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To cite this article: Anna-Belle Beau MSc, Alain Didier MD, Caroline Hurault-Delarue MSC, PhD, Jean-Louis Montastruc MD, PhD, Isabelle Lacroix PharmD, PhD & Christine Damase-Michel PharmD, PhD (2016): Prescription of asthma medications before and during pregnancy in France: An observational drug study using the EFEMERIS database, Journal of Asthma, DOI: 10.1080/02770903.2016.1214731

To link to this article: <http://dx.doi.org/10.1080/02770903.2016.1214731>



Accepted author version posted online: 22 Sep 2016.
Published online: 22 Sep 2016.



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Prescription of asthma medications before and during pregnancy in France: An observational drug study using the EFEMERIS database

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ABSTRACT

Objective: Asthma affects between 3% to 8% of pregnant women. Previous studies have suggested that women's prescriptions for asthma medications change during pregnancy. The aim was to describe the prescription of asthma medications before and during pregnancy in France. **Methods:** Women from the EFEMERIS, a French database assessing the drugs prescribed, dispensed and reimbursed during pregnancy, delivering between July 2004 and December 2012, were included. Women, who were dispensed asthma medications on at least two dates from 3 months prior to pregnancy through delivery, were considered. **Results:** 2,977 women out of 69,205 (4%) were selected. They were prescribed 2.4 ± 1.2 different anti-asthmatic drugs with 3.5 ± 2.7 different dispensing dates. Almost 62% of the women were dispensed at least one prescription for short-acting β_2 -agonist (SABA), 63% at least one inhaled corticosteroid (IC), 42% a fixed-combination of an IC and a long-acting β_2 -agonist (LABA) and 8% a LABA. An increase in SABA and IC prescriptions and a decrease in fixed-combination prescriptions were observed during pregnancy compared to pre-pregnancy period. A rapid drop in prescriptions for montelukast was observed. Among the 1,507 women who were prescribed asthma medication before pregnancy, one third had a drop in dispensed asthma medications from the beginning of pregnancy. **Conclusions:** The prevalence of dispensed asthma medications varies during pregnancy. There is a decrease in the prescriptions of fixed-combinations during pregnancy and an increase in the prescriptions of ICs. It appears important to study the potential impact of such changes on fetuses and newborns.

ARTICLE HISTORY

Received 10 December 2015

Revised 11 July 2016

Accepted 14 July 2016

KEYWORDS

Asthma medication; drug utilization study; pregnancy; EFEMERIS cohort

Introduction

Asthma affects between 3 and 8% of pregnant women, making it one of the most common medical conditions arising during pregnancy [1,2]. Medications take a central place in managing and controlling asthma [3]. Several previous studies have shown that women's prescriptions for asthma medications change during pregnancy. This change could be due to variations in asthma control during this period or to concerns about potential adverse effects on the fetus [5,6]. During pregnancy, asthma worsens in one third, improves in one third and remains stable in one third of the women [4]. Nevertheless, poorly controlled asthma during pregnancy has been reported to be associated with increased risks of gestational hypertension, pre-eclampsia and postpartum hemorrhage [7–11]. Poorly controlled asthma during pregnancy has also been shown to be associated with a rise in the risk of low birth weight and preterm birth [11–13]. French and international guidelines recommend continuing (the use of) asthma treatment during pregnancy [3,14].

A recent European study has shown that the prevalence of prescribed asthma medications varies from country to country [15]. An overall picture of anti-asthmatic prescriptions is not yet available in France. The aim of this study was to describe trends in asthma medication prescribing during pregnancy in France.

Methods

Data collection

We conducted a drug utilization study among pregnant women using data from the EFEMERIS (Evaluation chez la Femme Enceinte des MEDicaments et de leurs RISques) database. Detailed information about the EFEMERIS is available elsewhere [16,17]. In a word, EFEMERIS is a French database of pregnant women in the general population developed to assess drug prescriptions and the risks associated with drugs during pregnancy. This database currently includes over 100,000 pregnant women. The

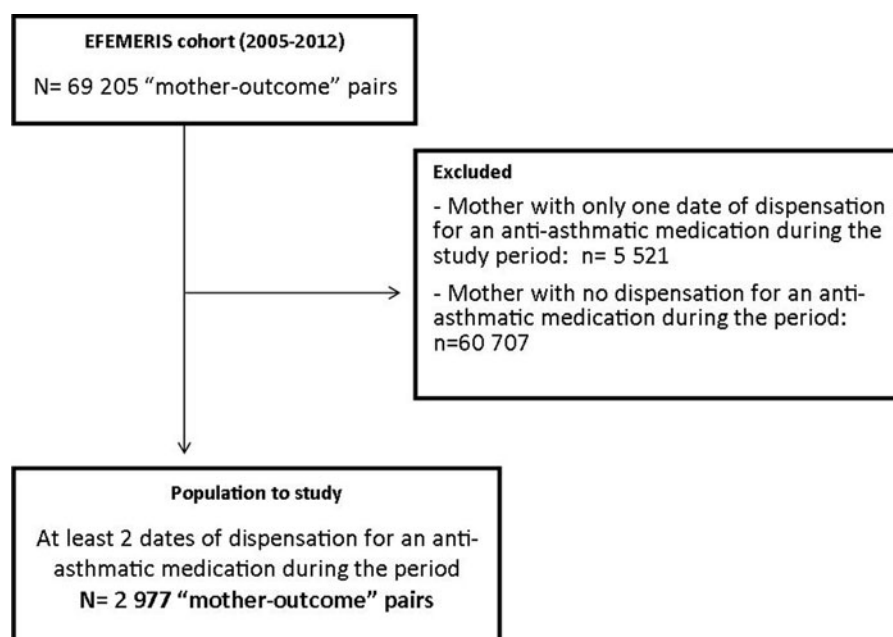


Figure 1. Selection of the study population.

present study concerns around 69,000 pregnant women who gave birth from 1st July 2005 to 31st December 2012. The data come from four different sources.

First, the French Health Insurance System (Caisse Primaire d'Assurance Maladie; CPAM) of Haute-Garonne (south western France) which records all reimbursed drugs (name, dispensation date, prescriber) that are prescribed and dispensed to patients under the general state coverage. All drugs are classified according to the World Health Organization's Anatomical Therapeutic Chemical classification (ATC classification). Second, the Mother and Child Protection Centre (Protection Maternelle et Infantile; PMI) records data from children's certificates filled out during compulsory medical examinations at birth, 9 months and 2 years. These health certificates contain data about the health of both mother and child. Third, the Prenatal Diagnosis Centre (Centre Pluridisciplinaire de Diagnostic Prénatal; CPDPN) centralizes data corresponding to all occurrences of major and minor congenital malformations in the maternity hospitals of the region for which therapeutic termination of pregnancy was considered (cause and date of termination). Fourth, the French hospital medical information system (Programme de médicalisation des systèmes d'information; PMSI) provides the type and date of termination of pregnancy from Toulouse University Hospital Centre. The onset of pregnancy was determined using LMP dates or/and prenatal ultrasound. The mother and her outcome (live birth or pregnancy loss) are linked with an anonymous irreversible code. Approval for setting-up the EFEMERIS was granted by the French Data Protection Agency on 7 April 2005 (authorization number: 05-1140).

Participants

Women from the EFEMERIS who delivered (or ended pregnancy) between 1 July 2005 and 31 December 2012 were included in the study (Figure 1). Women who were dispensed asthma medication on at least two dates from three months prior to pregnancy through their date of delivery were identified and selected for analysis.

Asthma medication

Information on asthma medication was obtained from ATC-codes R03: Inhaled Corticosteroids (ICs), Short-Acting B2-Agonists (SABA), Long-Acting B2-Agonists (LABA), fixed-combination of LABAs and ICs, leukotriene antagonists, theophylline and omalizumab. Medications labeled only for “chronic obstructive pulmonary disease” or “threatened preterm labor” in France were excluded.

Statistical analysis

The demographic characteristics of the pregnant women selected and their children's outcomes were assessed. The prescription rate was defined as the percentage of women who were dispensed anti-asthmatic drugs during the entire monitoring period (from 3 months before the beginning of pregnancy to the delivery date), and during each trimester of pregnancy as well as during the three months prior to pregnancy. The pattern of prescriptions among the group of women who received asthma medications was described. Continuous variables are expressed

as means ($\pm$ SD) and categorical variables as percentages. The Mac Nemar's Test was used for paired comparisons. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC USA).

Results

A total of 2977 pregnant women (4.3%) received asthma medications on at least two dates from 3 months before pregnancy to the end of pregnancy. From 2005 to 2012, the percentage of women who received at least two prescriptions for an asthma medication increased, rising from 3.5% in 2005 to 5.2% in 2012. Around 51% of the women were prescribed an anti-asthmatic medication during the 3 months before pregnancy, whereas 56% were prescribed the medication during the first trimester of pregnancy, 59% during the second and 52% during the third ($p < 0.0001$).

Demographic characteristics of pregnant women who were dispensed anti-asthmatic medications and their children

Characteristics for the 2977 women who were prescribed anti-asthmatic medications and their children are given in Table 1. The mean maternal age was 31.0 ± 5.2 years, almost 23% were unemployed at the beginning of their pregnancy and 6% were smokers during pregnancy. Nearly 6% of the women had long-term adverse health conditions (on a list of severe conditions that lead to full healthcare reimbursement defined by

French Health authorities) and 4% suffered from diabetes while pregnant. Women were dispensed 14.9 ± 8.2 different medications other than asthmatic medications during pregnancy. The rate of breastfed infants at birth was 64.9%. Rates of congenital anomaly and neonatal pathology were 2.9% and 6.8% respectively.

Anti-asthmatic prescriptions

Women were dispensed on average 2.4 ± 1.2 different anti-asthmatic substances with 3.5 ± 2.7 different dispensation dates during the study period. Overall, during the follow-up period (from the three months before to the end of pregnancy), 62% of women got a prescription for a SABA, 87% for an IC and 47% for a LABA (including 41% for a fixed-combination of ICs and LABAs). Salbutamol was the most prescribed SABA (59%), whereas formoterol was the LABA that was the most dispensed (28%). Budesonide (54%) and beclomethasone (34%) were the most commonly-prescribed ICs. Meanwhile, the fluticasone/salmeterol combination was the most prescribed fixed combination (21%). Montelukast was dispensed to 9% of the pregnant women. Only 4 women were dispensed omalizumab during the period. Most asthma medications (86%) were prescribed by a general practitioner, whereas only 10% were prescribed by a respiratory physician.

A decrease in the rate of fixed-combination prescriptions was observed starting in the first 2 months of pregnancy; at the same time, there was an increase in the rate of ICs and SABA prescribing (Figure 2). The budesonide, beclomethasone and salbutamol prescribing prevalence rose after the first 2 months of pregnancy while the fluticasone, formoterol, and salmeterol prescribing prevalence dropped during pregnancy (Figure 3). A sharp fall in the prevalence of montelukast prescribing was observed during pregnancy: from 7% of women taking the medication before pregnancy to less than 1% during the third trimester (Table 2). Almost 50% ($n = 1470$) of the women studied were not prescribed asthma medications during the 3 months before pregnancy whereas they were prescribed at least two during pregnancy.

Among the 1507 women who were prescribed at least one asthma medication before pregnancy, 50% ($n = 761$) were not prescribed asthma medication repeatedly (one prescription per trimester) throughout their pregnancy and 27% ($n = 413$) were not dispensed asthma medications after the first trimester of pregnancy. About one tenth of these 1507 women ($n = 151$) had only one prescription before pregnancy: 46% of them had a prescription for a fixed combination, 54% had an IC (associated with a SABA for 21%), and nearly one fifth (19%) were treated with montelukast. Moreover, 75% of these

Table 1. Characteristics of the women receiving dispensations of anti-asthmatic drugs.

Characteristics	N	Mean $\pm$ SD / n (%)
<i>Mothers</i>		
Age at delivery (years)	2977	31.0 ± 5.2
Multiparous	2368	1501 (63.4%)
Multiple pregnancy	2862	88 (3.1%)
Unemployed	2416	546 (22.6%)
Any tobacco use during pregnancy	2721	169 (6.2%)
Long-term adverse health condition	2977	174 (5.8%)
Diabetes during pregnancy	2722	104 (3.8%)
Hypertension	2722	46 (1.7%)
Pre-eclampsia	2722	20 (0.7%)
Pregnancy losses	2977	130 (4.4%)
Gestational age (on live-birth only)	2847	39.5 ± 1.7
Number of different active substances prescribed*	2977	14.9 ± 8.2
<i>Children</i>		
Female	2852	1378 (48.3%)
Breastfed infant at birth	2624	1704 (64.9%)
Neonatal pathology	2721	184 (6.8%)
Congenital anomaly	2855	84 (2.9%)
Birth weight (g)	2676	3269 ± 513
Birth height (cm)	2495	49.1 ± 2.4

Note. * Other than asthma medications.

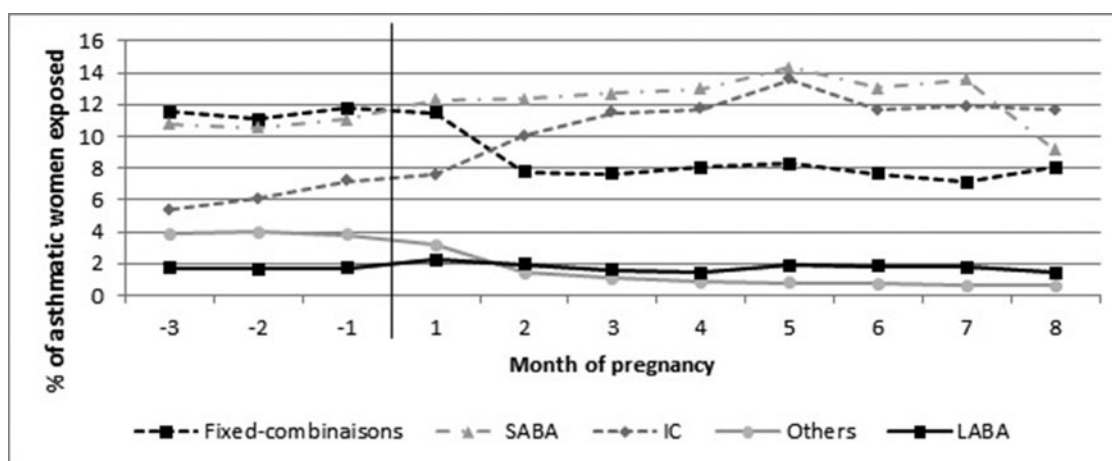


Figure 2. Prevalence of prescribing of asthma medication in the 3 months before and during pregnancy.

1507 women received a prescription for ICs during the 3 months before pregnancy; the percentage fell to 44% during the first trimester. Similar trends were observed for prescriptions for SABA and LABA, from around 50% before pregnancy to 30% during the first trimester. In all 14% of these 1507 women received a prescription for montelukast before pregnancy; the percentage fell to 7% during the first trimester and to 2% during the second and third trimesters.

Discussion

We presented the first French descriptive study on asthma medication prescribing before and during pregnancy. This study was conducted on a large sample size of

almost 3000 selected pregnant women. In the EFEMERIS database, 4.3% of the women were identified as asthmatic, using a selection criterion of at least two dates of drug dispensation during the period observed. We observed an increase in the prevalence of prescribed asthma medications between 2005 and 2012. The first main result of our study is that half of the women with a prescription for asthma medication before pregnancy did not get medication repeatedly (one prescription per trimester) throughout pregnancy (a reduction in prescriptions for asthma medications is observed during early pregnancy). The second main result is the change in the type of asthma medication prescribed during pregnancy, with a decrease in fixed-combinations and an increase in IC prescriptions.

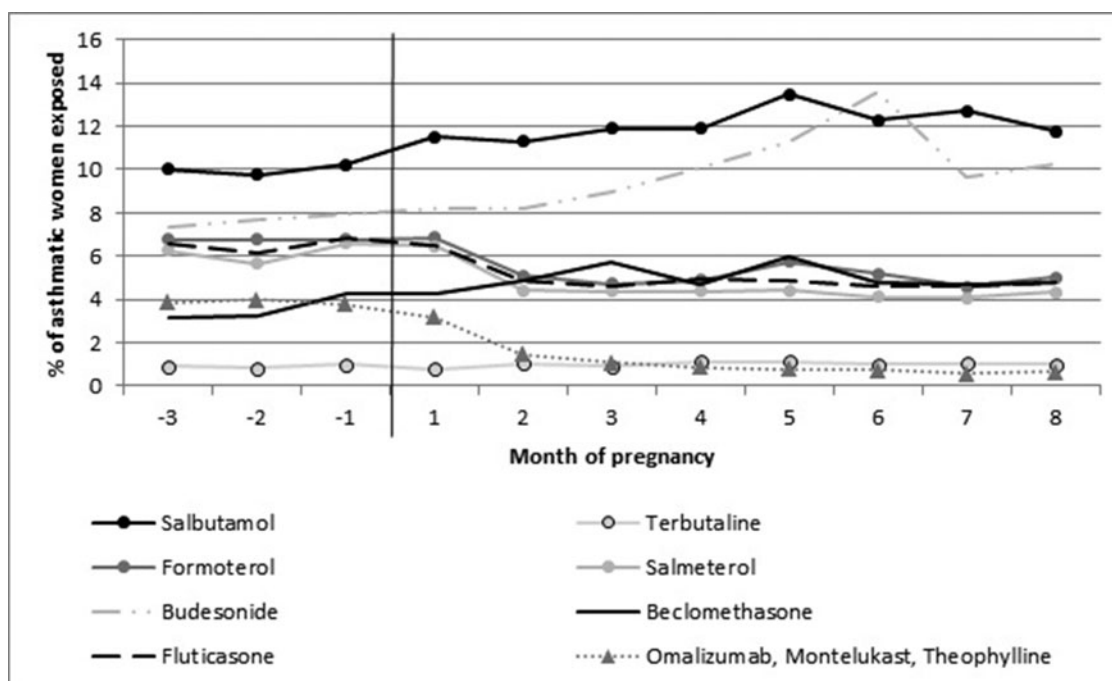


Figure 3. Prevalence of prescribing of asthma substances in the 3 months before and during pregnancy.

Table 2. Prevalence of asthma medication prescribing in our pregnant women population.

	3 months before (N = 2977)	Trimester 1 (N = 2977)	Trimester 2 (N = 2917)	Trimester 3 (N = 2845)
SABA (short-acting bronchodilators)	756 (25.4%)	867 (29.1%)	918 (31.5%)	776 (27.3%)
Salbutamol	699 (23.5%)	810 (27.2%)	859 (29.5%)	725 (25.5%)
Terbutaline	66 (2.2%)	66 (2.2%)	81 (2.8%)	67 (2.4%)
Pirbuterol	4 (0.1%)	3 (0.1%)	5 (0.2%)	2 (0.1%)
Indacaterol	0 (0.0%)	0 (0.0%)	1 (0.03%)	0 (0.0%)
Bambuterol	1 (0.03%)	0 (0.0%)	1 (0.03%)	0 (0.0%)
Ipratropium	10 (0.3%)	9 (0.3%)	16 (0.6%)	13 (0.5%)
LABA (long-acting bronchodilators) alone	104 (3.5%)	113 (3.8%)	100 (3.4%)	84 (2.9%)
Formoterol	77 (2.6%)	82 (2.8%)	77 (2.6%)	65 (2.3%)
Salmeterol	15 (0.5%)	20 (0.7%)	16 (0.6%)	14 (0.5%)
Tiotropium	10 (0.3%)	10 (0.3%)	4 (0.1%)	4 (0.1%)
Fenoterol/Ipratropium	6 (0.2%)	5 (0.2%)	4 (0.1%)	1 (0.03%)
ICs (inhaled corticosteroids) alone	485 (16.3%)	737 (24.8%)	886 (30.4%)	738 (25.9%)
Budesonide	249 (8.4%)	402 (13.5%)	551 (18.9%)	448 (15.7%)
Beclomethasone	226 (7.6%)	343 (11.5%)	355 (12.2%)	310 (10.9%)
Fluticasone	39 (1.3%)	38 (1.3%)	51 (1.8%)	36 (1.3%)
Fixed-combination of IC and LABA	739 (24.8%)	594 (19.9%)	508 (17.4%)	414 (14.6%)
Fluticasone+Salmeterol	386 (13.0%)	313 (10.5%)	244 (8.4%)	212 (7.1%)
Budesonide+Formoterol	310 (10.4%)	252 (8.5%)	225 (7.7%)	182 (6.4%)
Beclomethasone+Formoterol	57 (1.9%)	44 (1.5%)	43 (1.5%)	27 (1.0%)
Others				
Omalizumab	3 (0.1%)	2 (0.1%)	0 (0.0%)	1 (0.03%)
Montelukast	208 (7.0%)	115 (3.9%)	41 (1.4%)	26 (0.9%)
Theophylline	1 (0.03%)	1 (0.03%)	1 (0.03%)	1 (0.03%)

The observed growth in the prevalence of women having a prescription for an anti-asthmatic drug between 2004 and 2012 may be the reflection of either better asthma diagnoses or an increase in asthma prevalence in pregnancy over the years [1]. A rise in the prevalence of asthma diagnoses among pregnant women between 2001 and 2007 in the United States was also mentioned by Hansen et al. [2].

In 2013, a study using the UK General Practice Research Database identified 8.3% of pregnant women treated with anti-asthmatic drugs among whom 68% received a prescription for a SABA and 41% for an IC [4]. These rates are in line with those observed in our study. A North American study published in 2006 described patterns of asthma medication use during pregnancy in a cohort of 8149 women [5]. The results suggested that women reduce or stop anti-asthmatic drugs during early pregnancy, especially ICs.

More recently, in 2013, a Dutch study described prescription patterns in more than 2,000 pregnancies: a decline in asthma medication prescriptions during the first months of pregnancy was observed [6]. These results and our own show a change in asthma medication prescribing during early pregnancy. Montelukast and omalizumab are relatively new agents, marketed in France in 1998 and 2005, respectively, and physicians prefer to limit the number of drugs given during pregnancy, usually choosing older drugs. Certain French medical journals indicate that a IC and beta2 agonists are the reference treatment for continuous treatment of adult asthma (and that this must be the choice during pregnancy) and that these drugs must be avoided in pregnant women since

their safety during pregnancy has not yet been well established [18–21].

Moreover, the oral formulation of montelukast may lead the practitioner to believe that the medication has a greater systemic passage than inhaled medications. This could account for the drop in prescribing observed after the first trimester of pregnancy in our study population. These prescription patterns suggest that women and prescribers may have concerns about potential adverse effects on the fetus.

The guidelines emphasize that, for well-controlled asthma in pregnant women, there is no major argument for reducing treatment until the end of the pregnancy [3,22]. Nevertheless, it has been suggested that beclomethasone and budesonide which are the best-known ICs could be preferred during the first trimester for treating persistent asthma [14]. SABAs are the first group of medication to be used to treat asthma attacks with salbutamol and terbutaline being preferred [14]. Prescription rates in our population comply with the French recommendations [3,22,23]. In 2015, Kim et al. compared asthma medication prescriptions for pregnant asthmatic women with non-pregnant asthmatic women [24]. Consistent with our results, they found that fixed-combinations of ICs and LABAs, SABAs, LABAs and leukotriene antagonists were prescribed less for pregnant women, whereas IC monotherapy was prescribed to them more than to non-pregnant women.

The characteristics of women in our study were slightly different to those from pregnant women in the EFEMERIS database (age: 31.0 y versus 30.4 y, tobacco use: 6.2% versus 3.9%, and long-term adverse health

condition: 5.8% versus 2.5%) ($p < 0.05$). The outcomes for the children in the present study population, however, appeared similar to those of the pregnant women in the EFEMERIS database (birth weight: 3269 g versus 3269 g, neonatal pathologies: 6.8% versus 6.7%, congenital anomalies: 2.9% versus 2.7%) ($p > 0.05$) [16].

The methodological strengths of the EFEMERIS database are as follows: information about medication is registered prospectively so that the possibility of recall bias is avoided. The database contains real pregnancy-start and -end dates. The database also contains all pregnancies regardless of the outcome (live-birth, spontaneous abortion, elective or therapeutic termination or miscarriage). All anti-asthmatic medications in France are prescription-only drugs and, as such, the bias regarding the lack of data for over-the-counter drugs is avoided. Complete data were available on all asthma medications prescribed from three months before pregnancy to the delivery.

On the other hand, our study had several limitations that should be mentioned. Although administrative health databases are useful tools in observational drug utilization studies, it is not known whether the women actually take the medications, even if they have been dispensed by the pharmacist. The EFEMERIS database does not contain information on medication prescribed during hospitalization. EFEMERIS does not contain information about asthma symptoms, the degree of control or the exacerbations of asthma during pregnancy. In the absence of a clinical diagnosis of asthma, we used a proxy of the asthma condition to describe prescribing patterns among pregnant women. Our selection criterion was “having received at least two prescriptions for any asthma medication from the three months before pregnancy to the end of pregnancy.”

Even if some of the women selected may not have been suffering from asthma, we assume that this selection captured a realistic enough sample of asthmatic women. Moreover, the selection criterion may have induced a selection bias as women undergoing termination of pregnancy during the first trimester may not have a sufficiently long study period to be selected. This bias may explain the low rate of terminations of pregnancy observed in our study population.

Conclusions

The prevalence of asthma medication prescribing varies during pregnancy in France. A change in the type of asthma medication during pregnancy was observed with an increase in the prescribing of better evaluated medications. Half of the women who were dispensed asthma medication before pregnancy did not receive

a prescription for asthma medication regularly during their pregnancy and more than one out of four did not receive any asthma medication after the first month of pregnancy. It appears important to address the issue of such changes in order to study the potential impact for fetuses and newborns and to give better information for health professionals.

Acknowledgements

We are grateful to C. Bouilhac, L. Finotto, D. Petiot, C. Vayssière, S. Vidal, and G. Portolan for data collection.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Funding

The EFEMERIS database is funded by the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM - French Agency for the Safety of Health Products), the Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAMTS - French National Health Insurance System for Employees), and the Hospital Clinical Research Programme (PHRC).

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