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Can Drug Effects Explain the Recent Temporal Increase in Atonic Postpartum Haemorrhage?

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Abstract

Background: Rates of postpartum haemorrhage and atonic postpartum haemorrhage have increased in several high-income countries. We carried out a study to examine if drug use in pregnancy, or drug and other interactions, explained this increase in postpartum haemorrhage.

Methods: The linked administrative and hospital databases of the Québec Pregnancy Cohort were used to define a cohort of pregnant women in Québec, Canada, from 1998 to 2009 ($n = 138\,704$). Case–control studies on any postpartum haemorrhage and atonic postpartum haemorrhage were carried out within this population, with up to five controls randomly selected for each case after matching on index date and hospital of delivery (incidence density sampling). Conditional logistic regression was used to estimate the effects of drug use on postpartum haemorrhage and atonic postpartum haemorrhage.

Results: There was an unexpected non-linear, declining temporal pattern in postpartum haemorrhage and atonic postpartum haemorrhage between 1998 and 2009. Use of antidepressants (mainly selective serotonin reuptake inhibitors) was associated with higher rates of postpartum haemorrhage [adjusted rate ratio (aRR) 1.48, 95% confidence interval (CI) 1.23, 1.77] and atonic postpartum haemorrhage [aRR 1.40, 95% CI 1.13, 1.74]. Thrombocytopenia was also associated with higher rates of postpartum haemorrhage [aRR 1.52, 95% CI 1.16, 2.00]. There were no statistically significant drug interactions. Adjustment for maternal factors and drug use had little effect on temporal trends in postpartum haemorrhage and atonic postpartum haemorrhage.

Conclusions: Although antidepressant use and thrombocytopenia were associated with higher rates of atonic postpartum haemorrhage, antidepressant and other drug use did not explain temporal trends in postpartum haemorrhage.

Keywords: *Atonic postpartum hemorrhage, temporal trends, etiology, selective serotonin reuptake inhibitors, thrombocytopenia.*

Increases in atonic postpartum haemorrhage (PPH) and severe atonic PPH have been reported in several countries including Australia, Canada, Ireland, Scotland, Norway, Sweden, and the US since the 1990s.[1–11] These trends are important from a clinical and population health standpoint, as PPH in high-income countries is a cause of moderate and severe maternal morbidity (and rarely maternal mortality). However, several studies that have investigated changes in various maternal and obstetric factors have not identified any specific cause for the rising rates. Controlling for changes in maternal age, parity, pre-pregnancy weight, multiple pregnancy, previous caesarean delivery, labour induction, labour augmentation, caesarean delivery, and other risk factors has not adequately explained the temporal increases in atonic PPH.[1,2,5–14]

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However, many of these investigations used large population-based data sets with inadequate detail on pre-pregnancy weight and labour management. Therefore, it remains unclear whether temporal increases in atonic PPH represent true increases in haemorrhage due to changes in maternal characteristics, obstetric practice or other extraneous factors, or artefacts due to subtle changes in the diagnosis of this difficult to diagnose condition.

Nevertheless, the failed attempts at explaining the recent increase in atonic PPH have led to the aetiologic focus shifting from maternal and obstetric factors to potential drug effects and drug interactions.[9] The absence of reports of temporal increases in atonic PPH from low- and middle-income countries (which are less medicalised) also raises the possibility of a drug effect or drug interaction. The use of pharmaceutical agents in pregnancy including selective serotonin reuptake inhibitors (SSRIs), aspirin, and other antiplatelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs), and antihistamines has increased in high-income countries in recent decades,[15–18] and studies have shown increased rates of bleeding associated with the use of some of these agents either singly or in combination.[19–21] Drug interactions and interactions between drugs and specific medical conditions (such as alcoholism, liver disease, and thrombocytopenia) are other potential explanations for increases in rates of atonic PPH. We therefore carried out a population-based study examining the effects of the above-mentioned drugs and medical conditions on rates and temporal trends in PPH.

Methods

This population-based study was carried out using the linked administrative database of the Québec Pregnancy Cohort.[22] This database is the product of a linkage of the physician claims database (Régie de l'assurance maladie du Québec, the RAMQ database), the hospitalisation database (the MED-ECHO database), and the vital statistics database (Institut de la statistique du Québec, the ISQ database) in Québec, Canada. The prescription claims component of the RAMQ database included prospectively collected data on prescriptions filled by recipients of social assistance, and workers and their families who did not have access to a private drug insurance plan (in Québec all citizens are insured for physician visits and hospitalisations, whereas recipients of social assistance and workers and their families who do not have access to a private drug insurance are also insured for outpatient drug costs); 36% of women between 15–45 years in Québec were included in such coverage.[22] The MED-ECHO database recorded acute care hospitalisation data for all Québec residents. Information on hospitalisations for childbirth, including maternal characteristics, gestational age at delivery, and diagnoses and procedures was included in the database.[22] Gestational age in the Québec Pregnancy Cohort was defined as the duration between the first day of the last menstrual period and delivery, confirmed by ultrasound. The vital statistics database included information on all live births and stillbirths. Pregnancy-related variables in the cohort, such as birth weight, gestational age, and date of delivery, as well as specific International Classification of Diseases (ICD) codes, have been previously validated against patient charts.[23,24] Prescription information in the Québec Pregnancy Cohort has also been validated, and pregnant women covered by the RAMQ for their medications have co-morbidity profiles similar to pregnant women insured by a private medication insurance plan.[23] Information on women in the cohort included data from the date of entry into the cohort (i.e. the first day of the last menstrual period confirmed by ultrasound), through pregnancy and also the early postpartum period.

Study population

The study base was a dynamic population of women in Québec with a gestational age of 20 weeks or greater between 1 January 1998 and 31 December 2009 who were continuously insured by the RAMQ drug plan for at least 12 months prior to and during pregnancy. For each pregnancy, data on all filled prescriptions in the year preceding and during pregnancy including the date of filling the prescription, drug name, dosage, form, quantity, and duration were obtained. Data were also obtained on all inpatient and ambulatory medical services, including physician diagnoses made before and during pregnancy and in the immediate postpartum period.

Study design

We used a case–control study design that allowed us to assess drug exposures within biologically plausible time windows anchored to the moment of outcome

classification (as opposed to the alternative cohort design with time windows anchored to cohort inception).[25] This permitted the assessment of drug effects in women with recent drug exposure (i.e. in the month before childbirth when PPH did or did not occur) or past drug exposure. We attempted to carry out three primary base type case–control studies[26] within the study base (defined above) in order to examine the relationship between the drugs and specific medical conditions of interest and PPH. The outcomes of interest in the three case–control studies were (i) any PPH, (ii) atonic PPH, and (iii) severe atonic PPH.

Case definition

PPH in Canada is defined as a postpartum blood loss of ≥500 mL following a vaginal delivery, a postpartum blood loss of ≥1000 mL following a caesarean delivery or as diagnosed by the health care provider in the medical chart. For the case–control study on any PPH, all women whose pregnancies ended in a live birth or stillbirth and who had any type of PPH (i.e. an ICD-9 diagnosis code of 6660, 6661, 6662 or 6663 or an ICD-10 diagnosis code of O720, O721, O722, O723) were considered cases (secondary scheme of case ascertainment[26]). The second case–control study defined cases as women whose pregnancies ended in a live birth or stillbirth and who had atonic PPH (an ICD-9 diagnosis code of 6661 or an ICD-10 diagnosis code of O721). For the third case–control study, cases were defined as women whose pregnancies ended in a live birth or stillbirth and who had severe atonic PPH. However, absence of information on medical interventions in a substantial fraction of the study population (including information on blood transfusion and procedures to control bleeding) precluded us from carrying out this study on severe atonic PPH. The index date was defined as the date of delivery for all analyses.

Control definition

Controls for the first case–control analysis were identified from among women without PPH. Up to five controls were randomly selected for each case after matching on index date (+/− 1 month) and the hospital in which the delivery occurred (incidence density sampling). Because cases in the second case–control study (on atonic PPH) were a subset of the cases in the first case–control study (on any PPH), the appropriate subset of the controls selected for the first study served as the controls for the second case–control study.

Maternal use of drugs

Medications of interest included (i) SSRIs and other antidepressants (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, phenelzine, tranylcypromine, amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, trimipramine, bupropion, buspirone, maprotiline, l-tryptophane, mirtazapine, trazodone, and moclobemide), (ii) aspirin (any dose), (iii) other antiplatelet drugs: (clopidogrel, aggrenox, dipyridamole), (iv) NSAIDs and Cox-2 inhibitors (celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbirofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefanamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tiaprofenic acid, tolmetin, and valdecoxib), (v) beta-agonists (salbutamol, levosalbutamol, terbutaline, salmeterol, and formoterol), and (6) antihistamines (diphenhydramine, dimenhydrinate, and doxylamine). Identification of drug use was limited to prescription-drug use, and over-the-counter use of drugs such as aspirin and NSAIDs was not studied.

Drug use was examined in the 6 months before the index date (date of delivery). Within this time window, two mutually exclusive sub-windows were also examined, namely, (i) past use (drug use 180 days to 31 days before the index date), and (ii) recent use (drug use within 30 days prior to the index date). The two different time windows for drug exposure were studied in order to explore immediate and more remote effects of the drugs of interest and to evaluate the biologic plausibility of any observed effects.

Potential confounding variables

The following extraneous risk factors for PPH were also included in the analysis: maternal age at delivery, welfare status (i.e. receipt of social assistance), rural vs. urban residence, previous caesarean delivery, alcoholism, liver disease, thrombocytopenia, multiple pregnancy, pre-eclampsia, polyhydramnios, placenta previa, placental abruption, epidural analgesia, labour induction, prolonged first stage, prolonged second

stage, caesarean delivery, uterine rupture, cervical laceration, severe perineal tear, and chorioamnionitis.

Statistical analyses

Temporal trends in PPH and atonic PPH in the study population were assessed. Unadjusted and adjusted odds ratios were obtained from conditional logistic regression analyses of the two case–control studies and interpreted as incidence density rate ratios with 95% confidence intervals (CI).[27,28] For each case–control study, the adjusted models included three different sets of variables. The first model in each case–control study estimated the effect of each drug (antidepressants, aspirin, other antiplatelet drugs, beta-agonists and antihistamines) and each co-morbidity (alcoholism, liver disease, thrombocytopenia and asthma), along with year of delivery. Since conditional logistic regression only precludes estimation of the effect of matching variables that have exactly the same value for all members of a matched set,[29] we were able to estimate the effect of year of delivery, which was of a priori interest; differing values for 'month of delivery' (the matching variable used for incidence density sampling) and 'year of delivery' occurred in approximately one sixth of our matched sets when the month of delivery was January or December of any year. The second model additionally included maternal and obstetric risk factors, whereas the third model included all variables in the second model plus interaction terms (for combined antidepressant and aspirin use, combined beta-agonist and aspirin use, combined aspirin use and thrombocytopenia, and combined antidepressant use and thrombocytopenia). The population attributable fraction expressing the impact of drugs and co-morbidity was estimated based on the frequency of drug use/co-morbidity among the cases and the adjusted rate ratio (aRR) for their effect on PPH.[30]

Ethics approval

Ethics approval for the study was obtained from the Ethics Committee of Sainte Justine Hospital, Montréal.

Results

The study population included 138 704 deliveries that satisfied eligibility criteria for admission into the study population. Between 1998 and 2009, there was an unexpected decline in the rate of PPH (Figure 1), although the rate in 1998 [4.9%, 95% CI 4.2, 5.6] was approximately the same as the rate in 2009 [4.9%, 95% CI 4.4, 5.5; Table 1]. The same unexpected non-linear decline was evident in rates of atonic PPH (Table 1), although the rate in 2009 was again slightly higher than the rate in 1998 (Figure 1).

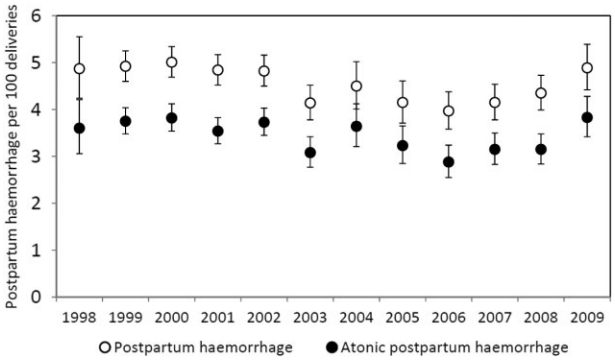

Figure 1. Rates of postpartum haemorrhage and atonic postpartum haemorrhage among pregnant women in the study population, Québec Pregnancy Cohort, 1998–2009.

A total of 6378 cases and 31 795 controls were available for analysis in the case–control study on any PPH. Year of delivery was associated with a decline in PPH [unadjusted rate ratio 0.99, 95% CI 0.99, 1.00]. Table 2 shows unadjusted rate ratios expressing the association between maternal drug use and other risk factors and PPH. Any use, past use, and recent use of

Table 1. Temporal trends in postpartum haemorrhage (PPH) and atonic PPH in the study population, Québec Pregnancy Cohort, 1998–2009

Year	Number of deliveries	PPH		Atonic PPH	
		Number	Rate (%)	Number	Rate (%)
1998	4275	208	4.87	154	3.60
1999	17 732	872	4.92	665	3.75
2000	17 378	870	5.01	664	3.82
2001	16 958	820	4.84	600	3.54
2002	16 820	811	4.82	628	3.73
2003	11 452	474	4.14	353	3.08
2004	6670	300	4.50	243	3.64
2005	7744	321	4.15	250	3.23
2006	9400	373	3.97	271	2.88
2007	10 729	445	4.15	338	3.15
2008	11 770	512	4.35	371	3.15
2009	7776	380	4.89	298	3.83

Table 2. Determinant frequencies among (any) postpartum haemorrhage cases and controls and unadjusted rate ratios with 95% confidence intervals

Determinant	Cases ($n = 6378$) Number (%)	Controls ($n = 31\,795$) Number (%)	Unadjusted rate ratio (95% CI)
Year of delivery	–	–	0.99 [0.99, 1.00]
Maternal age (year)[a]	26.9 ± 5.5	27.2 ± 5.6	1.01 [1.01, 1.02]
Any use[b]: antidepressants	158 (2.5)	567 (1.8)	1.40 [1.17, 1.68]
Aspirin	34 (0.5)	156 (0.5)	1.09 [0.75, 1.59]
NSAIDs/Cox-2	54 (0.9)	258 (0.8)	1.05 [0.78, 1.40]
Beta-agonists	524 (8.2)	2 567 (8.1)	1.02 [0.93, 1.13]
Doxylamine	804 (12.6)	4 024 (12.7)	0.99 [0.92, 1.08]
Past use[b]: antidepressants	156 (2.5)	536 (1.7)	1.46 [1.22, 1.75]
Aspirin	32 (0.5)	151 (0.5)	1.06 [0.72, 1.56]
NSAIDs	46 (0.7)	232 (0.7)	0.99 [0.72, 1.36]
Beta-agonists	459 (7.2)	2 321 (7.2)	0.98 [0.89, 1.09]
Doxylamine	796 (12.5)	3 985 (12.5)	0.99 [0.92, 1.08]
Recent use[b]: antidepressants	122 (1.9)	405 (1.3)	1.51 [1.23, 1.86]
Aspirin	24 (0.4)	94 (0.3)	1.28 [0.82, 2.01]
NSAIDs	11 (0.2)	33 (0.1)	1.69 [0.85, 3.37]
Beta-agonists	224 (3.5)	1 141 (3.6)	0.98 [0.85, 1.13]
Doxylamine	151 (2.4)	786 (2.5)	0.95 [0.80, 1.14]
Social assistance (No)	4518 (70.8)	21 804 (68.6)	1.12 [1.05, 1.19]
Place of residence (urban)	5327 (83.5)	26 372 (82.9)	1.07 [0.98, 1.18]
Previous caesarean	255 (4.0)	1 929 (6.1)	0.64 [0.56, 0.73]
Multi-foetal pregnancy	94 (1.5)	276 (0.9)	1.71 [1.35, 2.17]
Placenta previa/abruption previa/aprevia/abruption	295 (4.6)	906 (2.9)	1.66 [1.45, 1.90]
Polyhydramnios	2 (0.0)	2 (0.0)	5.00 [0.70, 5.50]
Prolonged labour	282 (4.4)	949 (3.0)	1.55 [1.34, 1.78]
Pre-eclampsia/eclampsia	271 (4.3)	796 (2.5)	1.73 [1.50, 1.99]
Epidural analgesia	3730 (58.5)	16 877 (53.1)	1.28 [1.21, 1.36]
Labour induction	1706 (26.8)	6 533 (20.6)	1.44 [1.35, 1.54]
Uterine rupture	21 (0.3)	54 (0.2)	1.94 [1.18, 3.22]
Cervical laceration	48 (0.8)	63 (0.2)	3.79 [2.60, 5.52]
High vaginal laceration	368 (5.8)	1 251 (3.9)	1.52 [1.35, 1.72]
Caesarean delivery	997 (15.6)	6 805 (21.4)	0.68 [0.63, 0.73]
Perineal laceration	539 (8.5)	1 405 (4.4)	2.01 [1.81, 2.23]
Chorioamnionitis	483 (7.6)	1 617 (5.1)	1.57 [1.41, 1.75]
Delivery hospitalisation			
Alcoholism	1 (0.0)	12 (0.0)	0.42 [0.05, 3.20]
Liver disease	19 (0.3)	61 (0.2)	1.56 [0.93, 2.61]
Thrombocytopenia	60 (0.9)	172 (0.5)	1.77 [1.31, 2.38]
Asthma	125 (2.0)	623 (2.0)	1.00 [0.82, 1.22]
Pregnancy and delivery hospitalisation			
Alcoholism	10 (0.2)	38 (0.1)	1.32 [0.66, 2.64]
Liver disease	39 (0.6)	179 (0.6)	1.09 [0.77, 1.54]
Thrombocytopenia	73 (1.1)	240 (0.8)	1.54 [1.18, 2.00]
Asthma	280 (4.4)	1 339 (4.2)	1.05 [0.92, 1.19]

[a]Mean ± standard deviation.

[b]Any drug use refers to drug use within 180 days prior to delivery; recent and past use refer to use 30 days prior, and between 180 days and 31 days prior to delivery, respectively.

Table 3. Results of conditional logistic regression analyses showing unadjusted and adjusted rate ratios for any postpartum hemorrhage

Determinant	Unadjusted rate ratio (95% CI)	Adjusted rate ratio (95% CI)
First model:		
Year of delivery	0.99 [0.99, 1.00]	0.98 [0.91, 1.07]
Maternal age (year)	1.01 [1.01, 1.02]	0.99 [0.99, 1.00]
Exposure in the 6 months prior to the index date		
Antidepressants	1.40 [1.17, 1.68]	1.42 [1.19, 1.70]
Aspirin	1.09 [0.75, 1.59]	1.11 [0.77, 1.62]
NSAIDs	1.05 [0.78, 1.40]	1.05 [0.78, 1.40]
Beta-agonists	1.02 [0.93, 1.13]	1.00 [0.90, 1.11]
Doxylamine	0.99 [0.92, 1.08]	0.97 [0.90, 1.06]
Alcoholism	1.32 [0.66, 2.64]	1.21 [0.60, 2.44]
Liver disease	1.09 [0.77, 1.54]	1.07 [0.75, 1.52]
Thrombocytopenia	1.54 [1.18, 2.00]	1.53 [1.17, 1.99]
Asthma	1.05 [0.92, 1.19]	1.00 [0.86, 1.16]
Second model (adjusted for maternal and obstetric factors[a]):		
Year of delivery	0.95 [0.84, 1.08]	0.99 [0.91, 1.08]
Maternal age (year)	1.01 [1.01, 1.02]	0.99 [0.99, 1.00]
Exposure in the 6 months prior to the index date		
Antidepressants	1.40 [1.17, 1.68]	1.48 [1.23, 1.77]
Aspirin	1.09 [0.75, 1.59]	1.11 [0.76, 1.62]
NSAIDs	1.05 [0.78, 1.40]	1.04 [0.77, 1.40]
Beta-agonists	1.02 [0.93, 1.13]	1.02 [0.92, 1.14]
Doxylamine	0.99 [0.92, 1.08]	0.98 [0.90, 1.06]
Alcoholism	1.32 [0.66, 2.64]	1.13 [0.56, 2.31]
Liver disease	1.09 [0.77, 1.54]	1.02 [0.71, 1.46]
Thrombocytopenia	1.54 [1.18, 2.00]	1.52 [1.16, 2.00]
Asthma	1.05 [0.92, 1.19]	1.00 [0.87, 1.17]
Third model (showing results for interaction terms only)[b]		
Antidepressants and aspirin	5.00 [0.70, 35.5]	3.13 [0.29, 34.3]
Beta-agonists and aspirin	1.32 [0.49, 3.52]	1.30 [0.43, 3.91]
Aspirin and thrombocytopenia	10.0 [0.91, 110.3]	5.81 [0.36, 94.5]
Antidepressants and thrombocytopenia	3.00 [0.72, 12.6]	1.23 [0.23, 6.65]

[a]The model included social assistance, residence urban, previous caesarean, multi-foetal pregnancy, placenta previa/abruption, polyhydramnios, prolonged labour, pre-eclampsia/eclampsia, epidural analgesia, labour induction, uterine rupture, cervical laceration, caesarean delivery, perineal laceration, vaginal laceration, chorioamnionitis, and all variables listed in the table.

[b]Rate ratios and 95% confidence intervals for interaction terms are from a third model that included all variables in the second model and four interaction terms.

antidepressants were associated with an increase in PPH. Several maternal and obstetric factors were associated with increases in PPH, including receipt of social assistance, multi-foetal pregnancy, placenta previa/abruption, prolonged labour, pre-eclampsia, epidural analgesia, labour induction, severe perineal laceration, uterine rupture, cervical laceration, high vaginal laceration, chorioamnionitis, and thrombocytopenia during the delivery hospitalisation or during the pregnancy and delivery hospitalisation. Previous caesarean delivery and caesarean delivery were the only protective factors (Table 2).

Table 3 shows the results of conditional logistic regression with unadjusted and aRRs expressing the relationship between variables in the first model (which included year of delivery, any use of specific drugs and specific co-morbid conditions) and the second model (which included year of delivery, any drug use, specific co-morbidity, and maternal and obstetric factors) and any PPH. In the latter model, which adjusted for maternal and obstetric factors, antidepressants [aRR 1.48, 95% CI 1.23, 1.77] and thrombocytopenia [aRR 1.52, 95% CI 1.16–2.00] were associated with any PPH. The population attributable

fraction for antidepressant use was 0.78% (i.e. <1% of PPH would be prevented if women stopped using antidepressants in pregnancy), whereas the population attributable fraction for thrombocytopenia was 0.37%. Concurrent exposure to antidepressants and aspirin, beta-agonists and aspirin, aspirin and thrombocytopenia, or antidepressants and thrombocytopenia was associated with higher rates of PPH, although none of these interactions were statistically significant (see interaction terms, Table 3). Adjustment for drug use, co-morbidity, and drug and other interactions (in addition to maternal and obstetric factors) did not alter the temporal trend in any PPH.

Similar results were obtained in analyses on atonic PPH. Table 4 shows the unadjusted rate ratios for drug use, specific morbidity, and maternal and obstetric factors. The factors associated with atonic PPH were similar to those associated with any PPH. Results of adjusted analyses were also similar (Table 5). Any use of antidepressants was associated with an increase in atonic PPH [aRR 1.40, 95% CI 1.13, 1.74] in the adjusted model, although thrombocytopenia was not [aRR 1.31, 95% CI 0.94–1.83]. The population attributable fraction for antidepressant use was 0.66% (i.e. <1% of atonic PPH would be prevented if women stopped using antidepressants in pregnancy). Although positive interactions were observed between antidepressants, aspirin, beta-agonists and thrombocytopenia, none were statistically significant.

Comment

Our studies showed expected associations between maternal and obstetric factors and postpartum and atonic PPH. Among the drug classes and co-morbidity studied, only antidepressants and thrombocytopenia were associated with an increased risk of PPH. Interactions between antidepressants, aspirin, beta-agonists and thrombocytopenia were not significant and temporal trends in PPH and atonic PPH were not changed by controlling for medication use, maternal characteristics and obstetric factors.

The absence of a temporal increase in PPH and atonic PPH in our study was surprising given the increases noted in other high-income countries.[1–11] One potential explanation for this phenomenon relates to the dynamic nature of our study population. Eligibility was dependent on inclusion in the RAMQ prescription database, which was restricted to recipients of social assistance, and workers and their families who did not have access to a private drug insurance plan. It is possible that temporal changes in the types of women who satisfied these socioeconomic criteria for entry into and exit from this population were responsible for the absence of an increase in atonic PPH. On the other hand, the rates of PPH and atonic PPH observed in our study were similar to rates observed elsewhere in Canada and in other countries such as Australia, Ireland, and Sweden (although the rates were higher than those observed in some Canadian provinces and the US).[1–4,7,9,12] Variation in international rates of PPH is not unexpected because accurate estimation of blood loss during childbirth represents a clinical challenge; diagnostic idiosyncrasies may be partly responsible for spatial differences in rates of PPH.

Numerous case reports and epidemiologic studies show an increased risk of bleeding associated with the use of SSRIs; the most common bleeding risk described has been a doubling of the rate of upper gastrointestinal bleeding.[31,32] However, few studies have examined the risk of PPH due to SSRIs.[19,33] One study from the US showed an increase in PPH associated with SSRI use [rate ratio 1.47, 95% CI 1.33, 1.62],[19] whereas another study from Ontario, Canada, yielded a modestly elevated increase in risk of PPH in the primary analysis [odds ratio of 1.30, 95% CI 0.98, 1.72].[32] The Ontario study focused on SSRI effects alone and excluded all women at increased risk of bleeding due to medical conditions (such as alcoholism, liver disease, and thrombocytopenia) or concomitant exposure to other drugs (such as antiplatelet agents). In our study, antidepressant (mainly SSRI) use was associated with an increase in PPH [rate ratio 1.48, 95% CI 1.23, 1.77] and atonic PPH rates [rate ratio 1.40, 95% CI 1.13, 1.74].

The frequency of antidepressant drug use in pregnancy in our study was approximately 1.8% among controls. This relatively low frequency is consistent with population rates of SSRI use for the period 1998–2009[34] and explains the small population attributable fraction (<1%) for PPH estimated in our study. On the other hand, some studies have documented rates of SSRI use as high as 7% and even 13%.[15,16] Nevertheless, even such frequent use of SSRI's would only explain about 3–6% of PPH because of the relatively modest effect of antidepressants on PPH (rate ratio 1.48, Table 3). Although these low population attributable fractions suggest that SSRI use is unlikely to

Table 4. Determinant frequencies among atonic postpartum haemorrhage cases and controls and unadjusted rate ratios with 95% confidence intervals

Determinant	Cases (4835) Number (%)	Controls (24 115) Number (%)	Unadjusted rate ratio (95% CI)
Year of delivery	–	–	0.93 [0.81, 1.08]
Maternal age (year)[a]	26.7 ± 5.5	27.2 ± 5.6	0.98 [0.98, 0.99]
Any use[b]: antidepressants	113 (2.3)	439 (1.8)	1.29 [1.05, 1.60]
Aspirin	26 (0.5)	124 (0.5)	1.05 [0.69, 1.61]
NSAIDs	40 (0.8)	202 (0.8)	0.99 [0.70, 1.39]
Beta-agonists	400 (8.3)	1 963 (8.1)	1.02 [0.91, 1.14]
Doxylamine	613 (12.7)	3 013 (12.5)	1.02 [0.93, 1.12]
Past use[b]: antidepressants	113 (2.3)	413 (1.7)	1.38 [1.11, 1.70]
Aspirin	25 (0.5)	120 (0.5)	1.04 [0.68, 1.61]
NSAIDs	34 (0.7)	184 (0.8)	0.92 [0.64, 1.33]
Beta-agonists	353 (7.3)	1 776 (7.4)	0.99 [0.88, 1.12]
Doxylamine	606 (12.5)	2 984 (12.4)	1.02 [0.92, 1.12]
Recent use[b]: Antidepressants	90 (1.9)	313 (1.3)	1.45 [1.14, 1.83]
Aspirin	20 (0.4)	75 (0.3)	1.34 [0.82, 2.20]
NSAIDs	9 (0.2)	23 (0.1)	1.98 [0.91, 4.31]
Beta-agonists	168 (3.5)	876 (3.6)	0.96 [0.81, 1.13]
Doxylamine	123 (2.5)	575 (2.4)	1.07 [0.88, 1.30]
Social assistance (No)	3469 (71.8)	16 640 (69.0)	1.15 [1.07, 1.23]
Place of residence (urban)	4050 (83.8)	20 087 (83.3)	1.06 [0.95, 1.18]
Previous caesarean	195 (4.0)	1 486 (6.2)	0.63 [0.54, 0.74]
Multi-foetal pregnancy	79 (1.6)	214 (0.9)	1.86 [1.43, 2.41]
Placenta previa/abruption	207 (4.3)	707 (2.9)	1.48 [1.27, 1.74]
Polyhydramnios	1 (0.02)	3 (0.0)	5.00 [0.31, 80.0]
Prolonged labour	249 (5.2)	759 (3.2)	1.73 [1.49, 2.02]
Pre-eclampsia/eclampsia	195 (4.0)	609 (2.5)	1.63 [1.38, 1.92]
Epidural analgesia	2902 (60.0)	12 938 (53.7)	1.34 [1.25, 1.43]
Labour induction	1359 (28.1)	4 990 (20.7)	1.54 [1.43, 1.65]
Perineal laceration	435 (9.0)	1 080 (4.5)	2.12 [1.89, 2.38]
Uterine rupture	15 (0.3)	38 (0.2)	1.97 [1.09, 3.59]
Cervical laceration	37 (0.8)	50 (0.2)	3.70 [2.42, 5.66]
High vaginal laceration	290 (6.0)	964 (4.0)	1.56 [1.36, 1.79]
Caesarean delivery	846 (17.5)	5 133 (21.3)	0.78 [0.72, 0.84]
Chorioamnionitis	377 (7.8)	1 247 (5.2)	1.59 [1.41, 1.80]
Delivery hospitalisation			
Alcoholism	1 (0.0)	10 (0.0)	0.50 [0.07, 3.91]
Liver disease	15 (0.3)	44 (0.2)	1.71 [0.95, 3.07]
Thrombocytopenia	40 (0.8)	135 (0.6)	1.50 [1.05, 2.14]
Asthma	95 (2.0)	494 (2.1)	0.96 [0.76, 1.20]
Pregnancy and delivery hospitalisation			
Alcoholism	7 (0.1)	31 (0.1)	1.13 [0.50, 2.56]
Liver disease	33 (0.7)	129 (0.5)	1.28 [0.87, 1.88]
Thrombocytopenia	46 (1.0)	176 (0.7)	1.31 [0.95, 1.82]
Asthma	215 (4.5)	1 035 (4.3)	1.04 [0.89, 1.21]

[a]Mean ± standard deviation.

[b]Any drug use refers to drug use within 180 days prior to delivery; recent and past use refer to use 30 days prior, and between 180 days and 31 days prior to delivery, respectively.

Table 5. Results of conditional logistic regression analyses showing unadjusted and adjusted rate ratios for atonic postpartum haemorrhage associated with any drug use and medical co-morbidity

Determinant	Unadjusted rate ratio 95% CI	Adjusted rate ratio (95% CI)
First model:		
Year of delivery	0.93 [0.81, 1.08]	0.97 [0.88, 1.08]
Maternal age (year)	0.98 [0.98, 0.99]	0.98 [0.98, 0.99]
Exposure in the 6 months prior to the index date		
Antidepressants	1.29 [1.05, 1.60]	1.32 [1.07, 1.64]
Aspirin	1.05 [0.69, 1.61]	1.09 [0.71, 1.66]
NSAIDs	0.99 [0.70, 1.39]	0.99 [0.71, 1.40]
Beta-agonists	1.02 [0.91, 1.14]	1.00 [0.88, 1.13]
Doxylamine	1.02 [0.93, 1.12]	0.99 [0.90, 1.09]
Alcoholism	1.13 [0.50, 2.56]	1.03 [0.45, 2.35]
Liver disease	1.28 [0.87, 1.88]	1.29 [0.87, 1.90]
Thrombocytopenia	1.31 [0.95, 1.82]	1.31 [0.94, 1.82]
Asthma	1.04 [0.89, 1.21]	0.99 [0.84, 1.17]
Second model (adjusted for maternal and obstetric factors[a]):		
Year of delivery	0.93 [0.81, 1.08]	0.95 [0.87, 1.05]
Maternal age (year)	0.98 [0.98, 0.99]	0.98 [0.98, 0.99]
Exposure in the 6 months prior to the index date		
Antidepressants	1.29 [1.05, 1.60]	1.40 [1.13, 1.74]
Aspirin	1.05 [0.69, 1.61]	1.08 [0.70, 1.66]
NSAIDs	0.99 [0.70, 1.39]	1.00 [0.71, 1.41]
Beta-agonists	1.02 [0.91, 1.14]	1.03 [0.91, 1.17]
Doxylamine	1.02 [0.93, 1.12]	1.00 [0.91, 1.10]
Alcoholism	1.13 [0.50, 2.56]	0.97 [0.42, 2.23]
Liver disease	1.28 [0.87, 1.88]	1.25 [0.84, 1.86]
Thrombocytopenia	1.31 [0.95, 1.82]	1.31 [0.94, 1.83]
Asthma	1.04 [0.89, 1.21]	0.99 [0.83, 1.17]
Third model (showing results for interaction terms only)[b]		
Antidepressants and aspirin	2.52 [0.23, 27.7]	3.54 [0.30, 41.8]
Beta-agonists and aspirin	1.00 [0.29, 3.45]	0.97 [0.25, 3.79]
Aspirin and thrombocytopenia	5.00 [0.31, 80.0]	6.45 [0.35, 120.0]
Antidepressants and thrombocytopenia	2.50 [0.46, 13.7]	2.09 [0.35, 12.3]

[a] The model included social assistance, residence urban, previous caesarean, multi-foetal pregnancy, placenta previa/abruption, polyhydramnios, prolonged labour, pre-eclampsia/eclampsia, epidural analgesia, labour induction, uterine rupture, cervical laceration, caesarean delivery, perineal laceration, vaginal laceration, chorioamnionitis, and all variables listed in the table.

[b]Rate ratios and 95% confidence intervals for interaction terms are from a third model that included all variables in the second model and four interaction terms.

explain increases in population rates of PPH, the consistent findings of an approximately 40% relative increase in the risk of PPH among SSRI users is clinically relevant (absolute increase of 1.8 per 100 given a PPH rate of 4.5%).[19,33]

Our study did not show an increased risk of PPH among women with asthma, and those using beta-agonists or aspirin. Although beta-agonists have not been directly implicated in the occurrence of PPH, some evidence suggests that women with asthma have higher rates of antepartum and PPH.[35–38] Studies of low-dose aspirin have yielded inconsistent results, with some studies showing an increase in PPH[18] and others showing no effect despite an increase in bleeding time;[39] a Cochrane review concluded that low-dose aspirin use in pregnancy does not increase the risk of PPH.[40]

Our concern with medication use and drug and other interactions arose because of reports of increases in upper gastrointestinal bleeding associated with SSRIs use in combination with NSAIDs/Cox-2 inhibitors, anticoagulants, and antiplatelet agents or among subjects with liver failure or cirrhosis.[31,32] Drug interactions involving SSRIs and antiplatelet drugs

resulting in excessive bleeding have also been observed among patients with acute myocardial infarction.[20] Similarly, serotonin-modulating drugs have been shown to increase fatality rates in cases of intra-cerebral haemorrhage when administered along with warfarin.[21] In our analyses, concurrent exposure to antidepressants, aspirin, beta-agonists, and thrombocytopenia increased the risk of PPH but these effects were not statistically significant. However, postpartum bleeding is different from gastrointestinal, myocardial, and intra-cerebral bleeding insofar as such blood loss is a normal and routine part of childbirth. Physiologic mechanisms that act to reduce PPH (e.g. contraction of the uterus) work in a setting of high vascularity and include factors very different from those associated with other types of bleeding. On the other hand, we cannot exclude the possibility that our negative results occurred because of misclassification of women who used aspirin and NSAIDs, or because of inaccuracies in the identification of women with co-morbidity. Another concern relates to the relatively small numbers of women with concurrent exposure to more than one drug/co-morbidity (Tables 2,4).

The strengths of our study include the comprehensive nature of our data source, which included information on PPH, clinical, and other risk factors for PPH and prescription drug use. Exposure misclassification with regard to drugs such as antidepressants would have been minimal, as the accuracy of the information in our data source has been previously validated.[23,24] Estimates of association between maternal and obstetric factors and PPH in this study were also similar to those obtained from studies using hospitalisation data from Canada excluding Québec (including the protective effect of caesarean delivery on PPH, which is a consequence of the different definitions of PPH used for vaginal vs. caesarean deliveries). Finally, our 'population-based' case–control study within a primary study base minimised the challenges associated with control selection since selection of controls representative of the study base could be ensured through incidence density sampling of a clearly defined population.[26]

Limitations of our study included problems typical of studies based on large linked databases. Also, difficulties in ascertaining blood loss during childbirth make the diagnosis of PPH challenging. However, the absolute rate of PPH was not a primary concern in our study, which was focused on PPH rates among users vs. nonusers of specific drugs and on the effect of adjustment for such drug use on temporal changes in PPH rates. Testing of the study hypotheses related to aspirin and NSAIDs should be regarded as preliminary, as our data source exclusively recorded medications dispensed by prescription. Substantial misclassification of aspirin and NSAID use in our study was therefore inevitable. Although our study size was large, the small numbers of women who were concurrently exposed to more than one drug/co-morbidity meant that the study lacked adequate statistical power for evaluating the interactions of interest. Similarly, small numbers precluded separate assessment of the effects of antidepressants by subtype (69% of recent use involved SSRIs). All pregnancies in the study population were included without adjustment for the potential non-independence of observations because of multiple deliveries to the same woman. Since the study population included 6378 cases of PPH among a total of 6248 women, this bias was not expected to significantly alter the precision of our estimates. Finally, the absence of procedure codes in a significant fraction of records prevented us from studying severe PPH. This limitation also prevented us from including operative vaginal delivery as a variable in our models.

Conclusions

Antidepressant use was associated with an increased risk of PPH and atonic PPH, whereas thrombocytopenia was associated with an increased risk of PPH. Other medications, such as aspirin and NSAIDs, and co-morbidity such as liver disease, were not significantly associated with PPH, and no statistically significant drug and related interactions were observed (although the study size limited our ability to assess such interactions). The results suggest that such drug use and drug interactions are unlikely to contribute to any substantial increase in atonic PPH. Other studies are needed to corroborate out findings and also to examine other novel hypotheses as potential explanations for the recent increase in atonic PPH.

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