Can We Rely on Pharmacy Claims Databases to Ascertain Maternal Use of Medications during Pregnancy?

AQ1 Jin-Ping Zhao[1], Odile Sheehy[1], Jessica Gorgui[1,2], and Anick Bérard*[1,2]

Background: Administrative databases are increasingly used to measure drug exposure in perinatal pharmacoepidemiology. We aimed to estimate the concordance between records of prescriptions filled in pharmacies and self-reported drug use during pregnancy. **Methods:** Data on self-reported medication use were collected at each trimester of pregnancy among a subsample from the Organization of Teratology Information Specialists Antidepressants in Pregnancy Cohort. Women were eligible if they were Quebec resident and provided their pharmacist's contact information. Maternal self-reports were compared with prescriptions filled in pharmacies, which are transferred to pharmaceutical services file of Quebec provincial health plan database (Régie de l'asssurance maladie du Québec). Positive and negative predictive values (PPV and NPV) for medications taken chronically (antidepressants, thyroid hormones), acutely (antibiotics), and as needed (antiemetics, asthma medications) were calculated. **Results:** Among the 93 participants (mean age = 30.2 ± 3.8 years), 41.9% (n = 39) took at least one antidepressant during pregnancy according to self-reports, and 39.8% (n = 37) according to pharmacy records. Other commonly used drugs were antiemetics (self-reported 22.6%, pharmacy record 24.7%), antibiotics (20.4%, 16.1%), asthma medications (15.1%, 15.1%), and thyroid hormones (10.8%, 8.6%). PPVs and NPVs were: (1) chronic medication: antidepressants PPV = 100% (95% confidence interval [CI], 100–100%), NPV = 96% (95% CI, 92–100%); thyroid hormones PPV = 100% (95% CI, 100–100%), NPV = 98% (95% CI, 95–100%); (2) Acute medication: antibiotics PPV = 87% (95% CI, 70–100%), NPV = 92% (95% CI, 86–98%); (3) as needed medications: antiemetics: PPV = 78% (95% CI, 62–95%), NPV = 96% (95% CI, 91–100%); asthma: PPV = 33% (95% CI, 3–64%), NPV = 99% (95% CI, 97–100%). **Conclusion:** The high PPV and NPV validate the use of filled prescription data in large databases as a measure of medication exposure.

Birth Defects Research (Part A) 00:000–000, 2016.

Key words: pharmacy claims; self-report drug use; validation; pregnancy; exposure; RAMQ

Introduction

Pregnant women commonly take prescription medications during pregnancy. In Quebec, Canada, the estimated prevalence rate is 59% (Berard and Sheehy, 2014), which is comparable to rates in the rest of Canada, in the European countries (Bakker et al., 2006), and in the United States (Glover et al., 2003). However, human teratogenic risks are undetermined for 91% of medications approved for marketing in the United States since 1980 (Adam et al., 2011). Therefore, scientifically valid data on the safety of medication use during pregnancy are a major public health concern. In perinatal pharmacoepidemiological studies, maternal medication exposure can be evaluated through medical records, patient interviews and prescription filling database from pharmacy records.

However, each method is prone to information bias and may result in exposure misclassification (Sjahid et al., 1998; Sarangarm et al., 2012). The administrative databases are increasingly being used to measure drug exposure in perinatal pharmacoepidemiology, and have many advantages, mainly prospective data collection and completeness of registration (Grzeskowiak et al., 2012). Although these databases have the major advantage of providing information on filled prescriptions, their main limitation is the lack of information on patient compliance. Hence, the validity of a true measure of exposure during gestational period is questionable (Olesen et al., 2001). It is recognized that when using health care databases, the validity of the data must be investigated (Noize et al., 2009), and data exists on the concordance between maternal self-report of medication use and filled prescriptions provided by administrative databases in several databases (De Jong van den Berg et al., 1999; Olesen et al., 2001; Sarangarm et al., 2012).

Quebec's administrative database (Régie de l'asssurance maladie du Québec, RAMQ) has been used to assess risks and benefits of drug use during pregnancy (Berard et al., 2015). A previous validation study has found that information contained within the prescription claims database of RAMQ is particularly accurate and complete (Tamblyn et al., 1995). To our knowledge, the pharmaceutical services file of the RAMQ database has not been validated. Therefore, we do not know if we can rely on pharmacy claims databases to ascertain maternal use of medications during pregnancy. This study aims to determine the concordance between pharmacy records on filled prescriptions and maternal self-reports of medication use during pregnancy.

Additional Supporting information may be found in the online version of this article.

[1]Research Center, CHU Sainte-Justine, Montreal, Canada
[2]Faculty of Pharmacy, University of Montreal, Montreal, Canada
Supported by Fonds de Recherche du Québec - Santé (FRQ-S); grant number: 30962 to A.B.
*Correspondence to: Anick Bérard, FISPE Professor Research Center, CHU Sainte-Justine, 3175, chemin de la Côte-Ste-Catherine, Montréal (Québec) H3T 1C5. E-mail: anick.berard@umontreal.ca

Published online 0 Month 2016 in Wiley Online Library (wileyonlinelibrary.com). Doi: 10.1002/bdra.23604

J_ID: BDRA Customer A_ID: BDRA23604 Cadmus Art: BDRA23604 Ed. Ref. No.: 16-0124.R2 Date: 17-December-16 Stage: Page: 2

Materials and Methods

STUDY SAMPLE

This study was conducted within a subgroup of women sampled within the Organization of Teratology Information Specialists (OTIS) Antidepressants in Pregnancy Cohort. The OTIS cohort study was designed to evaluate the effect of prenatal antidepressant use on maternal behavior and on child development, and the methodology has been described in detail elsewhere (Karam et al., 2012, 2016). Briefly, between 2006 and 2010, 432 pregnant women (within 14 completed weeks of gestation) were recruited from those who called the OTIS counselling services throughout the United States and Canada with questions about medication exposure in pregnancy, either independently or through their health care providers. The first day of the last menstrual period (first day of gestation) was defined using data on gestational age, which was validated against patients' charts (Vilain et al., 2008). Participants were also recruited from the OTIS Web site and in the Obstetrics and Gynecology Clinic of CHU Sainte Justine.

The current study included women who: (1) participated in the OTIS study, (2) were a Quebec resident, and (3) provided their pharmacist's contact information. A total of 206 women met the inclusion criteria and were invited to participate by means of telephone. There were 9 women who refused to participate, and 53 could not be contacted (e.g., change of address, no longer using the same telephone number). An online consent form was created and sent to women who expressed an interest (139 online, 5 paper copy). Overall, 105 women (51.0%) agreed to participate in this study. The main reasons for refusal to participate were: time constraints, inability to recall the pharmacy in which prescription was filled, and confidentiality concerns.

After consent was granted, contact information such as name, telephone number, and address of the pharmacies were collected. Twelve women were further excluded as pharmacy records were unattainable. Finally, 93 women were included in the study to measure the validity of pharmacy claims database (Fig. 1). Thus, we calculate a participation rate of 45% within all eligible women, and a response rate of 70% within those who we were able to reach, which is comparable with similar studies (Norrie et al., 2009; Terry et al., 2009). This study was approved by the Sainte-Justine Hospital Ethics Committee on April 25th, 2012.

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DATA SOURCE

Interviews. Women included in this study were contacted by phone at every trimester of their pregnancy (first trimester: $\leq$14 weeks' gestation; second trimester: 15–26 weeks' gestation; and third trimester: $\geq$27 weeks' gestation). A trained Teratology Information Specialist conducted a telephone interview at the time of the subject enrollment (within 14 completed weeks of gestation), and a telephone interviewer-administered questionnaire was used to collect, among other information, their use of prescription drugs before and during pregnancy. This particular questionnaire was created by adding questions on antidepressants use before and during pregnancy to the regular OTIS questionnaire (Chambers et al., 2001). During the interview, the interviewer started with the open-ended questions. If women answering "yes" to the question "were you using medication prescribed by a physician before and during pregnancy?", they were asked to indicate the brand name, duration and dosage.

After the open-ended questioning, the women were asked (1) whether they had diagnosed with any from a list of 12 medical conditions before pregnancy; (2) whether they had used any medications for these conditions; (3) whether they had experienced any from a list of seven complications since the beginning of this pregnancy; and (4) whether they had used any medications to treat these complications (brand name, dosage, and duration) (Supplementary Table 1, which is available online). For those who had taken antidepressants before and during pregnancy, they were asked to specify which antidepressants, dosage, when it started, and how long they had been taking that medication.

After the initial interview, each woman was provided a pregnancy diary in which she was asked to record any additional medication exposure as the pregnancy progressed. This had to include the drug name, their doses, quantities and duration of use. There were additional calls at the second and third trimester of pregnancy to update records of pregnancy exposures and to remind women to maintain the pregnancy diary as those were used as a memory aid for the interviews. The investigator then registered drugs using their brand name. Over-the-counter (OTC) drugs available on prescription were excluded from the analysis.

Pharmacy records. We obtained pharmacy records for the duration of pregnancy from community pharmacies in which participants were registered. Once details of participants were obtained, their pharmacists were contacted and a copy of the consent form was provided. Pharmacy records of participants were then retrieved by means of fax. Pharmacy records are transferred directly to the pharmaceutical services file of the RAMQ database, which contains prospectively collected data on all prescriptions dispensed in community pharmacies. Drug name, dispensing date, dosage, drug form, number of days supplied, quantity of the drug dispensed, and reimbursement for the prescription are included in the pharmacy record (Rahme et al., 2012). The RAMQ database also contains information on medical services, including physician-based diagnoses, physician and emergency department visits, medical procedures and patient characteristics, as well as health care providers (Nakhai-Pour et al., 2011). Medications

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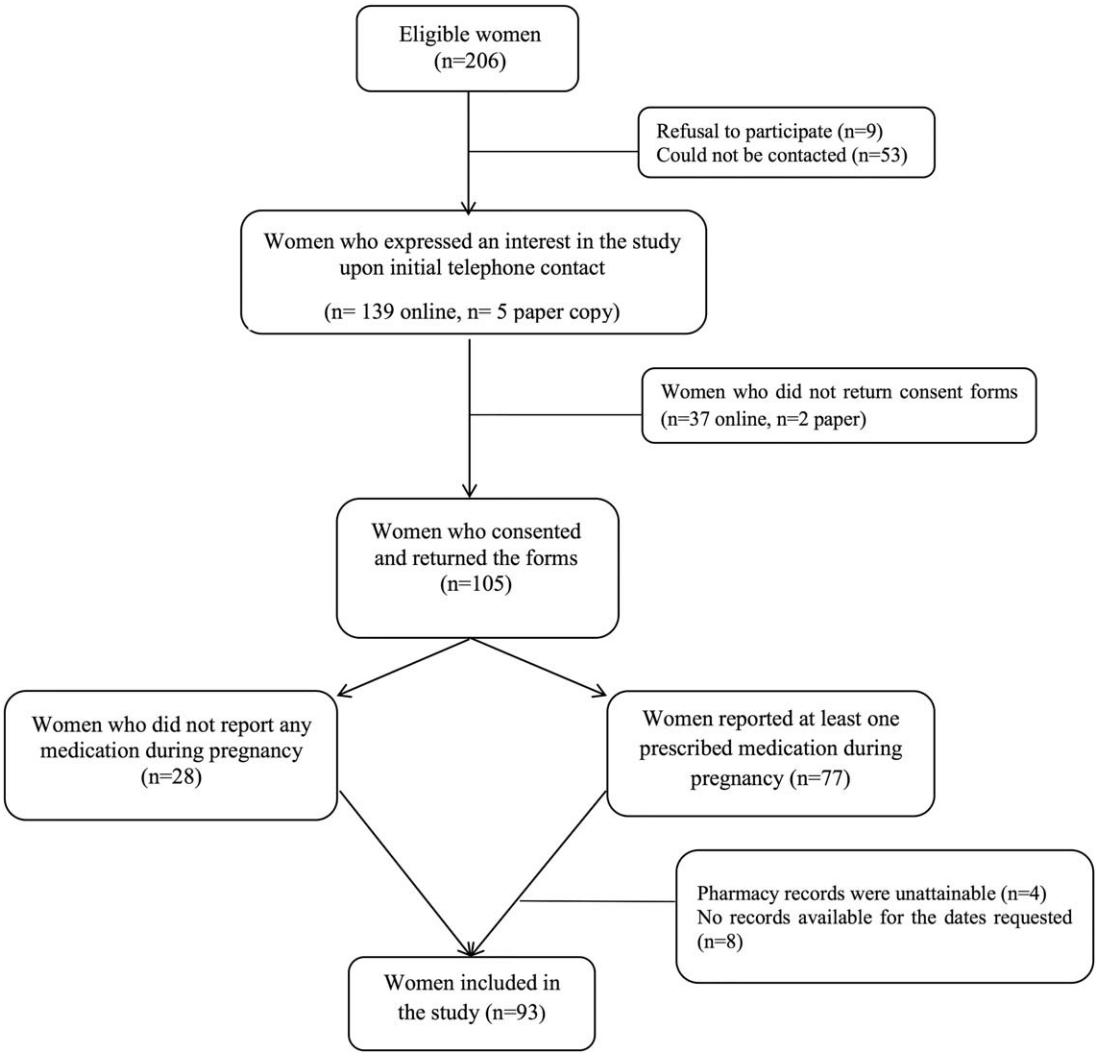

FIGURE 1. *Flow diagram outlining the derivation of the final study sample.*

taken in hospital and OTC drugs that are not prescribed are not included in records of reimbursed prescriptions in claims data (Rahme et al., 2012).

The linkage between pharmacy records and self-reported data on medication use was made by matching the full name of the participant, their date of birth, telephone number, and health insurance number.

STATISTICAL ANALYSIS

All statistical analyses were performed using SAS software (Version 9.2). The validity of the prescription fillings were assessed using reports by the mothers. We then estimated the positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (CI) of having the same drug class dispensed at the pharmacy and being self-reported by the mother during pregnancy. The PPV was calculated by dividing the number of women with a specific drug class that were both dispensed at the pharmacy and self-reported users, by the number of women with this specific drug class dispensed at the pharmacy. The NPV was calculated by dividing the number of women who neither had a specific drug class dispensed at the pharmacy, nor were self-reported users, by the number of women that did not have the specific drug class dispensed in the pharmacy. The PPVs and NPVs were initially calculated for the entire pregnancy, to determine which drug classes were both dispensed at the pharmacy and reported by the mother at least once during pregnancy. Subsequently, we repeated the PPV and NPV calculations for the first trimester only.

To measure the exposure in the first trimester, all prescriptions filled within 30 days preceding the first day of last menstrual period were included, as the majority of prescriptions (94.5%) were for 30 days or less (Tamblyn

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et al., 1995). Specifically, pharmacy claims with exact durations of prescribed medications were used to determine if a medication was used between the 1st day of gestation and the end of pregnancy, or in which trimester.

Characteristics presented in Table 1 were compared between participants and nonparticipants using Chi-square and Fischer's exact tests for dichotomous variables, Wilcoxon rank sum test for ordinal variables, and Student *t* and Mann-Whitney tests for normally and nonnormally distributed continuous variables, respectively.

Results

CHARACTERISTICS OF THE STUDY SAMPLE

At recruitment, the mean age of the mothers was 30.2 years (SD = 3.8 years). The majority of participants were Caucasian (91.4%), had at least a post-secondary education (85.0%), living with spouse (95.7%), and taking vitamins during pregnancy (95.7%). Over half of the mothers had an annual family income higher than $80,000. One third were primiparous (36.6%), and had a depression and/or anxiety diagnosis (43.0%) (Table 1). The mean gestational ages for the first interview were 10.7 ± 3.0 weeks for the participants and 10.4 ± 3.2 weeks for the nonparticipants ($p = 0.57$). Participants had significantly more planned pregnancy than the nonparticipants (82.8% vs. 67.3%; $p = 0.02$). There were no significant differences on any other measured characteristics between the participants and the nonparticipants, such as maternal age, gestational age at the recruitment, education, ethnicity, marital status, occupation, primiparity, medical history, family income, vitamin, alcohol, caffeine, tobacco, and OTC medication use during first trimester of pregnancy.

TABLE 1. *Characteristics of the Study Cohort (n = 206)*

Variable	Participants *n* = 93, (45%)	Non-participants *n* = 113, (55%)
Maternal age,[a] years	30.2 ± 3.7	30.95 ± 4.25
Caucasian ethnicity	84 (90.3)	99 (87.61)
Post-secondary education	78 (83.9)	89 (78.76)
Household annual income (CAN$)		
<40,000	8 (8.6)	24 (21.24)
40,000$–79,999	31 (33.3)	34 (30.09)
≥80,000	52 (55.9)	53 (46.90)
Living with spouse	87 (93.5)	107 (94.69)
Working	83 (89.2)	93 (82.30)
Gestational age at time of recruitment,[a] weeks	10.01 (3.19)	10.93 (2.91)
Pregnancy planned	77 (82.8)	87 (76.99)
Primiparity	34 (36.6)	35 (30.97)
Smoking during 1st trimester	6 (6.5)	15 (13.27)
Alcohol intake during 1st trimester	3 (3.2)	8 (7.08)
Caffeine intake during 1st trimester	39 (41.9)	61 (53.98)
OTC medication use during 1st trimester	42 (45.2)	50 (44.25)
Vitamin intake during 1st trimester	89 (95.7)	105 (92.92)
Medical history[b] (past and present)		
Depression and/or anxiety diagnosis	40 (43.0)	38 (33.63)
Asthma	19 (20.4)	19 (16.81)
Hypertension	3 (3.2)	2 (1.77)
Diabetes	3 (3.2)	2 (1.77)
Thyroid disorders	11 (11.8)	11 (9.73)
Dyslipidemia	5 (5.4)	9 (7.96)
Sexually transmitted diseases	6 (6.5)	15 (13.27)

[a]Mean ± SD.

[b]Groups are not mutually exclusive since a woman could have more than one disease.

MEDICATION USE

According to self-reports, women who took prescribed drugs during pregnancy have taken an average of two (range: 1–7) different therapeutic class during this time. Women filled their questionnaires by indicating specific drug names (commercial or generic) both for prescription and OTC medication. Agreements between self-reported medications and pharmacy records varied by therapeutic class, as shown in Tables 2 and 3. Among the 93 participants, 41.9% ($n = 39$) took at least one antidepressant during the entire pregnancy according to self-reports, and 39.8% (n = 37) according to the pharmacy record. The PPV for antidepressants and thyroids hormones (i.e., the probability that an antidepressant/thyroid hormone was both dispensed and actually taken by the mother at least once during the entire pregnancy) was 100% (95% CI, 100–100%). The PPV for regular long-term asthma medications (fluticasone, budesonide) was relatively high, 80% (95% CI, 45–100%). Similar PPVs were found for antibiotics 87% (95% CI, 70–100%); and antiemetics 78% (95% CI, 62–95%). Nonregular asthma medications taken on an "as needed" basis showed a lower PPV 33% (95% CI, 3–64%).

Although the PPVs were high for all therapeutic classes during pregnancy, these estimates were even higher for medications taken chronically than for medications taken acutely or as an "as needed" basis. The NPVs (i.e., the probability that a therapeutic class was not dispensed and not taken according to self-reports) were high (>90%) for all therapeutic classes. In the first trimester the results were similar to those for the entire pregnancy. Indeed, the PPVs were extremely high for medications taken chronically (antidepressants, thyroid hormones, asthma medications taken chronically), slightly lower for antibiotics and

TABLE 2. *Concordance between Pharmacy Records and Self-Reported Medication Use in the Entire Pregnancy and First Trimester of Pregnancy (n = 93)*

	Entire pregnancy				First trimester of pregnancy			
Therapeutic class[a]	**Pharmacy record *n* (%)**	**Self-reported *n* (%)**	**PPV[b] (95% CI)**	**NPV[c] (95% CI)**	**Pharmacy record *n* (%)**	**Self-reported *n* (%)**	**PPV[b] (95% CI)**	**NPV[c] (95% CI)**
Chronic:								
Antidepressants	37 (39.8)	39 (41.9)	100.0 (100.0-100.0)	96.4 (91.5-100.0)	33 (35.5)	39 (41.9)	100.0 (100.0-100.0)	90.0 (82.4-97.6)
SSRI	29 (78.4)	30 (76.9)	100.0 (100.0-100.0)	98.4 (95.3-100.0)	25 (75.8)	30 (76.9)	100.0 (100.0-100.0)	92.6 (86.4-99.0)
NaSSAs	2 (5.4)	3 (7.7)	100.0 (100.0-100.0)	98.9 (96.8-100.0)	2 (6.1)	3 (7.7)	100.0 (100.0-100.0)	98.9 (97.0-100.0)
SARI	2 (5.4)	3 (7.7)	100.0 (100.0-100.0)	98.9 (96.8-100.0)	2 (6.1)	2 (5.1)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
NDRI	4 (10.8)	4 (10.3)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	4 (12.1)	4 (10.3)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
SNR	7 (18.9)	8 (20.5)	100.0 (100.0-100.0)	98.8 (96.4-100.0)	7 (21.2)	7 (17.9)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
Tricyclic	2 (5.4)	1 (2.6)	50.0 (19.2-100.0)	100.0 (100.0-100.0)	1 (3.0)	1 (2.6)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
Thyroid hormones	8 (8.6)	10 (10.8)	100.0 (100.0-100.0)	97.7 (94.5-100.0)	7 (7.5)	8 (8.6)	100.0 (100.0-100.0)	98.8 (96.4-100.0)
Asthma medication[d]	5 (5.4)	10 (10.8)	80.0 (45.0-100.0)	93.2 (88.0-100.0)	3 (3.2)	6 (6.5)	100.0 (100.0-100.0)	97.0 (93.4-100.0)
Acute:								
Antibiotics	15 (16.1)	19 (20.4)	86.7 (69.5-100.0)	92.3 (86.4-98.2)	8 (8.6)	7 (7.5)	37.5 (10.0-71.0)	95.3 (90.8-99.8)
As needed:								
Antiemetics	23 (24.7)	21 (22.6)	78.3 (61.5-95.1)	95.7 (90.9-100.0)	22 (23.7)	20 (21.5)	77.3 (59.8-94.8)	95.8 (91.1-100.0)
Asthma medication[e]	9 (9.7)	4 (4.3)	33.3 (3.0-64.1)	98.8 (96.5-100.0)	5 (5.4)	4 (4.3)	20.0 (0.0-55.0)	97.0 (93.0-100.0)

[a]The classes are not mutually exclusive since a woman could take more than one therapeutic class during her pregnancy.

[b]PPV: number of women with a specific therapeutic class dispensed at the pharmacy and also reported by the women/number of women with this specific therapeutic class dispensed at the pharmacy.

[c]NPV: number of women without a specific therapeutic class dispensed at the pharmacy and neither reported by the women/number of women without a dispensation of this specific therapeutic class at the pharmacy.

[d]Asthma medication: fluticasone, budesonide.

[e]Asthma medication: salbutamol.

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; NaSSAs, noradrenergic and specific serotonergic antidepressants; SARI, serotonin antagonist and reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

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TABLE 3. *Pharmacy Records and Self-Reported Medication Use during Pregnancy: Women Who Reported Taking at Least One Prescribed Medication (n = 93)*

	Entire pregnancy *n* (%)		1st Trimester *n* (%)		2nd Trimester *n* (%)		3rd Trimester *n* (%)	
Therapeutic class[a] Chronic:	**Pharmacy record**	**Self-reported**	**Pharmacy record**	**Self-reported**	**Pharmacy record**	**Self-reported**	**Pharmacy record**	**Self-reported**
Antidepressant	37 (39.8)	39 (41.9)	33 (35.5)	39 (41.9)	25 (26.9)	34 (36.6)	25 (26.9)	30 (32.3)
SSRI	29 (78.4)	30 (76.9)	25 (75.8)	30 (76.9)	18 (72.0)	25 (73.5)	22 (88.0)	21 (70.0)
NaSSAs	2 (5.4)	3 (7.7)	2 (6.1)	3 (7.7)	1 (4.0)	2 (5.9)	1 (4.0)	2 (6.7)
SARI	2 (5.4)	3 (7.7)	2 (6.1)	2 (5.1)	2 (8.0)	3 (8.8)	2 (8.0)	3 (10.0)
NDRI	4 (10.8)	4 (10.3)	4 (12.1)	4 (10.3)	2 (8.0)	2 (5.9)	0 (0)	2 (6.7)
SNRI	7 (18.9)	8 (20.5)	7 (21.2)	7 (17.9)	5 (20.0)	6 (17.6)	3 (12.0)	6 (20.0)
Tricyclic	2 (5.4)	1 (2.6)	1 (3.0)	1 (2.6)	1 (4.0)	0 (0.0)	2 (8.0)	0 (0.0)
Antidiabetics	3 (3.2)	2 (2.2)	3 (3.2)	2 (2.2)	1 (1.1)	1 (1.1)	1 (1.1)	0 (0.0)
Antihypertensives	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.0)
Thyroid hormones	8 (8.6)	10 (10.8)	7 (7.5)	8 (8.6)	7 (7.5)	8 (8.6)	7 (7.5)	9 (9.7)
Asthma medication[b]	5 (5.4)	10 (10.8)	3 (3.2)	6 (6.5)	2 (2.2)	7 (7.5)	3 (3.2)	3 (3.2)
Acute:								
Antibiotics	15 (16.1)	19 (20.4)	8 (8.6)	7 (7.5)	7 (7.5)	10 (10.8)	6 (6.5)	*7 (7.5)*
Antivirals	6 (6.5)	1 (1.1)	4 (4.3)	1 (1.1)	1 (1.1)	1 (1.1)	2 (2.2)	0 (0.0)
Progestatives	2 (2.2)	4 (4.3)	0 (0.0)	1 (1.1)	1 (1.1)	3 (3.2)	2 (2.2)	3 (3.2)
As needed:								
Antiemetics	23 (24.7)	21 (22.6)	22 (23.7)	20 (21.5)	11 (11.8)	11 (11.8)	6 (6.5)	4 (4.3)
Asthma medication[c]	9 (9.7)	4 (4.3)	5 (5.4)	4 (4.3)	3 (3.2)	3 (3.2)	5 (5.4)	2 (2.2)
Benzodiazepines	4 (4.3)	1 (1.1)	2 (2.2)	1 (1.1)	1 (1.1)	0 (0.0)	3 (3.2)	0 (0.0)

[a]The classes are not mutually exclusive since a woman could take more than one therapeutic class during her pregnancy.

[b]Asthma medication: fluticasone, budesonide.

[c]Asthma medication: salbutamol.

SSRI, selective serotonin reuptake inhibitor; NaSSAs, noradrenergic and specific serotonergic antidepressants; SARI, serotonin antagonist and reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

comparable for medications taken as needed (Table 2). Of note, a difference in the trend between self-report and pharmacy claims can be observed when looking at the patterns of use of antidepressant classes, specifically selective serotonin reuptake inhibitors (Table 3).

Medication use obtained from pharmacy records and self-reports of participants are summarized in Tables 2 and 3. The most commonly used therapeutic classes, according to the two sources, are antidepressants, antiemetics, and antibiotics.

Discussion

Our study demonstrates that pharmacy data on dispensed medication are a valuable tool to ascertain maternal use of medications during pregnancy. To our knowledge, this is the first study that validates the pharmaceutical services file of the RAMQ database using pharmacy records, by comparing it with self-reports of medication use in mothers. The PPVs and NPVs were high for all drug classes during pregnancy in particular in drugs used to treat chronic conditions ($\geq$80%).

Our findings are consistent with earlier studies that compare self-reported information with other pharmacy claims databases for drug exposure in the general population (Monster et al., 2002; Nielsen et al., 2008), and specific populations such as: the elderly (Noize et al., 2009), chronic glucocorticoid users (Curtis et al., 2006), and pregnant women (De Jong van den Berg et al., 1999; Olesen et al., 2001; Sarangarm et al., 2012). Similarly to the RAMQ database, if drugs were used "as needed" or "acutely," agreement of self-reports on drug usage and dispensed medication was not as strong as for drugs used for chronic diseases. Existing validation studies of the RAMQ databases show validity for diagnostic codes (Kulaga and

Berard, 2010; Blais et al., 2013). This study is the first to demonstrate validity of recorded dispensed prescriptions compared with self-reported compliance.

Previous validation studies indicate that the quality of the data collected can be largely affected by the way subjects are interviewed (Mitchell et al., 1986). In the current study, the telephone interview consists of detailed and structured questions regarding drug use, diseases, and symptoms requiring treatment during pregnancy. The questionnaire was available in both French and English, and has been validated in pregnant women (Karam et al., 2012). The pregnancy diary is a standard diary in OTIS studies (Chambers et al., 1996).

In the present study, the most commonly used therapeutic class during pregnancy, according to the two data sources, was antidepressants (41.9% in self-reports, 39.8% in pharmacy records). This rate is much higher than findings from the Quebec Pregnancy Cohort (QPC) study (Berard and Sheehy, 2014) and from Kallen's Sweden antidepressant use during pregnancy validation study (Kallen et al., 2011), where the prevalence rate of antidepressant use before and during pregnancy is of 4.5% in both studies. Although the QPC study and the present study used the same database (pharmaceutical services file of the RAMQ), study subjects in QPC, as well as in Kallen's study include all pregnant women, whereas those included in the present study were pregnant women who particularly sought contact with OTIS regarding questions/concerns about medication exposure (mainly antidepressants) during their pregnancy.

The major strength of this study is the use of telephone interviews supplemented with pregnancy diary as the reference standard. In the pregnancy diary, women logged the specifics of their medications on a daily basis. Therefore, in the present study, the possible recall bias in self-reporting medication could have been diminished by supplementing our information with the pregnancy diary as it should have no recall bias (West et al., 1995). To our knowledge, we are the only group to have interviewed each participant at each trimester of pregnancy with a detailed, structured, and validated questionnaire. In most similar studies, the interview was conducted months or years after delivery (de Jong-van den Berg et al., 1993; van Gelder et al., 2013). Recall interval is an important predictor for recall accuracy (West et al., 1995).

Other strengths of our study was the use of electronic consent forms; an easy, fast, and efficient solution for the participants and our research team. The women had the option of returning the consent by mail or electronically, but the majority (97%) preferred to complete the form electronically. Second, as data were originally collected for another study, the potential for bias was reduced as the research question was formulated after data from the self-reported questionnaire were collected. In addition, women were unaware of the comparison of self-reports to pharmacy records. Third, data were collected prospectively both from women (each trimester) and pharmacy records (data already routinely collected). Given that the majority of prescriptions are prescribed for $\leq$30 days (Tamblyn et al., 1995), and that women collect medications on a monthly basis at their pharmacy further confirms maternal drug exposure and pharmacy records; this helped reduce the potential for the discordance between the trimesters of exposure in the maternal recall vs. the pharmacy record. Finally, it is important to note that pharmacists had a 95% rate of participation.

Our study may have been limited by a small sample size. Additionally, pharmacy records of women who were pregnant in 2006 were more difficult to obtain, as the medications are removed from the pharmacy record after a few years, depending on the pharmacy. Information on consultations with community pharmacies during pregnancy were collected at the end of the pregnancy, which may introduce the possibility of selection bias as patients were excluded based on the absence of pharmacy records differentially between exposed and nonexposed women. This could result in an underestimation of the number of dispensed prescriptions. Prescription records before pregnancy were not available for many women; hence, prescriptions with durations overlapping into the first trimester were not accounted for.

Consequently, this may also cause an underestimation of the number of prescriptions dispensed in pharmacies in the first trimester. We observed a difference between participants and nonparticipants in terms of planned pregnancies, as the nonparticipating women had less planned pregnancies than the participants. It could be speculated that maternal recall may be more accurate in the participants, which in turn may lead to an overestimation of the accuracy of the data collected herein. However, we do not believe that this difference affects the reporting rates notably given that there was no significant difference in any other measured characteristics, including socioeconomic status and education level which are thought to influence recall (de Jong et al., 1995; Radin et al., 2013; Pisa et al., 2015).

Additionally, generalizability tends to be a limitation in all volunteer-based studies, as is the case for ours. However, given the particularity of the pregnancy period, pregnant women in general tend to have better recall to any exposure that occurred during this time, although the level of accuracy in their reports may decrease with increasing trimesters (Olson et al., 1997; Troude et al., 2008). This is understandable given that the period of organogenesis is the most important when it comes to medication exposure. The absence of significant differences between participants and nonparticipants confirms that our sample was indeed representative of the source population.

Although we acknowledge that we have a higher prevalence of anti-depressant users in the study presented

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herein, these women remain representative of any chronic users of any drug class during pregnancy. Of note, our results are also in line with studies that were conducted in larger samples without a particular over-represented subgroup of exposed or diseased women during pregnancy (de Jong-van den Berg et al., 1993; De Jong van den Berg et al., 1999). Therefore, we believe that our cohort is representative of pregnant women exposed to any medication.

CONCLUSIONS

The PPVs and NPVs were high for all therapeutic classes during pregnancy, particularly for medications taken for chronic conditions. This demonstrates high validity between records of dispensed prescriptions in Québec's administrative databases and true exposure in pregnancy. This study gives us confidence in the data on drug exposure recorded in the file of the RAMQ pharmaceutical services, and, therefore, the Quebec Pregnancy Cohort.

Acknowledgments

A.B. is a consultant for plaintiffs in the litigation involving antidepressants and birth defects. All other authors declare no financial interest relating to the subject discussed in this manuscript.

References

Adam MP, Polifka JE, Friedman JM. 2011. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am J Med Genet C Semin Med Genet 157C:175–182.

Bakker MK, Jentink J, Vroom F, et al. 2006. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG 113:559–568.

Berard A, Sheehy O. 2014. The Quebec Pregnancy Cohort–prevalence of medication use during gestation and pregnancy outcomes. PLoS One 9:e93870.

Berard A, Sheehy O, Zhao JP, Nordeng H. 2015. Use of macrolides during pregnancy and the risk of birth defects: a population-based study. Pharmacoepidemiol Drug Saf 24:1241–1248.

Blais L, Berard A, Kettani FZ, Forget A. 2013. Validity of congenital malformation diagnostic codes recorded in Quebec's administrative databases. Pharmacoepidemiol Drug Saf 22:881–889.

Chambers CD, Braddock SR, Briggs GG, et al. 2001. Postmarketing surveillance for human teratogenicity: a model approach. Teratology 64:252–261.

Chambers CD, Johnson KA, Dick LM, et al. 1996. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 335:1010–1015.

Curtis JR, Westfall AO, Allison J, et al. 2006. Agreement and validity of pharmacy data versus self-report for use of osteoporosis medications among chronic glucocorticoid users. Pharmacoepidemiol Drug Saf 15:710–718.

de Jong-van den Berg LT, Waardenburg CM, Haaijer-Ruskamp FM, et al. 1993. Drug use in pregnancy: a comparative appraisal of data collecting methods. Eur J Clin Pharmacol 45:9–14.

de Jong PCMP, Berns MPH, van Duynhoven YTHP, et al. 1995. Recall of medication during pregnancy: Validity and accuracy of an adjusted questionnaire. Pharmacoepidemiol Drug Saf 4:23–30.

De Jong van den Berg LT, Feenstra N, Sorensen HT, Cornel MC. 1999. Improvement of drug exposure data in a registration of congenital anomalies. Pilot-study: pharmacist and mother as sources for drug exposure data during pregnancy. EuroMAP Group. Europen Medicine and Pregnancy Group. Teratology 60: 33–36.

Glover DD, Amonkar M, Rybeck BF, Tracy TS. 2003. Prescription, over-the-counter, and herbal medicine use in a rural, obstetric population. Am J Obstet Gynecol 188:1039–1045.

Grzeskowiak LE, Gilbert AL, Morrison JL. 2012. Exposed or not exposed? Exploring exposure classification in studies using administrative data to investigate outcomes following medication use during pregnancy. Eur J Clin Pharmacol 68:459–467.

Kallen B, Nilsson E, Olausson PO. 2011. Antidepressant use during pregnancy: comparison of data obtained from a prescription register and from antenatal care records. Eur J Clin Pharmacol 67:839–845.

Karam F, Berard A, Sheehy O, et al. 2012. Reliability and validity of the 4-item perceived stress scale among pregnant women: results from the OTIS antidepressants study. Res Nurs Health 35: 363–375.

Karam F, Sheehy O, Huneau MC, et al. 2016. Impact of maternal prenatal and parental postnatal stress on 1-year-old child development: results from the OTIS antidepressants in pregnancy study. Arch Womens Ment Health 19:835–843.

Kulaga S, Berard A. 2010. Congenital malformations: agreement between diagnostic codes in an administrative database and mothers' reports. J Obstet Gynaecol Can 32:549–554.

Mitchell AA, Cottler LB, Shapiro S. 1986. Effect of questionnaire design on recall of drug exposure in pregnancy. Am J Epidemiol 123:670–676.

Monster TB, Janssen WM, de Jong PE, de Jong-van den Berg LT, et al. 2002. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 11:379–384.

Nakhai-Pour HR, Broy P, Sheehy O, Berard A. 2011. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ 183:1713–1720.

Nielsen MW, Sondergaard B, Kjoller M, Hansen EH. 2008. Agreement between self-reported data on medicine use and prescription records vary according to method of analysis and therapeutic group. J Clin Epidemiol 61:919–924.

Noize P, Bazin F, Dufouil C, et al. 2009. Comparison of health insurance claims and patient interviews in assessing drug use: data from the Three-City (3C) Study. Pharmacoepidemiol Drug Saf 18:310–319.

Norrie G, Farquharson RG, Greaves M. 2009. Screening and treatment for heritable thrombophilia in pregnancy failure: inconsistencies among UK early pregnancy units. Br J Haematol 144:241–244.

Olesen C, Sondergaard C, Thrane N, et al. 2001. Do pregnant women report use of dispensed medications? Epidemiology 12: 497–501.

Olson JE, Shu XO, Ross JA, et al. 1997. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. Am J Epidemiol 145:58–67.

Pisa FE, Casetta A, Clagnan E, et al. 2015. Medication use during pregnancy, gestational age and date of delivery: agreement between maternal self-reports and health database information in a cohort. BMC Pregnancy Childbirth 15:310.

Radin RG, Mitchell AA, Werler MM. 2013. Predictors of recall certainty of dates of analgesic medication use in pregnancy. Pharmacoepidemiol Drug Saf 22:25–32.

Rahme E, Roussy JP, Lafrance JP, et al. 2012. Concordance with guideline recommendations: previous and more recent nonsteroidal anti-inflammatory drug prescriptions in Quebec, Canada. Pharmacoepidemiol Drug Saf 21:420–427.

Sarangarm P, Young B, Rayburn W, et al. 2012. Agreement between self-report and prescription data in medical records for pregnant women. Birth Defects Res A Clin Mol Teratol 94:153–161.

Sjahid SI, van der Linden PD, Stricker BH. 1998. Agreement between the pharmacy medication history and patient interview for cardiovascular drugs: the Rotterdam elderly study. Br J Clin Pharmacol 45:591–595.

Tamblyn R, Lavoie G, Petrella L, Monette J. 1995. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol 48:999–1009.

Terry MB, Flom J, Tehranifar P, Susser E. 2009. The role of birth cohorts in studies of adult health: the New York women's birth cohort. Paediatr Perinat Epidemiol 23:431–445.

Troude P, L'Helias LF, Raison-Boulley AM, et al. 2008. Perinatal factors reported by mothers: do they agree with medical records? Eur J Epidemiol 23:557–564.

van Gelder MM, van Rooij IA, de Walle HE, et al. 2013. Maternal recall of prescription medication use during pregnancy using a paper-based questionnaire: a validation study in the Netherlands. Drug Saf 36:43–54.

Vilain A, Otis S, Forget A, Blais L. 2008. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiol Drug Saf 17:345–353.

West SL, Savitz DA, Koch G, et al. 1995. Recall accuracy for prescription medications: self-report compared with database information. Am J Epidemiol 142:1103–1112.

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