Prenatal Opioid Analgesics and the Risk of Adverse Birth Outcomes

Susan B. Brogly,[a,b] *Maria P. Velez,*[b,c] *Martha M. Werler,*[d] *Wenbin Li,*[b] *Andi Camden,*[b,e,f] *and Astrid Guttmann*[b,e,f,g]

Background: It is unclear whether confounding accounts for the increased risk of preterm birth and small for gestational age (SGA) birth in opioid analgesic exposed pregnancies.

Methods: Using universal coverage health data for Ontario, we assembled a cohort of mother–infant pairs without opioid use disorder (627,172 pregnancies and 509,522 women). We estimated risk ratios (RRs) between opioid analgesics and preterm birth, SGA birth, and stillbirth; neonatal abstinence syndrome was a secondary outcome. We used high-dimensional propensity scores and sensitivity analyses for confounding adjustment.

Results: 4% of pairs were exposed, mainly to codeine (2%), morphine (1%), and oxycodone (1%). Compared with unexposed, the adjusted risk of preterm birth was higher with any (1.3, 95% confidence interval [CI] = 1.2, 1.3), first- (RR: 1.2, 95% CI = 1.2, 1.3), and second-trimester (RR: 1.3, 95% CI = 1.2, 1.4) opioid analgesic exposure. Preterm birth risk was higher for first- and second-trimester codeine, morphine, and oxycodone exposure, and for third-trimester morphine. There was a small increase in SGA with first-trimester exposure to any opioid analgesic or to codeine. Exposed pregnancies had an elevated stillbirth risk with any (RR: 1.6, 95% CI = 1.4, 1.8), first- and second-trimester exposure. Few infants had neonatal abstinence syndrome (N = 143); the risk was higher in exposed (RR: 3.6, 95% CI = 2.1, 6.0). In sensitivity analyses of unmeasured confounding, an elevated risk in exposed pregnancies persisted for preterm birth but not SGA.

Conclusions: Opioid analgesic-exposed pregnancies had a small increased risk of preterm birth and possibly stillbirth after accounting for confounding by indication and sociodemographic factors.

Keywords: Opioid analgesics; Pregnancy; Preterm birth; Small for gestational age birth; Stillbirth; Neonatal abstinence syndrome; Confounding

BACKGROUND

High rates of opioid use in pregnant women are a public health concern in the United States and Canada.[1–3] Among reproductive-age women, almost one-fourth of those privately insured and over one-third of Medicaid beneficiaries filled a prescription for an opioid annually in 2008–2012.[4] Overall, 2%–4% of pregnancies in the United States were exposed to opioid analgesics for pain.[5,6] Opioid analgesics include morphine-like agonists (e.g., morphine, hydromorphone, codeine, and oxycodone), meperidine-like agonists (e.g., demerol), and synthetic opioid analogs (e.g., tramadol). Opioids are known to cross the placenta and have the potential for fetal harm.[7] Evidence concerning the safety of opioid analgesics for pain in pregnancy is unclear.[8,9]

A population-based study of births in Sweden from 1996 to 2011 reported a small increased risk of preterm birth for infants exposed to opioid analgesics in the second or third trimester (OR: 1.12, 95% confidence interval [CI] = 1.03, 1.20), but only a limited set of potential confounders (year of birth, maternal age, parity, smoking in early pregnancy, and BMI) were considered.[10] The authors found no association with small for gestational age (SGA) birth.[10] Another study observed increased risk of preterm birth with codeine exposure (OR: 1.10, 95% CI = 0.95, 1.30) among deliveries in Norway.[11] This latter estimate was adjusted for many covariates (maternal age, plurality, education, BMI, folic acid intake, alcohol intake, proteinuria, first-trimester high blood pressure, hospitalization, vaginal bleeding, number of ultrasound visits, placenta previa, abruptio placentae, oligohydramnios, polyhydramnios, asthma, cardiac disease, and musculoskeletal pain). Other types of opioid analgesic medications; however, were not examined. A study from a pregnancy registry in Ontario reported an association between opioid exposure and preterm birth (OR: 1.63, 95% CI = 1.52, 1.75). This study did not specifically examine opioid analgesics: exposure was defined as any prenatal illicit opioid use, prescribed opioid analgesic use, and/or opioid agonist therapy, and timing of prenatal exposure was unavailable.[12]

A recent Swedish study of deliveries from 2007 to 2013 evaluated possible unmeasured confounding using different reference groups: infants exposed to acetaminophens alone, infants whose mothers had an opioid analgesic prescription before but not during pregnancy, and unexposed siblings. This study also adjusted for multiple potential confounders,

including demographic factors on both the individual and neighborhood levels, reproductive history, maternal history of illness, and medication use. The authors concluded that, while associations between any opioid analgesic exposure and preterm birth and SGA birth could largely be explained by confounding, a small increased risk could not be ruled out.[13]

We, therefore, sought to examine whether the small increased risk of preterm birth could be entirely explained by confounding in our population-based study, and further, to estimate associations by morphine equivalent dose and trimester of exposure. Using a large contemporary database of universal healthcare insurance, comprehensive data on all narcotic prescriptions during pregnancy, and probabilistic bias analysis of unmeasured confounding, we report on the risk of preterm birth, SGA birth, and stillbirth after prenatal opioid analgesic exposure. Neonatal abstinence syndrome (NAS) was a secondary infant outcome.

METHODS

Study Cohort

We followed a population-based cohort of pregnancies using the administrative health data sources in the single-payer healthcare system in Ontario. Universal coverage for physician care and hospital services is provided to all Ontario residents through the Ontario Health Insurance Program (OHIP). Datasets were linked by encoded identifiers and analyzed at ICES (www.ices.on.ca). ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data for health system evaluation and improvement. ICES maintains a validated database of pregnancies, pregnancy outcomes, and mother–infant linkage from these healthcare data, the MOMBABY database. Infants in MOMBABY were matched to mothers using a unique maternal-infant matching number.

The study cohort included mother–infant pairs with an estimated date of confinement after April 7, 2013—which corresponded to 280 days after the Narcotics Monitoring System database (NMS, described below) was established—through March 31, 2018 to prevent over-selecting preterm and SGA births.[14] Deliveries before April 7, 2013 or after March 31, 2018 were eligible provided the estimated data of confinement fell within the study period. To reduce confounding, we excluded women with a diagnosis of opioid use disorder or an opioid overdose within 2 years before delivery (International Classification of Diseases [ICD]-10: F11.1X, F11.2X, F11.9X)[2,15,16] and those treated with methadone or buprenorphine for opioid use disorder.

Prenatal Opioid Analgesic Exposure

We searched maternal records for prenatal opioid analgesic prescriptions (butorphanol, buprenorphine for pain, codeine, fentanyl, hydrocodone, meperidine, methadone for pain, morphine, opium, oxycodone, pentazocine, tapentadol,

and tramadol) in the NMS database. The NMS is part of the Ontario Narcotics Strategy to address misuse of prescription narcotics and other controlled substances. The NMS database contains information (medication, prescription date, fill date, dose, and quantity) for all community pharmacy-dispensed prescriptions for narcotics, controlled substances, and other monitored drugs, irrespective of whether the prescription was paid for under the publicly funded drug program, private insurance, or cash. The prescription fill date must have overlapped the pregnancy period to be considered prenatal medication. For most pairs, the pregnancy period was defined using the maternal obstetric gestational age in the MOMBABY dataset abstracted from the maternal delivery record. For infants for whom the maternal obstetric gestational age variable was missing in MOMBABY (N = 599), we used the gestational age variable in MOMBABY from the infant record. For infants who had neither variable in MOMBABY (N = 1,166), we followed the validated algorithm for administrative healthcare data and imputed 39 weeks for births without an ICD-10 preterm indicator and 35 weeks for those with a preterm indicator.[17] We classified opioid analgesic exposure as any use versus no use, and first trimester (conception to <14 weeks gestation), second trimester (14 weeks gestation to <27 weeks gestation), and third trimester (27 weeks gestation to delivery) versus no use; women had an indicator for each trimester of exposure. We considered opioid analgesics as a single class and by specific agents (e.g., codeine) where feasible. In sensitivity analyses, we determined the daily dose of the opioid analgesic dispensed in milligram (mg) of morphine equivalents and then multiplied this by the number of days supplied in pregnancy. We classified the total cumulative morphine equivalent dose over pregnancy as none, >0–75 mg, 76–150 mg, 151–300 mg, and >300 mg.

Birth Outcomes

We identified study outcomes from the MOMBABY database; the hospital discharge abstracts database (DAD)—mandatory submissions from hospitals to in the Canadian Institute for Health Information; the OHIP database—the physician fee-for-service claims file; and the National Ambulatory Care Reporting System database—mandatory submissions from hospitals for emergency department visits. The MOMBABY dataset was used to identify preterm deliveries (≥20 weeks gestation to <37 weeks gestation) and stillbirths (fetal demise ≥20 weeks gestation). Preterm birth was further classified as provider-initiated or spontaneous following the approach used with Canadian administrative health data.[18] SGA births were identified using the infant's birthweight from MOMBABY and the 10th percentile Canadian weight cut-offs for gestational age and sex.[19] NAS was a secondary outcome and was identified in the DAD (ICD-9: 779.5, 292.0 and 760.72 and ICD-10: P961, P962, P04.4).[2,16,20]

Confounding

A priori confounders included maternal age, parity, socioeconomic status determined by the woman's neighborhood income quintile, diabetes, Elixhauser comorbidity score, obesity, hypertension, pain, prescribed prenatal benzodiazepines or barbiturates, and year of delivery. Maternal socioeconomic status at delivery was determined using postal codes to rank average neighborhood income among other neighborhoods in the census area and was classified as household size-adjusted income in quintiles. Data on other prescribed prenatal psychotropic medications in NMS were only available for benzodiazepines and barbiturates.

To ensure the similarity of mother–infant pairs exposed to opioid analgesics and those unexposed, we generated a high-dimensional propensity score (HDPS) for all pairs in the cohort.[21] The HDPS approach used a computer algorithm to empirically identify candidate covariates, prioritize covariates, and integrate them into a propensity score. We drew potential covariates from the healthcare claims data in the year before pregnancy (physician visits, emergency department and inpatient diagnostic codes, and prescription records), in addition to forcing inclusion of the *a priori* confounders. We generated a separate HDPS for each trimester of exposure. The HDPS procedure was developed for use in pharmacoepidemiologic studies with administrative healthcare data and has been used with ICES data.[22,23] A complete list of confounders and data elements used in the HDPS can be found in the eTable; http://links.lww.com/EDE/B787.

Statistical Analysis

Because of the large study size, we assessed differences between maternal characteristics by opioid analgesic exposure using standardized differences; we deemed a difference of greater than 0.10 to be important.[24] We used generalized linear models to estimate the risk ratio (RR) between opioid analgesic exposure and each study outcome. We estimated unadjusted associations, and then adjusted models using the *a priori* confounders alone—for comparison only—and the inverse probability treatment weighting with propensity scores described above. We stabilized the HDPS to improve precision.[25] Because preterm deliveries in the second trimester in the unexposed group were not at risk of preterm birth in the third trimester, we excluded them from models of third-trimester exposure and preterm birth. Inclusion of second-trimester births in the unexposed group could increase the denominator of the RR and artificially underestimate the relative risk with third-trimester exposure.[26]

We conducted several sensitivity analyses for SGA and preterm birth. These included: (1) classifying exposure as cumulative morphine equivalent dose in pregnancy (to estimate associations according to the amount of opioid analgesic exposure), (2) excluding mother–infant pairs that were not singleton pregnancies (to assess a possible influence of multiples), (3) including siblings only (to further examine confounding), (4) restricting to one pregnancy per woman (to assess whether statistical independence was violated), (5) modeling prenatal opioid analgesic exposure as a time-dependent variable (to examine possible misclassification of exposure time), and (6) probabilistic bias analysis (to assess the effect of possible unmeasured confounding). For the probabilistic bias analysis, we followed the method of Lash et al[27] and created a dichotomous variable to represent the unmeasured confounder (i.e., variables unavailable in the ICES data that predicted both opioid analgesic use and risk of the particular outcome). We then selected the prevalence of the unmeasured confounder from a uniform distribution between 1% and 5% for women unexposed to opioid analgesics and who did not have the particular pregnancy outcome (i.e., preterm birth, SGA birth) and between 2-10% for women exposed to opioid analgesics and whom did not have the pregnancy outcome; women who had the pregnancy outcome had an additional 2%–5% prevalence. Plausible values for the unmeasured confounder prevalence were informed by the prior Swedish study.[13] Psychotropic medications had the greatest difference between opioid analgesic users and nonusers in the Swedish study and were incompletely measured in our study (i.e., NMS had data only on benzodiazepines and barbiturates); we used the distribution in the Swedish cohort to inform the likely distribution of the unmeasured confounder in our bias analysis. To perform a single reconstruction of the data, we conducted a Bernoulli trial for all women, based on their probabilities, to assign whether they had the unmeasured confounder.[27] We then subjected the reconstructed dataset to generalized linear models, with the model now containing the unmeasured confounder. We repeated the process 1,000 times and calculated bias-corrected RRs and 95% CIs as the median, and 2.5th and 97.5th percentiles of the distribution, respectively. To create the Bayesian prior distribution used in the Lash et al. method,[27] we assigned 50% probability to the null effect and 50% to the sensitivity analysis result of Sujan et al.[13] (0.99, 95% CI = 0.85, 1.14 for preterm birth and 0.91, 95% CI = 0.70, 1.19 for SGA birth). We compared the results from the probabilistic bias analysis with the RR and 95% CIs from the HDPS models.

Ethics

The Queen's University Health Sciences Research Ethics Board approved this study.

RESULTS

During the study period, there were 651,180 births in Ontario. After excluding women without OHIP coverage (N = 357), a history of opioid dependence (N = 23,527), age >50 (N = 113) or a pregnancy with more than three fetuses (N = 11), we included 627,172 (96%) of the pregnancies in the study cohort. The 627,172 pregnancies occurred among 509,522 women (N = 399,234 women with one pregnancy; N = 103,189 with two pregnancies, N = 6,844 with three

pregnancies, N = 247, with four pregnancies, and N = 8 with five pregnancies). Of the 627,172 pregnancies 616,442 (98%) were singletons, 10,538 (2%) twins, and 192 (<1% triplets).

A total of 25,755 (4%) pregnancies were exposed to prenatal opioid analgesics including codeine (N = 14,701), morphine (N = 6,802), oxycodone (N = 5,454), tramadol (N = 1,123), meperidine (N = 148), fentanyl (N = 91), and other opioid analgesic (N = 76). The total morphine equivalent dose during pregnancy among exposed women was >0–75 mg: 23%, 76–150 mg: 41%, 151–00: mg 19%, and >300 mg: 18%. The characteristics of the women by prenatal opioid analgesic use are shown in Table 1. Women who used opioid analgesics prenatally were more likely to have used opioid analgesics in the year before pregnancy (34% vs. 10%), to have a diagnosis of pain in the year before pregnancy (24% vs. 10%), tended to have slightly more comorbidities, and were more likely to have a prenatal prescription for benzodiazepines or barbiturates (7% vs. 1%).

Table 2 shows the unadjusted and adjusted associations between any prenatal opioid analgesic exposure and the study outcomes. After adjusting for *a priori* confounders, pregnancies exposed to opioid analgesics had an elevated risk of preterm birth (RR: 1.4, 95% CI = 1.3, 1.4) and stillbirth (RR: 1.5, 95% CI = 1.3, 1.7) compared with unexposed pregnancies. There was no association between any exposure and SGA birth. Although the number of infants with NAS was small, as expected, the risk was considerably higher in infants exposed to opioid analgesics (RR: 6.8, 95% CI = 4.6, 10). We observed greater attenuation of the estimated RR when weighting by HDPS compared with adjusting using *a priori* confounders alone; for preterm birth, the estimate was RR: 1.3, 95% CI = 1.2, 1.3 and for NAS, RR: 3.6, 95% CI = 2.1, 6.0. The proportion of preterm births that were spontaneous—as opposed to provider-initiated—was similar in the opioid analgesic exposed (N = 1,850, 69%) and unexposed (N = 31,469, 73%) groups. Opioid analgesic-exposed pregnancies had an elevated stillbirth risk with any exposure vs. none (RR: 1.6, 95% CI = 1.4, 1.8) adjusted using HDPS.

Estimating associations between opioid analgesics by trimester of exposure and adverse infant outcomes (Table 3) showed that the risk of preterm birth was elevated for first (RR: 1.2, 95% CI = 1.2, 1.3) and second (RR: 1.3, 95% CI = 1.2, 1.4) trimester exposure compared with no exposure. There was a small increase in SGA birth in first trimester exposed compared with unexposed pregnancies (RR: 1.1, 95% CI = 1.0, 1.2). The number of stillbirths was small, yet an increased risk was estimated with first (RR: 1.5, 95% CI = 1.3, 1.8) and second (RR: 1.4, 95% CI = 1.1, 1.7) trimester exposure. We also estimated associations with specific analgesics (Table 4). The risk of preterm birth was higher for first- and second-trimester exposure to codeine, morphine, and oxycodone, and for third-trimester morphine exposure. The small increase in SGA birth in first-trimester exposed compared with unexposed pregnancies was suggested with codeine and

morphine. The number of stillbirths was relatively small to examine associations by specific agents.

In sensitivity analyses (Table 5), when we examined associations by morphine equivalent dose, the RRs for preterm birth were higher for doses above 300 mg compared with unexposed than were the RRs estimated for other exposure categories. We observed associations between stillbirth and the two lowest dose categories. Dose was associated with duration of use: women who used opioid analgesics for more than one trimester tended to have a higher morphine equivalent dose. Other sensitivity analyses for preterm birth suggested that the estimated RRs between any opioid analgesic exposure and trimester of exposure were similar to those of the primary analyses when excluding: (1) mother–infant pairs that were not singleton pregnancies, (2) infants without a sibling, and (3) >1 pregnancy during the study period per woman. When we modeled prenatal opioid analgesic exposure as time-dependent, the hazard ratio of preterm birth for any opioid analgesic exposure versus none was 1.5, 95% CI = 1.5, 1.6 supporting our primary analyses. Although results of bias analysis of possible unmeasured confounding were attenuated compared with HDPS adjusted estimates, a small increase in the risk of preterm birth with any, first-, or second-trimester opioid analgesic exposure persisted compared with no exposure. In sensitivity analyses for SGA there was no association with morphine equivalent dose. Bias analysis suggested that the higher SGA risk associated with opioid analgesic exposure could be explained by confounding. Due to the confounder distribution and the HDPS adjusted SGA estimate close to 1, the bias analysis results moved the RR towards the left of one suggesting an unrealistic protective effect. Finally, in sensitivity analysis that was performed for stillbirth, the increased risk with first and second-trimester exposure persisted.

DISCUSSION

In this population-based study of births to women without a documented history of opioid dependence, those exposed to opioid analgesics prenatally had a small increased risk of preterm birth, SGA birth, and stillbirth after accounting for confounding by indication and sociodemographic factors using HDPS. Bias analyses to further adjust for possible unmeasured confounding were attenuated compared with those adjusted using the HDPS, but a small increase in the risk of preterm birth persisted with any exposure to opioid analgesics, and first-, and second-trimester exposure, compared with no exposure. Like previous studies, our association was partially explained by unmeasured confounding.[13] Results of sensitivity analyses for SGA birth generally suggested that the higher risk associated with opioid analgesic exposure could be explained by confounding.

Preterm Birth

Consideration of confounding by indication is needed when assessing the safety of prenatal opioid analgesics.

TABLE 1. Characteristics of 627,172 Pregnancies in the Ontario Cohort by Prenatal Opioid Analgesic Exposure

Characteristic	Exposed to Prenatal Opioid Analgesics (N = 25,755)	Unexposed to Prenatal Opioid Analgesics (N = 601,417)	Standardized Difference
Trimester of exposure, *n* (%)			
First	12,284 (48)	N/A	N/A
Second	9,357 (36)		
Third	9,488 (37)		
Total prenatal morphine equivalent of opioid analgesic, *n* (%)[a]			
>0–75 mg	5,807 (23)	N/A	N/A
76–150 mg	10,505 (41)		
151–300 mg	4,884 (19)		
>300 mg	4,554 (18)		
Opioid analgesic use in the year before pregnancy	8,767 (34)	60,712 (10)	0.60
Mean duration of analgesic use in the year before pregnancy (weeks) ± SD	5.8 ± 14	0.4 ± 2.8	0.52
Singleton pregnancy	25,205 (98)	593,237 (98)	0.03
Maternal age at delivery			
<20	549 (2)	12,244 (2)	0.10
20–24	3,377 (13)	61,573 (10)	
25–29	6,891 (27)	161,054 (27)	
30–34	8,723 (34)	224,000 (37)	
≥35	6,215 (24)	142,546 (24)	
Year of delivery			
2013	4,477 (17)	93,753 (16)	0.10
2014	5,638 (22)	120,309 (20)	
2015	5,300 (21)	119,916 (20)	
2016	5,032 (20)	120,932 (20)	
2017	4,401 (17)	121,074 (20)	
2018	907 (4)	25,433 (4)	
SES quintile			
1–2	12,041 (47)	256,080 (43)	0.08
3	5,216 (20)	123,450 (21)	
4	4,923 (19)	123,628 (21)	
5	3,575 (14)	98,259 (16)	
Maternal pain diagnosis, year before pregnancy			
Any	6,144 (24)	58,749 (10)	0.39
Low back pain	4,891 (19)	47,234 (8)	0.33
Migraine	882 (3)	5,376 (1)	0.17
Chronic	747 (3)	5,295 (1)	0.15
Limb	354 (1)	2,951 (1)	0.09
Facial	64 (0)	917 (0)	0.02
Other	391 (2)	1,930 (0)	0.13
Maternal diabetes	824 (3)	9,797 (2)	0.10
Maternal obesity	1,168 (5)	14,520 (2)	0.12
Maternal hypertension	901 (4)	12,938 (2)	0.08
Elixhauser comorbidity score ≥1	457 (2)	4,263 (1)	0.11
Prescribed prenatal benzodiazepines or barbiturates	1,723 (7)	8,424 (1)	0.27
Prior live birth	4,509 (18)	111,258 (19)	0.03

[a]Morphine equivalent dose could not be determined for five women.
SES, socioeconomic status.

Women who use opioid analgesics for pain in pregnancy may have other important risk factors associated with both treatment indication and the risk adverse pregnancy outcomes. Our findings suggest a small increased risk of preterm birth after first- or second-trimester exposure and that unmeasured confounding are unlikely to account for the observed association. Our results add to the Swedish population-based cohort study, which noted that confounding accounted for some, but perhaps not all, of the increased risk.[13] Earlier population-based studies in Sweden and Norway estimated small (~10%)

TABLE 2. Association Between Any Prenatal Opioid Analgesic Exposure and Birth Outcomes

Outcome[a]	Opioid analgesic exposure	No. of infants	No. of outcomes	Unadjusted	Adjusted for a priori confounders	Adjusted with HDPS
Preterm birth	None	601,417	43,213	1.0	1.0	1.0
	Any	25,755	2,693	1.5 (1.4, 1.5)	1.4 (1.3, 1.4)	1.3 (1.2, 1.3)
SGA birth	None	589,133	57,255	1.0	1.0	1.0
	Any	25,064	2,402	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (0.9, 1.0)
Stillbirth	None	601,047	3,536	1.0	1.0	1.0
	Any	25,725	235	1.6 (1.4, 1.8)	1.5 (1.3, 1.7)	1.6 (1.4, 1.8)
NAS	None	601,417	106	1.0	1.0	1.0
	Any	25,755	37	8.2 (5.6, 12)	6.8 (4.6, 10)	3.6 (2.1, 6.0)

[a]Outcome data unavailable on SGA for 12,975 infants and stillbirth for 400 infants.

TABLE 3. Association Between Trimester of Opioid Analgesic Exposure and Birth Outcomes

Outcome[a]	Trimester of opioid analgesic exposure	Number of infants[a]	Number of outcomes	Unadjusted	Adjusted with HDPS
Preterm birth	None	601,417	43,213	1.0	1.0
	First	12,284	1,420	1.6 (1.5, 1.7)	1.2 (1.2, 1.3)
	Second	9,357	1,166	1.7 (1.6, 1.8)	1.3 (1.2, 1.4)
	Third	9,488	951	1.4 (1.3, 1.5)	1.0 (1.0, 1.1)
SGA birth	None	589,133	57,255	1.0	1.0
	First	11,929	1,260	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
	Second	9,081	889	1.0 (1.0, 1.1)	1.0 (0.9, 1.0)
	Third	9,258	851	1.0 (0.9, 1.0)	0.9 (0.8, 1.0)
Stillbirth	None	601,047	3,536	1.0	1.0
	First	12,273	115	1.6 (1.3, 1.9)	1.5 (1.3, 1.8)
	Second	9,345	89	1.6 (1.3, 2.0)	1.4 (1.1, 1.7)
	Third	9,477	71	1.3 (1.0, 1.6)	1.1 (0.8, 1.4)
NAS	None	601,417	106	1.0	1.0
	First	12,284	25	12 (7.5, 18)	2.2 (1.0, 4.6)
	Second	9,357	22	13 (8.4, 21)	1.1 (0.5, 2.8)
	Third	9,488	29	17 (12, 26)	4.7 (2.4, 9.3)

[a]Outcome data unavailable on SGA for 12,975 infants and stillbirth for 400 infants.
[a]Those exposed to opioid analgesics in >1 trimester and had the outcome are shown for each trimester of exposure.

increases in the risk of preterm birth with second- or third-trimester opioid analgesic exposure[10] and prenatal codeine exposure compared with no exposure.[11] The opportunity for exposure is diminished for earlier deliveries.[26] To address this potential bias, we excluded second-trimester deliveries from models of third-trimester exposure and preterm birth and also performed a sensitivity analysis with time-dependent opioid analgesic exposure. The risk of preterm birth was higher for first- and second-trimester exposure to codeine, morphine, and oxycodone compared with no exposure. The most common opioid analgesic prescriptions were codeine, morphine, and oxycodone; therefore, we were only able to estimate associations with these specific agents.

Opioid Dependence

We addressed possible confounding in the assembly of our cohort by excluding women with opioid dependence

recorded in the administrative health data. Some of these high-risk women, however, likely could not be identified with administrative data alone. Opioid analgesic use in the year before pregnancy was identified in 34% of the exposed and 10% of the unexposed groups. Although this may represent women with chronic pain, it may include those with undocumented opioid dependence. The small number of infants with NAS diagnosed in the unexposed group (N = 37, 0.006%) likely indicates the use of illicit opioids and/or misuse of prescription opioids or possibly NAS signs from a nonopioid (e.g., selective serotonin reuptake inhibitor). The HDPS adjusted risk of NAS was almost four-fold higher in exposed compared with unexposed infants.

Confounding Adjustment

The HDPS approach uses an algorithm to empirically identify covariates—in addition to *a priori* variables—among

TABLE 4. Association Between Trimester of Specific Opioid Analgesic Exposures and Birth Outcomes

Outcome[a]	Trimester of Opioid Analgesic Exposure	Number of Infants	Number of Outcomes	Unadjusted	Adjusted with HDPS
Preterm birth	None	601,417	43,213	1.0	1.0
	First codeine	6,737	726	1.5 (1.4, 1.6)	1.2 (1.1, 1.3)
	Second codeine	5,111	579	1.6 (1.5, 1.7)	1.3 (1.2, 1.4)
	Third codeine	4,919	428	1.2 (1.1, 1.3)	1.0 (0.9, 1.1)
	First morphine	2,528	309	1.7 (1.5, 1.9)	1.3 (1.1, 1.4)
	Second morphine	2,546	348	1.9 (1.7, 2.1)	1.4 (1.3, 1.6)
	Third morphine	2,716	323	1.6 (1.5, 1.8)	1.3 (1.1, 1.4)
	First oxycodone	2,984	404	1.9 (1.7, 2.1)	1.4 (1.2, 1.5)
	Second oxycodone	2,010	298	2.1 (1.9, 2.3)	1.4 (1.2, 1.6)
	Third oxycodone	2,035	231	1.6 (1.4, 1.8)	1.0 (0.9, 1.2)
SGA birth	None	601,417	57,255	1.0	1.0
	First codeine	6,529	685	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
	Second codeine	4,966	481	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
	Third codeine	4,797	418	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)
	First morphine	2,456	267	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)
	Second morphine	2,470	225	0.9 (0.8, 1.1)	0.9 (0.8, 1.0)
	Third morphine	2,659	249	1.0 (0.9, 1.1)	0.9 (0.8, 1.0)
	First oxycodone	2,893	306	1.1 (1.0, 1.2)	1.0 (0.9, 1.1)
	Second oxycodone	1,943	215	1.1 (1.0, 1.3)	0.9 (0.8, 1.1)
	Third oxycodone	1,973	203	1.1 (0.9, 1.2)	0.9 (0.8, 1.0)
Stillbirth	None	601,417	3,536	1	1.0
	First codeine	6,732	76	1.9 (1.5, 2.4)	1.6 (1.3, 2.1)
	Second codeine	5,106	54	1.8 (1.4, 2.4)	1.2 (0.9, 1.7)
	Third codeine	4,915	42	1.5 (1.1, 2.0)	1.2 (0.9, 1.7)
	First morphine	2,524	25	1.7 (1.1, 2.5)	1.4 (0.9, 2.2)
	Second morphine	2,543	18	1.2 (0.8, 1.9)	1.2 (0.7, 1.9)
	Third morphine	2,713	14	0.9 (0.5, 1.5)	0.7 (0.4, 1.2)
	First oxycodone	2,981	22	1.3 (0.8, 1.9)	1.4 (0.9, 2.1)
	Second oxycodone	2,005	21	1.8 (1.2, 2.7)	1.5 (0.9, 2.4)
	Third oxycodone	2,030	17	1.4 (0.9, 2.3)	1.2 (0.7, 1.9)

[a]Outcome data unavailable on SGA for 12,975 infants and stillbirth for 400 infants.

the vast administrative data elements and integrate them into a propensity score.[21] Adjusting for large numbers of covariates ascertained from patients' healthcare claims data with HDPS may improve control of confounding as these variables may collectively be proxies for unobserved factors.[21] RRs for preterm birth and NAS adjusted for *a priori* confounders were further attenuated by HDPS adjustment. Given the suspected direction of confounding to upwardly bias the estimated RR, the HDPS may better adjust for confounding. It must also be considered, however, that the HDPS is a computer-automated selection algorithm and thus causal intermediates may have been included.[28] We attempted to prevent against this by only including data elements in the year before pregnancy. If causal intermediates were inadvertently included our RRs could be underestimated. Regardless, our findings suggest a small increased risk of preterm birth in opioid analgesic exposed pregnancies. There is greater opioid prescribing in Canada than Sweden,[29] yet our study findings and those of the former Swedish study—studies were done in different contexts of opioid use—had similar estimates, suggesting the robustness of our results.

SGA Birth

Our results suggested a small increase in SGA birth with the first trimester exposed compared with unexposed pregnancies for any opioid analgesic exposure and for codeine and morphine. A small increased risk with first-trimester exposure to any analgesic persisted in sensitivity analyses, except for bias analysis of confounding; the latter suggested that confounding explained the small increased risk.

Stillbirth

Pregnancies exposed to prenatal opioid analgesics in the first and second trimester had an elevated risk of stillbirth. The number of stillbirths in our study was small (235 in exposed pregnancies, 3,536 in unexposed) which limited the precision of associations with specific agents. The risk of stillbirth from prenatal opioids for pain has not previously been studied and therefore we could not incorporate estimates from prior

TABLE 5. Results of Sensitivity Analyses Between Prenatal Opioid Analgesic Exposure and Birth Outcomes

Sensitivity Analysis	Opioid Analgesic Exposure Versus None	Preterm Birth	SGA Birth	Stillbirth
Exposure defined as total MEQ in pregnancy	>0–75 mg	1.2 (1.1, 1.3)	0.9 (0.9, 1.0)	1.6 (1.2, 2.1)
	76–150 mg	1.2 (1.1, 1.3)	1.0 (0.9, 1.0)	1.8 (1.5, 2.1)
	151–300 mg	1.3 (1.2, 1.4)	1.0 (0.9, 1.1)	1.3 (0.9, 1.8)
	>300 mg	1.7 (1.5, 1.8)	0.9 (0.8, 1.0)	1.0 (0.6, 1.6)
Restricted to singleton pregnancies	Any	1.3 (1.2, 1.3)	1.0 (0.9, 1.0)	1.6 (1.4, 1.8)
	First trimester	1.2 (1.1, 1.3)	1.1 (1.0, 1.2)	1.6 (1.3, 1.9)
	Second trimester	1.3 (1.2, 1.4)	0.9 (0.9, 1.0)	1.4 (1.1, 1.8)
	Third trimester	1.0 (0.9, 1.1)	0.9 (0.8, 1.0)	1.1 (0.8, 1.4)
Restricted to siblings only	Any	1.3 (1.2, 1.4)	1.0 (1.0, 1.1)	1.6 (1.4, 1.9)
	First trimester	1.3 (1.2, 1.4)	1.2 (1.0, 1.3)	1.6 (1.2, 2.0)
	Second trimester	1.3 (1.2, 1.5)	1.0 (0.9, 1.1)	1.3 (1.0, 1.8)
	Third trimester	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)	1.2 (0.9, 1.6)
Restricted to one pregnancy per woman	Any	1.3 (1.2, 1.3)	0.9 (0.9,1.0)	1.5 (1.3, 1.7)
	First trimester	1.2 (1.1, 1.3)	1.1 (1.0, 1.1)	1.5 (1.2, 1.8)
	Second trimester	1.3 (1.2, 1.4)	0.9 (0.9, 1.0)	1.2 (0.9, 1.6)
	Third trimester	1.0 (1.0, 1.1)	0.9 (0.8, 0.9)	1.1 (0.9, 1.5)
Opioid analgesics modeled as a time-dependent exposure	Any	1.5 (1.5, 1.6)[a]	-	-
Probabilistic bias analysis of unmeasured confounding	Any	1.2 (1.1, 1.2)	0.9 (0.8, 0.9)	-
	First trimester	1.1 (1.0, 1.2)	1.0 (0.9, 1.1)	-
	Second trimester	1.2 (1.1, 1.3)	0.9 (0.8, 0.9)	-
	Third trimester	0.9 (0.9, 1.0)	0.8 (0.8, 0.9)	-

[a]Hazard Ratio from a Cox model: small for gestational age.
MEQ, morphine equivalent dose.

studies in our bias analysis. Elevated risks, however, are documented in pregnant women treated prenatally with opioid agonists for opioid dependence.[2,30–32]

Strengths and Limitations

A strength of our population-based study includes detailed records of opioid analgesic prescriptions regardless of out-of-pocket, private insurance, or drug beneficiary coverage. Only a small proportion of NMS records for the Ontario population (<3%) could not be linked to the ICES data due to missing patient identifiers. Our contemporary data included 627,172 pregnancies from 2013 through 2018. We used ICES validated measures of preterm birth and stillbirth. SGA birth and NAS were based on coding and algorithms used in prior studies to minimized misclassification. Limitations of our study include the use of an unexposed group of mother–infant pairs unexposed to any analgesic as well as pairs exposed to an analgesic other than opioids. Using this combined reference group, we would expect to estimate a RR that falls between those estimated using either reference group separately. Another limitation is that we had information on the date the opioid analgesic prescription was written and the date it was filled—the latter was used to define our exposed group—but could not confirm whether the woman actually used the medication; such misclassification would be expected to underestimate the association with opioid analgesics. ICES data do not consistently include pregnancy losses before 20 weeks, and this could be related to exposure and our study outcomes. Finally, detailed race–ethnicity and smoking data were unavailable in ICES data for adjustment.

Summary

Prenatal opioid analgesic exposure and adverse pregnancy outcomes are ongoing concerns.[32,33] Our approach to control confounding did not fully attenuate the small increased risk of preterm delivery in opioid analgesic exposed pregnancies and exemplifies the importance of adjustment for maternal characteristics to reduce confounding bias. Our findings for opioid analgesic exposure during pregnancy show that the risk of preterm birth was higher with a greater morphine equivalent dose, suggested a possible association with stillbirth, and confirmed an increased risk of NAS. These results add to an accumulating body of evidence consistent with the hypothesis that opioid treatment for pain in pregnancy may carry risks to the fetus, which will be important to women and clinicians in selecting treatment.

Service Ontario. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended nor should be inferred.

The dataset from this study is held securely in the coded form at ICES. Although data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the programs may rely upon coding templates or macros that are unique to ICES.

REFERENCES

1. Desai RJ, Hernandez-Diaz S, Bateman BT, Huybrechts KF. Increase in prescription opioid use during pregnancy among Medicaid-enrolled women. *Obstet Gynecol.* 2014;123:997–1002.
2. Brogly SB, Turner S, Lajkosz K, et al. Infants born to opioid-dependent women in Ontario, 2002-2014. *J Obstet Gynaecol Can.* 2017;39:157–165.
3. Knoppert D. The worldwide opioid epidemic: implications for treatment and research in pregnancy and the newborn. *Paediatr Drugs.* 2011;13:277–279.
4. Ailes EC, Dawson AL, Lind JN, et al; Centers for Disease Control and Prevention (CDC). Opioid prescription claims among women of reproductive age—United States, 2008-2012. *MMWR Morb Mortal Wkly Rep.* 2015;64:37–41.
5. Marsh CA, Cragan JD, Alverson CJ, Correa A. Case-control analysis of maternal prenatal analgesic use and cardiovascular malformations: Baltimore-Washington Infant Study. *Am J Obstet Gynecol.* 2014;211:404.e1–404.e9.
6. Broussard CS, Rasmussen SA, Reefhuis J, et al; National Birth Defects Prevention Study. Maternal treatment with opioid analgesics and risk for birth defects. *Am J Obstet Gynecol.* 2011;204:314.e1–314.11.
7. Pritham UA, McKay L. Safe management of chronic pain in pregnancy in an era of opioid misuse and abuse. *J Obstet Gynecol Neonatal Nurs.* 2014;43:554–567.
8. Chan F, Koren G. Is periconceptional opioid use safe? *Can Fam Physician.* 2015;61:431–433.
9. Yazdy MM, Desai RJ, Brogly SB. Prescription opioids in pregnancy and birth outcomes: a review of the literature. *J Pediatr Genet.* 2015;4:56–70.
10. Källén B, Borg N, Reis M. The use of central nervous system active drugs during pregnancy. *Pharmaceuticals (Basel).* 2013;6:1221–1286.
11. Nezvalová-Henriksen K, Spigset O, Nordeng H. Effects of codeine on pregnancy outcome: results from a large population-based cohort study. *Eur J Clin Pharmacol.* 2011;67:1253–1261.
12. Corsi DJ, Hsu H, Fell DB, Wen SW, Walker M. Association of maternal opioid use in pregnancy with adverse perinatal outcomes in Ontario, Canada, from 2012 to 2018. *JAMA Netw Open.* 2020;3:e208256.
13. Sujan AC, Quinn PD, Rickert ME, et al. Maternal prescribed opioid analgesic use during pregnancy and associations with adverse birth outcomes: a population-based study. *PLoS Med.* 2019;16:e1002980.
14. Patel K, Shapiro DE, Brogly SB, et al; P1025 team of the International Maternal Pediatric Adolescent AIDS Clinical Trials Group. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. *J Infect Dis.* 2010;201:1035–1044.
15. Haight SC, Ko JY, Tong VT, Bohm MK, Callaghan WM. Opioid use disorder documented at delivery hospitalization—United States, 1999-2014. *MMWR Morb Mortal Wkly Rep.* 2018;67:845–849.
16. Brogly SB, Hernández-Diaz S, Regan E, Fadli E, Hahn KA, Werler MM. Neonatal outcomes in a Medicaid population with opioid dependence. *Am J Epidemiol.* 2018;187:1153–1161.
17. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernández-Díaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. *Pharmacoepidemiol Drug Saf.* 2013;22:16–24.
18. Ray JG, Bartsch E, Park AL, Shah PS, Dzakpasu S. Estimated reductions in provider-initiated preterm births and hospital length of stay under a universal acetylsalicylic acid prophylaxis strategy: a retrospective cohort study. *CMAJ Open.* 2017;5:E508–E516.
19. Kramer MS, Platt RW, Wen SW, et al; Fetal/Infant Health Study Group of the Canadian Perinatal Surveillance System. A new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics.* 2001;108:E35.
20. Davies H, Gilbert R, Johnson K, et al. Neonatal drug withdrawal syndrome: cross-country comparison using hospital administrative data in England, the USA, Western Australia and Ontario, Canada. *Arch Dis Child Fetal Neonatal Ed.* 2016;101:F26–F30.
21. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology.* 2009;20:512–522.
22. Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN. Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children. *JAMA.* 2017;317:1544–1552.
23. Vigod SN, Gomes T, Wilton AS, Taylor VH, Ray JG. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. *BMJ.* 2015;350:h2298.
24. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat Simul Comput.* 2009;38:1228–1234.
25. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med.* 2015;34:3661–3679.
26. Matok I, Azoulay L, Yin H, Suissa S. Immortal time bias in observational studies of drug effects in pregnancy. *Birth Defects Res A Clin Mol Teratol.* 2014;100:658–662.
27. Lash TL, Fink AK. Semi-automated sensitivity analysis to assess systematic errors in observational data. *Epidemiology.* 2003;14:451–458.
28. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology.* 2009;20:488–495.
29. Ladha KS, Neuman MD, Broms G, et al. Opioid prescribing after surgery in the United States, Canada, and Sweden. *JAMA Netw Open.* 2019;2:e1910734.
30. Lacroix I, Berrebi A, Garipuy D, et al. Buprenorphine versus methadone in pregnant opioid-dependent women: a prospective multicenter study. *Eur J Clin Pharmacol.* 2011;67:1053–1059.
31. Maeda A, Bateman BT, Clancy CR, Creanga AA, Leffert LR. Opioid abuse and dependence during pregnancy: temporal trends and obstetrical outcomes. *Anesthesiology.* 2014;121:1158–1165.
32. Whiteman VE, Salemi JL, Mogos MF, Cain MA, Aliyu MH, Salihu HM. Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. *J Pregnancy.* 2014;2014:906723.