : une étude pilote.

- Équipe de recherche: J Sokunthea Yourk, A Forget, F Kettani, MF Beauchesne, L Blais

Objectif principal

- Comparer les doses quotidiennes prescrites et utilisées de CSI entre les approches « SMART » et dose-fixe.

Résultats: Adhésion

Yourk J et coll.

	SMART	Dose-fixe	p-value
Nombre de patients	31	109	
*Dose quotidienne prescrite (µg/j)	415 ± 149	624 ± 343	<0,00
*Dose prise durant le suivi (µg/j)	286 ± 191	323 ± 282	0,40
Différence : Dose prescrite – dose prise (µg/j)	130 ± 217	301 ± 338	0,00
% de la dose prescrite prise	64,5 ± 34,2	51,7 ± 36,1	0,08
Nb de CSI/BALA dispensés par année	4,4 ± 3,2	3,7 ± 3,1	0,28

Conclusion

Yourk J, et coll.

- La combinaison CSI/BALA semble être mieux utilisée avec l'approche SMART qu'avec l'approche dose-fixe, probablement en raison de sa commodité.

Impact des BALA en grossesse sur les issues périnatales

Clinical recommendations

- Asthma affect 8.8% of pregnant women
- **US Guidelines for managing asthma during pregnancy** (NAEPP expert panel report 2004)
 - Uncontrolled asthma is **RISKIER** for the mother and the fetus than intake of asthma medications
 - Regular use of a controller therapy for women with persistent asthma at doses as high as at other times recommended
 - Inhaled corticosteroids (ICS)
 - ICS+ long-acting beta₂-agonists (LABA) for moderate to severe asthma
 - Treatment with as needed short-acting beta₂-agonists (SABA) might be sufficient for mild intermittent asthma

- Asthma during pregnancy and perinatal outcomes**

LBW ¹	SGA ¹	Preterm delivery ¹	Perinatal death ²	Congenital malformation ³
RR=1.46 (1.22-1.75)	RR=1.22 (1.14-1.31)	RR=1.41 (1.22-1.61)	OR=1.12 (0.87-1.45)	OR=1.30 (1.20-1.40)

- Uncontrolled asthma during pregnancy and perinatal outcomes**

LBW ⁴	SGA ⁴	Preterm delivery ⁴	Still birth ⁶	Congenital malformation ⁵
RR=3.02 (1.87-4.89)	RR=0.78 (0.25-2.48)	RR=1.54 (0.89-2.69)	OR = 1.28 (0.72 – 2.28)	OR=1.48 (1.04-2.09)

1) Murphy et al. BJOG 2011; 2) Breton et al. Thorax. 2009; 3) Blais et al. Birth Defects Res A Clin Mol Teratol. 2010; 4) Namazy et al. ERJ 2012 5) Blais et al. JACI 2008 6) Tata et al. Thorax 2008

Beta2-agonists use during pregnancy and the risk of congenital malformations

Eltonsy et al. *Birth Defects Res A Clin Mol Teratol.* 2011;91(11):937-47

Objective: To investigate the association between exposure to SABA and LABA in the first trimester of pregnancy and the risk of congenital malformations among women with asthma

Methods

- **Study design**

- Asthma and Pregnancy Cohort

- **Inclusion criteria**

- All pregnancies from asthmatic women, 1990-2002
 - Dx of asthma + ≥ 1 filled prescription for an asthma Rx in the 2 years prior or during pregnancy
- Stillbirths and newborns
- Women aged between 13 and 50 years old
- Women covered by the **RAMQ Public Drug Insurance Plan** for at least one year prior and throughout the pregnancy

Methods

- **Exclusion criteria**

- Oral beta₂-agonists use during the first trimester
- Chronic oral corticosteroids use in the year preceding pregnancy
- Women with rheumatic disease, Cushing disease, iodine deficiency, adrenal tumors, and folic acid deficiency

Methods

- **Exposure:** LABA use (yes/no) during the first trimester of pregnancy
- **Outcomes:** any, major and specific CM at birth or during the first year of life
- **Covariables:** sociodemographic, pregnancy-related, maternal and fetal conditions, asthma-related
- **Statistical analyses**
 - GEE models

Results

- Cohort: **13,117** pregnancies

Characteristics of Pregnancies According to LABA Use during the First Trimester

	LABA users	LABA non users	<i>p</i> value
	<i>No. of pregnancies (%)</i>		
	165 (1.3)	12,952 (98.7)	
Socio-demographic variables			
Maternal age (years)			
<18	7 (4.2)	848 (6.6)	< 0.001
18–34	134 (81.2)	11,309 (87.3)	
≥35	24 (14.6)	795 (6.1)	
Receipt of social assistance during pregnancy or one year before	102 (61.8)	10,308 (79.6)	< 0.001
Urban area of residence at delivery	130 (78.8)	10,482 (80.9)	0.487
Level of education at delivery (years)			
≤11	76 (46.1)	7702 (59.5)	0.001
12–15	64 (38.8)	3627 (28.0)	
≥16	14 (8.5)	656 (5.1)	
Missing	11 (6.7)	967 (7.5)	
Maternal & fetal conditions			
Chronic hypertension	9 (5.5)	305 (2.4)	0.018
Pregnancy induced hypertension	8 (4.9)	580 (4.5)	0.082
Diabetes mellitus	12 (7.3)	292 (2.3)	< 0.001
Gestational diabetes	28 (17.0)	987 (7.6)	< 0.001
Epilepsy	4 (2.4)	135 (1.0)	0.098
Use of teratogenic drugs in first trimester	5 (3.0)	164 (1.3)	0.062
Uterine complications during pregnancy	4 (2.4)	249 (1.9)	0.056
Fetal infections during pregnancy	4 (2.4)	85 (0.7)	0.026
Nullipara	67 (40.6)	4095 (31.8)	0.014
Multiple pregnancy	2 (1.2)	188 (1.5)	0.999

Results

Characteristics of Pregnancies According to LABA Use during the First Trimester

	LABA users	LABA non users	<i>p</i> value
	<i>No. of pregnancies (%)</i>		
	165 (1.3)	12,952 (98.7)	
Asthma-related variables			
Daily dose of inhaled corticosteroids in first trimester* (µg)			
0	8 (4.9)	8629 (66.6)	< 0.001
>0-500	80 (48.5)	3855 (29.8)	
>500	77 (46.7)	468 (3.6)	
Use of other controller medications in first trimester [†]	22 (13.3)	374 (2.9)	< 0.001
Use of intranasal corticosteroids in first trimester	25 (15.2)	494 (3.8)	< 0.001
Use of oral corticosteroids in first trimester	31 (18.8)	421 (3.3)	< 0.001
Emergency department visit or hospitalization for asthma in first trimester	22 (13.3)	633 (4.9)	< 0.001
Exacerbations for asthma in first trimester [‡]	31 (18.8)	784 (6.1)	< 0.001
Asthma severity in the year before pregnancy			
Mild	48 (29.1)	10,723 (82.8)	< 0.001
Moderate	47 (28.5)	1563 (12.1)	
Severe	70 (42.4)	666 (5.1)	
Asthma control in the year before pregnancy			
Controlled	35 (21.2)	7958 (61.4)	< 0.001
Un-controlled	130 (78.8)	4994 (38.6)	

* ICS reported in beclomethasone-equivalent

Results

Adjusted Odds Ratios of Any and Major Malformations in Association with SABA and LABA Use during the First Trimester of Pregnancy

	No. of pregnancies	Any malformations		Major malformations	
		No. of cases (%)	OR (95% CI)	No. of cases (%)	OR (95% CI)
SABA use in first trimester					
Yes	7182	691 (9.6)	1.04 (0.92–1.17)	410 (5.7)	0.93 (0.80–1.08)
No	5935	551 (9.3)	reference	352 (5.9)	reference
LABA use in first trimester					
Yes	165	21 (12.7)	1.37 (0.92–2.17)	13 (7.9)	1.31 (0.74–2.31)
No	12,952	1221 (9.4)	reference	749 (5.8)	reference

Results

- 17 specific groups of congenital malformations

- | | | |
|---|---------------------------------|--|
| • Anencephalus | • Respiratory system | • Other musculoskeletal malformations |
| • Spina bifida | • Cleft palate and/or cleft lip | • Integument |
| • Other malformations of the nervous system | • Digestive system | • Chromosomal |
| • Eye, ear, face and neck | • Genital organs | • Congenital hydrocele |
| • Cardiac system | • Urinary system | • Other and unspecified congenital anomalies |
| • Circulatory system | • Limbs | |

- LABA use associated with increased risk of

- Cardiac malformations: aOR=**2.38**; 95% CI:1.11-5.10
- Genital malformations: aOR=**6.84**; 95% CI: 2.58-18.10
- Other and unspecified malformations:
 - Any: aOR=**3.43**; 95% CI:1.39-8.45
 - Major: aOR=**3.97**; 95% CI:1.29-12.20

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

Cossette B, Beauchesne M-F, Lemièrre C, et al. to be submitted to Thorax

Objective: To assess the impact of LBA and ICS use during pregnancy on the prevalence of LBW, preterm birth, and SGA

Methods

- **Data sources**

- RAMQ and MED-ECHO

- **Study design**

- Asthma and Pregnancy Cohort
 - Pregnancies from asthmatic women ending in a singleton delivery (live birth or stillbirth) between **1998 and 2008**
 - Age ≤ 50 years old
 - Coverage by the RAMQ Drug Insurance Plan for at least 1 year before and during pregnancy

Methods

● Outcomes

- LBW: <2500 g
- SGA: birth weight <10th percentile for gestational age and gender
- Preterm delivery: <37 wk

● Exposure

- LABA: use or no use during the entire pregnancy
- Average daily doses of ICS (fluticasone-equivalent) during the entire pregnancy
 - Low dose: 0, >0–62.5, >62.5–125, >125–250
 - Medium dose: >250–500
 - High dose: > 500 µg/d

Methods

- **Potential confounders**
 - Sociodemographic
 - Pregnancy-related
 - Maternal chronic conditions
 - Asthma-related variables
- **Statistical analysis**
 - GEE models

Results

Table II. Women's characteristics according to LABA use during pregnancy

	LABA	
	No	Yes
No. pregnancies	6,726	650
	%	
Maternal characteristics		
Age (years)		
<18	1.9	0.6
18–34	85.4	82.8
>34	12.7	16.6
Social assistance	55.6	60.6
Maternal chronic conditions		
Chronic hypertension	2.9	3.2
Diabetes mellitus	3.6	4.8
Pregnancy-related variables		
Gestational diabetes	9.5	14.5
Eclampsia/preeclampsia	2.9	4.2
Asthma-related variables		
Severity of asthma prior to pregnancy		
Mild	83.6	42.8
Moderate	12.1	31.5
Severe	4.3	25.7
During pregnancy		
>3 SABA (doses/wk)	32.0	63.8
≥1 ED visit for asthma	12.9	21.1
≥1 hospit. for asthma	1.0	3.7

Results

- Cohort: 7,376 pregnancies

Table I. Women's characteristics according to the average daily ICS dose during pregnancy

	ICS $\mu\text{g/d}$ (fluticasone equivalent)					
	None	0–62.5	>62.5–125	>125–250	>250–500	>500
No. pregnancies	3,178	1,652	1,303	686	409	148
	%					
Maternal characteristics						
Age (years)						
<18	1.6	2.2	2.1	1.9	0.2	2.0
18–34	86.7	86.1	83.8	83.8	79.5	77.0
>34	11.7	11.7	14.0	14.3	20.3	20.9
Social assistance	51.5	59.3	56.9	60.6	62.6	72.3
Maternal chronic conditions						
Chronic hypertension	2.7	3.0	2.9	2.5	3.7	6.1
Diabetes mellitus	3.2	4.0	2.9	5.0	4.4	8.1
Pregnancy-related variables						
Gestational diabetes	9.1	9.5	10.1	11.1	13.4	16.9
Eclampsia/preeclampsia	2.7	3.3	3.1	2.9	3.2	5.4
Asthma-related variables						
Severity of asthma prior to pregnancy						
Mild	90.9	86.4	80.2	58.9	29.8	8.8
Moderate	8.0	9.9	14.7	28.0	43.5	29.1
Severe	1.1	3.8	5.1	13.1	26.7	62.2
During pregnancy						
>3 SABA (doses/wk)	15.9	25.0	46.8	80.5	85.6	91.9
≥ 1 ED visit for asthma	6.3	15.0	21.1	21.1	25.4	22.3
≥ 1 hospit. for asthma	0.3	1.2	1.8	2.5	2.9	5.4

Results

Table II. Adjusted ORs of LBW, BP, and SGA related to the average daily ICS* dose and LABA use during pregnancy

	LBW	Preterm delivery OR (95% CI)	SGA
Daily ICS dose			
None	Reference	Reference	Reference
>0–62.5	0.70 (0.53–0.90)	0.77 (0.61–0.95)	0.91 (0.76–1.09)
>62.5–125	1.03 (0.79–1.34)	1.08 (0.87–1.35)	1.15 (0.95–1.39)
>125–250	1.18 (0.83–1.67)	1.23 (0.91–1.66)	1.12 (0.87–1.45)
>250–500	1.20 (0.81–1.78)	1.28 (0.90–1.82)	1.26 (0.91–1.76)
>500	1.57 (0.86–2.87)	1.45 (0.76–2.80)	1.50 (0.92–2.44)
LABA	0.81 (0.58–1.12)	0.84 (0.61–1.15)	0.92 (0.70–1.20)

Discussion: LABA and perinatal outcomes

- Large sample size
- Drug data prospectively collected, independently of the outcomes
 - ✓ No recall bias
- Valid data
 - ✓ Asthma and CM diagnoses (Blais. PDS 2006, Blais. Submitted to PDS 2012)
 - ✓ Pregnancy-related variables (birth weight, gestational age, date of conception, and date of delivery) (Vilain. PDS 2008)
 - ✓ Index of asthma severity and control (Firoozi. Thorax 2007)
- Adjustment for several important confounders

Discussion: LABA and perinatal outcomes

- Exposure to medications based on dispensed prescriptions and not the actual intake
- No data on drugs dispensed at hospital
- Clinical data and some confounders missing (spirometry, symptoms, cigarette, BMI, ...)
- Cohort formed only of women covered by the public drug insurance
 - Cohort underrepresented by women with high socioeconomic status, which limits generalizability
- Possibility of residual confounding due to the level of asthma severity and control

Conclusions: LABA and perinatal outcomes

Evidence of safety

- LABA not associated with LBW, SGA, and preterm-birth
 - No apparent residual confounding by asthma severity/control

Conclusions: LABA and perinatal outcomes

Questionable safety

- LABA significantly associated with congenital malformations
 - residual confounding by asthma severity/control
 - effect of LABA on the steroids function
 - unknown pharmacological mechanisms
- A trend between higher doses of ICS and LBW, SGA, and preterm-birth
 - residual confounding by asthma severity
 - inhibition of fetal adrenal function

Traitement hospitalier des exacerbations de femmes asthmatiques durant et hors grossesse

- Équipe de recherche: B Cossette, A Forget, MF Beauchesne, C Lemièrre, P Larivée, É Rey, M Couturier et L Blais
- **Objectif principal:** Évaluer si le traitement des exacerbations d'asthme des femmes au Centre hospitalier universitaire de Sherbrooke (CHUS) diffère selon leur statut de grossesse
 - Utilisation BD CIRESSS du CHUS, croisement RAMQ, MED-ÉCHO

Principaux résultats

Cossette B et coll.

	Exacerbations when Pregnant	Exacerbations when Non-pregnant
	n=43	n=39
In the year preceding exacerbation		
Asthma severity		
Mild	21 (48.8)	8 (20.5)
Moderate	5 (11.6)	5 (12.8)
Severe	17 (39.5)	26 (66.7)
ICS*, mean $\pm$ SD	171.8 $\pm$ 204.8	178.6 $\pm$ 177.7
Use of LABA	11 (25.6)	16 (41.0)
SABA (doses/wk), n (%)		
0-3	18 (41.9)	7 (18.0)
4-10	7 (16.3)	5 (12.8)
> 10	18 (41.9)	27 (69.2)
Asthma control, n (%)	15 (34.9)	6 (15.4)
OCS, mean # prescriptions $\pm$ SD	2.4 $\pm$ 3.0	2.9 $\pm$ 3.0
Hypertension	5 (11.6)	4 (10.3)
Diabetes (includes gestational diabetes)	8 (18.6)	2 (5.1)

Résultats

Cossette B et coll.

	Exacerbations when Pregnant	Exacerbations when Non-pregnant
	n=43	n=39
Age, mean $\pm$ SD	26.2 $\pm$ 5.2	24 $\pm$ 5.5
Receipt of social assistance	26 (60.5)	24 (61.5)
Type of medical visit		
Hospital based outpatient clinic	11 (25.6)	1 (2.6)
Emergency room	21 (48.8)	27 (69.2)
Hospitalization	11 (25.6)	11 (28.2)
Duration of medical care		
1 day (%)	12 (27.9)	19 (48.7)
Median (min. – max.)	3.0 (1 – 36)	2.0 (1 – 20)
FEV1 ,% pred, mean $\pm$ SD**	59.4 $\pm$ 18.8	55.8 $\pm$ 15.3
Use of SABA		
None***	8 (18.6)	5 (12.8)
> 0 ug – 1200 ug	17 (39.5)	15 (38.5)
> 1200 ug	18 (41.9)	19 (48.7)
Systemic corticosteroids, %		
Given in hospital	31 (72.1)	32 (82.1)
Given in hospital	23 (53.5)	25 (64.1)
Filled at pharmacy****	21 (48.8)	24 (61.5)

Table 2. Adjusted rate ratios of use of systemic corticosteroids according to pregnancy status

	RR (IC 95%)
At time of exacerbation	
Pregnant versus non-pregnant	0.70 (0.59-0.84)
Age, years	
18-34	Reference
Other	1.06 (0.81-1.39)
Receipt of social assistance	0.97 (0.79-1.20)
Type of medical encounter	
Hospital based outpatient clinic	Reference
Emergency room	0.78 (0.56-1.10)
Hospitalization	0.82 (0.56-1.20)
Use of SABA for acute exacerbation	
0 ug – 1200 ug	Reference
> 1200 ug	1.33 (1.02-1.73)
In the year preceding exacerbation	
Asthma severity	
Mild	Reference
Moderate	1.14 (0.79-1.63)
Severe	0.77 (0.59-1.01)
Uncontrolled asthma	1.22 (0.84-1.78)
Hypertension	0.78 (0.63-0.96)
Diabetes	1.39 (1.07-1.80)

Conclusion

Cossette B, et coll.

- Lors d'exacerbations traitées dans un établissement de soins tertiaires, les femmes asthmatiques sont moins fréquemment traitées par corticostéroïdes systémiques pendant qu'en dehors de la grossesse
- La prise en charge des femmes asthmatiques lors d'exacerbations varie en fonction du statut de grossesse, les femmes enceintes étant plus fréquemment vues en clinique externe et hospitalisées

Formation d'étudiants

- **Doctorat Sciences pharmaceutiques**

- Benoît Cossette
- M-C Cyr
- Shérif Eltonsy

- **MSc Sciences pharmaceutiques**

- Jonathan Assayag
- François Després
- Mariia Samoilenko

- **MSc Pharmacothérapie avancée**

- Fanny Arbour
- Nicolas Dugré
- Josiane Bégin
- Caroline Brais
- Josiane Larochelle
- Marie-Hélène Turgeon

- **Stagiaires**

- François Després
- Julia Sokunthea Yourk
- Jenny Yu
- Lea Dikranian
- Marie Couturier
- Claudie Rodrigue

Personnel de recherche

■ **Coordonnatrice /agentes de recherche**

- Geneviève Lalonde
- Amélie Forget
- Fatima Kettani

■ **Assistantes de recherche**

- Raphaëlle DeChantal
- Noémie Borduas
- Camille DeChantal
- Julia Sokunthea Yourk
- Mélanie Lessard
- Émilie Roy-Robertson
- Nawal Bouchama
- Maude Nicolau
- Jocelyne L'Archevêque

Partenaires financiers

- IRSC
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- Novartis
- Pfizer