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Neonates With In-Utero SSRI Exposure (NeoWISE): a retrospective cohort study examining the effect of newborn feeding method on newborn withdrawal

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Abstract

Introduction

Up to 30% of newborns with in-utero selective serotonin reuptake inhibitor (SSRI) exposure experience withdrawal symptoms. The impact of newborn feeding method on alleviating withdrawal has not been investigated. We examined the effect of newborn feeding method (breastfeeding versus formula) among a cohort of Neonates With In-utero SSRI Exposure (NeoWISE).

Methods

This population-based retrospective cohort study included newborns born in Ontario hospitals between April 1, 2012, and March 31, 2020 to Ontario Drug Benefit Program beneficiaries who filled at least one SSRI prenatal prescription. Linked administrative health and registry data were used. Method of newborn feeding was available from birth to hospital discharge. The primary outcome was newborn withdrawal. The secondary outcome was transfer to the Neonatal Intensive Care Unit (NICU). Adjusted risk ratios (adjRR) in breast- versus formula-fed newborns and our outcomes were estimated using generalized linear models. Propensity scores based on antepartum and intrapartum characteristics and inverse probability of treatment weighting were used to balance differences in maternal-newborn characteristics by treatment.

Results

Overall, 5,079 newborns were included in the NeoWISE Cohort, with 3,321 (65.4%) exclusively breastfeeding from birth to hospital discharge. Among the breastfed newborns, 50 (1.5%) had neonatal withdrawal versus 41 (2.3%) in the formula-fed newborns. There was no difference in risk of withdrawal in breast versus formula-fed newborns (adjRR 0.86, 95% CI 0.56, 1.34). Breastfed newborns had a reduced risk of transfer to the NICU compared to formula-fed newborns (adjRR 0.80, 95% CI 0.66, 0.97); however, this finding did not persist in sensitivity analysis.

Conclusion

The rate of newborn withdrawal was low in this cohort of SSRI-exposed neonates and was not associated with feeding method in the hospital. The results of this study inform shared decision-making around newborn feeding for perinatal women who take SSRI medications.

Keywords

selective serotonin reuptake inhibitors; pregnancy; breastfeeding; lactation, poor neonatal adaptation syndrome; newborn withdrawal

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Introduction

Adequate treatment of mental health disorders during the perinatal period from pregnancy up to one year after birth [1] is essential for maternal and fetal/newborn health [2]. Pharmacological management is recommended for the treatment of moderate to severe perinatal mental health disorders when psychological interventions are not effective [2, 3]. 'Selective serotonin reuptake inhibitors' (SSRI) are the most prescribed antidepressant medication in both the general and perinatal populations [4].

Up to 30% of newborns with in-utero SSRI exposure will experience withdrawal signs which are often self-limiting and of short duration [5–7]. These signs include poor muscle tone, tremors, jitteriness, irritability, seizures, feeding difficulties, sleep disturbances, hypoglycemia, and respiratory distress [8–11]. It is unknown if the observed signs are a serotonin syndrome (toxicity) or withdrawal [12, 13], and some authors have described it as a behavioural syndrome [14]. Thus, a range of terms are found in the extant literature with the term withdrawal most commonly used [15–19]. This contrasts with extensive research examining the withdrawal symptoms of newborns from in-utero opioid exposure and a well-defined 'Neonatal Abstinence Syndrome' (NAS), now termed 'Neonatal Opioid Withdrawal Syndrome' (NOWS) [20].

Few studies of in-utero antidepressant (AD) medication exposure included newborn withdrawal as an outcome measure or considered the effect of newborn feeding method [11, 21–24]. In a small observational cohort study of newborns with in-utero SSRI or other AD medication exposure ($n = 247$), newborns receiving formula feedings were three times as likely to have withdrawal as compared to newborns who were breastfeeding or receiving mixed feeds [25]. This study, like other studies, included only a small number of newborns who were exposed to antidepressant medications from different categories, leading to difficulty in estimating the effect of in-utero SSRI exposure among breastfed newborns [10, 23]. Therefore, newborn feeding method represents an important area of investigation.

While there is evidence regarding the benefits of breastfeeding among in-utero opioid-exposed newborns on reducing the risk of NOWS, including shortened length of hospital stay, reduced need for pharmacotherapy to treat signs of NOWS, and fewer admissions to NICU [26–28], there is a dearth of research among **Neonates With In-utero SSRI Exposure** (NeoWISE). Breastfeeding may offer a protective effect to the newborn by transferring low amounts of SSRIs through the breastmilk. While these low amounts have not been associated with adverse outcomes in the newborn [29], this small exposure may be sufficient to mitigate SSRI withdrawal effects. Given there are more pregnant women taking SSRIs than opioids, the study of potential withdrawal following SSRI exposure is warranted. Evidence is needed to confirm whether breastfeeding can reduce the incidence of withdrawal in NeoWISE in order to strengthen existing recommendations in perinatal and neonatal care guidelines for this population [7, 8, 13]. Furthermore, it is necessary to determine if NeoWISE would benefit from additional breastfeeding support and follow-up in the first days and weeks after birth.

This study aimed to identify if initiated newborn feeding method was associated with neonatal withdrawal and transfer

to the NICU among neonates exposed to SSRIs in-utero. We hypothesized that breastfeeding would be associated with a lower risk of withdrawal and transfer to the NICU due to the benefit of SSRI medication transfer through breast milk and the close skin-to-skin contact with the mother during breastfeeding. This hypothesis was informed by an observational cohort study investigating newborn outcomes following in-utero AD medication exposure [25], and our clinical experience.

Methods

Study design & data sources

We conducted a population-based retrospective cohort study using administrative health and registry data holdings at ICES (formally known as the 'Institute for Clinical and Evaluative Sciences,' Supplementary Table 1). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze de-identified health care and demographic data for health system evaluation and improvement. We obtained linked pregnancy and neonatal outcomes from the Better Outcomes Registry & Network (BORN) Ontario, which captures 99% of maternal and newborn health records for in-hospital births [30]. These datasets were linked using unique encoded identifiers and analyzed at ICES. This study was approved by the Queen's Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (REB NURS-576-23).

Study cohort

The cohort included all live-born newborns born in Ontario hospitals between April 1, 2012 and March 31, 2020 to pregnant women who were beneficiaries of the Ontario Drug Benefit (ODB) Program [31, 32] and who filled at least one SSRI prescription in pregnancy. The ODB funds medication for Ontarians on social assistance, >65 years of age, or with high medical complexity and high medication costs. SSRI medications included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline.

The ICES MOMBABY dataset was used to identify the pregnancy period. For most pairs, the pregnancy period was defined using the maternal obstetrical gestational age in the MOMBABY dataset abstracted from the maternal delivery record. For newborns whose maternal obstetrical gestational age variable was missing in MOMBABY, we used the gestational age variable in MOMBABY from the newborn record.

Newborns were excluded if a) the mother was a non-resident of Ontario, b) the mother did not have an ODB drug claim during pregnancy, c) maternal age was less than 15 years of age or greater than 49 years of age, d) they were twin or higher order multiple birth, and/or e) maternal-newborn records could not be linked.

Exposure

As recorded in BORN, the study exposure was newborn feeding method defined as "the type of oral feeding given to the newborn from the time of birth to discharge from hospital

or birth centre” [79]. The exposure of interest was being exclusively breastfed or exclusively formula-fed from birth to hospital discharge. Exclusively breastfed was defined as receiving only breastmilk from birth until hospital discharge. Newborns who received mixed feeding (i.e. breastmilk plus breastmilk substitute) were excluded from the primary analysis but were included in the sensitivity analyses. Newborns with unknown feeding and no feeding were excluded.

Covariates

Potential confounders of the relationship between feeding method and our study outcomes included gestational age, type of birth, parity, maternal age, neighbourhood income quintile, and other in-utero substance exposure, including other antidepressant medications [33, 34], alcohol [12], tobacco [35–38], opioids [12, 34], benzodiazepines [33, 34, 39], and antipsychotic medications [33]. These covariates were selected based on previous studies and demographic and clinical variables readily available within the identified databases. We included rurality and the maternal Elixhauser co-morbidity index, which is a validated index that includes a group of 30 ICD diagnosis codes [40, 41], to adjust for pre-existing maternal health conditions.

In the year prior to or during pregnancy, other prescribed and dispensed psychotropic medications obtained from the ODB that were evaluated as potential confounders included: other antidepressants (i.e. serotonin and noradrenaline reuptake inhibitors (SNRI), noradrenergic and specific serotonergic antidepressants (NaSSA), tricyclic antidepressants (TCA), atypical, monoamine oxidase inhibitors (MAOI)), and other psychotropics (i.e. antipsychotics, benzodiazepines, tranquilizer/sedative/hypnotic, mood stabilizers, GABAergic, 5-HT1A agonists). Opioids (i.e. morphine, meperidine, codeine, fentanyl, nalbuphine, hydromorphone, oxycodone, tramadol, buprenorphine/naloxone, methadone) were identified from the Narcotic Monitoring System (NMS) [42], which contains all dispensed narcotics and controlled substances in Ontario regardless of insurance coverage or type of medication payment.

Maternal demographic information was obtained from two databases: the Registered Persons Database (RPDB) [43] and BORN. The RPDB was used to identify maternal sex, age, rural/urban residence, and neighbourhood income quartile. Data on parity, type of birth, intention to breastfeed, alcohol use in pregnancy, smoking at the time of birth, and delivery date were obtained from BORN. Newborn information was obtained from BORN, including newborn sex, birth weight (grams), newborn resuscitation in the first 30 minutes of life, and 5-minute Apgar score (<7 , ≥ 7). An Apgar score of 7 to 10 is considered to be a reassuring indication of postnatal adaptation after birth [44].

Outcomes

Data on our study outcomes were obtained from BORN and the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) [45]. The primary outcome was neonatal withdrawal, indicated by the presence of ICD-10 code P96.1 ‘neonatal withdrawal symptoms from maternal use of drugs of addiction’, which is a subcategory of the P96 code

‘conditions originating in the perinatal period’ on the discharge abstract [45]. The secondary outcome was transfer to the NICU (Supplementary Table 2).

Statistical approach

Differences in maternal and newborn characteristics by feeding method were compared using standardized differences where a standardized difference of $>10\%$ indicated an imbalance between exposure groups [46]. Maternal age was reported as a mean and standard deviation (SD). Gestational age was categorized as <37 weeks or ≥ 37 weeks, and 5-minute Apgar scores as <7 or ≥ 7 . Type of birth was categorized as vaginal or cesarean. Neighbourhood income was reported in quintiles with 1 being the lowest and 5 being the highest.

To address the imbalance between groups and ensure the similarity of maternal-newborn pairs based on feeding method, we used propensity scores and inverse probability of treatment weights (IPTW) [47]. The covariates listed above were the independent variables in our propensity score logistic models with exclusive breastfeeding versus exclusive formula feeding as the dependent variable (Supplementary Table 3).

We conducted sensitivity analysis by 1) including only newborns with third trimester SSRI exposure should this be the etiologic exposure for withdrawal [48], and 2) defining exposure as any breastfeeding rather than exclusive should there be a benefit of any breastmilk. The timing of in-utero SSRI medication exposure was determined using the dispensing date and quantity dispensed. The following categories were used: trimester one (conception to 13+6/7 weeks) [49, 50], trimester two (14 0/7 weeks to 27+6/7 weeks), trimester three (28+0/7 weeks to end of pregnancy at approx. 40 weeks), or all trimesters [51]. For the latter sensitivity analysis, logistic models were rerun to estimate the propensity score comparing any breastfeeding (i.e. breastmilk +/- formula or other breastmilk substitute) versus formula feeding only. For each sensitivity analysis, the balance between groups was assessed and associations between feeding method and study outcomes were compared to those of the primary analysis.

As a post-hoc sensitivity analysis, we excluded NeoWISE in the cohort with in-utero opioid exposure. This was done to explore the contribution of in-utero opioid exposure to the development of symptoms leading to a diagnosis of neonatal withdrawal.

To estimate the treatment effect, we fit a weighted generalized linear regression model to compute a relative risk of treatment with robust standard errors using REPEATED statement in PROC GENMOD. We then estimated the risk ratio (log-link function) between newborn feeding method defined above and newborn withdrawal and the secondary outcome of NICU admission adjusted for confounding. We calculated the E-value according to the method proposed by VanderWeele and Ding [52] as a post-hoc analysis examining where unmeasured confounding explained feeding exposure and NICU admission.

The findings of this study were reported following the **RE**porting of studies Conducted using **Ob**servational **R**outinely collected **D**ata for non-interventional **P**harmaco **E**pidemiological research (RECORD-PE) [53].

Results

A total of 9,926 newborns were included in the NeoWISE Cohort (Supplementary Figure 1). This included 9,014 pregnant women who filled at least one prescription for ≥ 1 SSRIs during pregnancy. Escitalopram (37%) and sertraline (30%) were the most frequent SSRI medication exposures (Supplementary Table 4). After excluding newborns missing feeding information ($n=2,503$), there were 5,079 newborns in the final NeoWISE Cohort with 3,321 (65.4%) exclusively breastfed and 1,758 (34.6%) formula-fed only. Approximately half of the cohort ($n=2,916$, 57.4%) had SSRI exposure in trimester three (Supplementary Table 5). The median maternal age (IQR) of exclusively breastfeeding and formula-feeding newborns was 25 years (22–30) and 26 years (22–31) respectively.

As shown in Table 1, there were imbalances in NeoWISE by feeding method. In comparison to breastfed newborns, those who were formula-fed were more likely to have older mothers who lived in an urban area, had a lower neighbourhood income quintile, had a previous live birth, reported smoking at the time of delivery, and gave birth by cesarean delivery. Formula-fed newborns had a slightly lower gestational age. These imbalances in maternal and newborn characteristics were balanced after propensity score weighting (Table 1). Maternal-newborn pairs missing neighbourhood income quintile data ($n=18$) were excluded.

The risk of neonatal withdrawal was similar in exclusively breastfed newborns as compared with formula-fed newborns unadjusted (1.5% vs 2.3%, $RR=0.66$, 95% CI 0.44, 1.00) and adjusted models ($adjRR=0.86$, 95% CI = 0.56, 1.34) (Table 2). In terms of the secondary outcome, there was a lower risk of transfer to the NICU among breastfed newborns as compared with formula-fed newborns in both the unadjusted and adjusted models (7.2% vs 10.8%, $adjRR=0.80$, 95% CI = 0.66, 0.97) (Table 2). Based on the E-value, an unmeasured confounder with 1.21-fold association with feeding and NICU admission could account for our observed findings.

Sensitivity analysis

In the sensitivity analysis restricting the NeoWISE Cohort to only those with third-trimester SSRI exposure, the risk of withdrawal in exclusively breastfed versus formula-fed newborns (1.8% vs 3.2 %, $adjRR=0.77$, 95% CI 0.47, 1.28) was similar to our primary result. Associations with the risk of transfer to the NICU in only third trimester SSRI exposure were similar ($adjRR=0.83$, 95% CI 0.66, 1.04) although no longer statistically different, likely reflecting the smaller sample size and power (Table 2).

In the sensitivity analysis comparing any amount of breastfeeding (+/- formula or breastmilk substitute) versus formula feeding only, there was no difference in risk of neonatal withdrawal (1.9% vs 2.3%, $adjRR=0.96$, 95% CI = 0.66, 1.40) nor risk of transfer to NICU (9.7% vs 10.8%, $adjRR=0.93$, 95% CI = 0.79, 1.10) (see Table 2). We excluded NeoWISE in the cohort with in-utero opioid exposure ($n=457$ formula-fed only and $n=666$ exclusively breastfed). This sensitivity analysis confirmed no association between newborn feeding method and neonatal withdrawal

diagnosis when newborns with in-utero opioid exposure were excluded in the unadjusted ($RR=1.03$, 95% CI 0.49, 2.18) and adjusted models ($RR=1.16$, 95% CI 0.54, 2.52); wider confidence interval were noted.

Discussion

In our population-based NeoWISE Cohort, there was an overall low risk of neonatal withdrawal and no difference in risk among exclusively breastfed and formula-fed newborns. This finding persisted in both sensitivity analyses. Our finding regarding the low prevalence of neonatal withdrawal contrasts with the results of higher rates in other studies, ranging from 11.2% to 63.2% [11, 25, 39, 54–57]. The vast differences in withdrawal prevalence may be attributed to the outcome variable definition, the method used to identify withdrawal signs in newborns with in-utero AD exposure, and the selected cut-off scores. In a recent population-based cohort study in the USA, Cornet et al. reported that 11.2% of newborns with exposure to SSRIs after 20 weeks gestation had delayed neonatal adaptation; delayed neonatal adaptation was defined as a 5-mins Apgar score ≤ 5 , resuscitation at birth, or admission to the NICU for respiratory support. Levinson-Castiel et al. reported neonatal abstinence syndrome occurring in 30% of newborns, 13% of whom had severe symptoms, in their cohort study of newborns exposed to SSRIs or venlafaxine [55]. Neonatal abstinence syndrome was identified by a Finnegan score of ≥ 8 as severe, 4–7 as mild and 0–3 as normal [55]. Oberlander et al. [39] and Chambers et al. [11] reported similar rates of approximately 30%.

Ferreria et al. reported that 63.2% had one or more neonatal behavioural signs in their retrospective chart study of newborns with in-utero SSRI or venlafaxine exposure ($n=79$) [56]. Kieviet et al. reported a rate of 64% of newborns diagnosed with withdrawal and 20% of these had severe symptoms in their observational cohort study of newborns ($n=247$) in the Netherlands with at least third-trimester in-utero exposure to serotonergic AD exposure (i.e. SSRI, SNRI, or NaSSA), [25]. Withdrawal was defined as at least one Finnegan score of ≥ 4 during the inpatient hospitalization, with ≥ 4 being mild and ≥ 8 being severe withdrawal [25].

It is not possible to know how clinicians assessed the newborns in our study; however, the threshold to identify withdrawal may have been higher than prior studies given our lower rate of withdrawal. Clinicians may be using clinical practice guidelines that were intended for caring for newborns with opioid exposure to inform their clinical care and management of newborns with other in-utero substance exposures, given that no validated instrument exists to assess for the presence of neonatal SSRI withdrawal. For example, according to an Ontario guideline, if newborns were assessed using the 'Finnegan Neonatal Abstinence Scoring System' and there were three consecutive scores ≥ 8 or a score of ≥ 12 (either an average of 2 scores or two consecutive scores of ≥ 12) [58], they may have received a diagnosis of withdrawal and thus be assigned the P96.1 diagnosis code. This higher threshold may have contributed to our study's observed low rate of withdrawal.

In a secondary analysis of two observational studies ($n=214$), Yang et al. [59] reported that 33% of newborns

Table 1: Baseline characteristics of maternal-newborn pairs exposed to SSRI in pregnancy in the NeoWISE cohort before and after propensity weighting

Variable	Before propensity weighting (n = 5,079)			After propensity weighting* (n = 5,061)		
	Formula feeding only	Breastfeeding only	Std Diff	Formula feeding only	Breastfeeding only	Diff Std
	N = 1,758, n (%)	N = 3,321, n (%)		N = 1,754 (%)	N = 3,307 (%)	
Maternal age at delivery- mean (years) (SD)	26.9 (5.9)	26.0 (5.6)	0.155	26.2	26.2	0.007
Maternal smoking at the time of birth	781 (44.5)	1,053 (31.8)	0.263	36.1	36.3	0.003
Alcohol Exposure in pregnancy	37 (2.1)	76 (2.3)	0.013	2.12	2.2	0.005
Exposure 1 year prior to or during pregnancy	445 (25.4)	743 (22.5)	0.068	23.1	23.3	0.004
Other antidepressant medications	705 (40.2)	1,107 (33.5)	0.140	36.0	35.8	0.004
Other Psychotropics	457 (26.1)	666 (20.1)	0.141	21.9	22.2	0.007
Opioid	524 (29.9)	601 (18.2)	0.276	22.4	22.3	0.002
Type of birth (Cesarean)	89 (5.1)	117 (3.5)	0.076	4.0	4.1	0.005
Gestational age (<37 weeks)	1,246 (71.0)	2,025 (61.2)	0.208	65.2	64.8	0.008
Previous live birth(s)						
Nearest Census-Based Neighbourhood Income Quintile*						
2	418 (23.8)	793 (24.0)	0.003	23.7	23.9	0.004
3	262 (14.9)	519 (15.7)	0.021	15.4	15.4	0.001
4	147 (8.4)	370 (11.2)	0.095	10.5	10.3	0.008
5	88 (5.0)	236 (7.1)	0.089	6.6	6.4	0.007
Living in a rural area	245 (14.0)	370 (18.2)	0.116	17.1	16.8	0.008
Elixhauser co-morbidity Index Score						
1	84 (4.8)	118 (3.6)	0.061	3.9	3.9	0.001
2	35 (2.0)	46 (1.4)	0.047	1.7	1.7	0.000

*n = 18 were missing information on neighbourhood income and were excluded from the propensity score analysis.

had withdrawal signs which were significantly higher in preterm as compared to full-term newborns (54% vs 31%, $p = 0.020$) [59]. Only 1.4% of newborns in their study were noted to have a Finnegan score of ≥ 8 indicating the need for intervention, with restless sleep, tremors and mottling as the most common withdrawal signs reported [59]. Their findings of a 1.4% rate of withdrawal signs [59] is more consistent with our study results (1.5% and 2.3% for exclusively breastfed and formula-fed newborns, respectively). Our study included both term and preterm newborns.

The setting may also have influenced study results. Participants recruited by Kieviet et al. [25] were from a psychiatric, obstetric and paediatric clinic that included providers with psychiatric disorder expertise. It is possible that these participants had more severe perinatal mental health disorders as compared to our population-based sample where mothers were beneficiaries of a publicly funded drug benefit

program. Study participants receiving care at the specialized centre described by Kieviet et al. [25] may have had more focused assessment and monitoring during their postnatal inpatient stay than our study participants. In Ontario, there are few integrated perinatal mental health programs and the existing programs are predominantly provided on an outpatient basis [60]. Therefore, we can assume that most newborns in our study likely received the same routine monitoring and care as newborns unexposed to SSRIs.

During our study timeframe, the Ontario Government provided concerted efforts to implement the 'Baby Friendly Initiative' (BFI) [61–63]. The BFI recommendations include providing skin-to-skin contact for all newborns regardless of feeding method, promoting and encouraging maternal-newborn togetherness, and initiating early and frequent breastfeeding, to name a few. Efforts to implement these evidence-based practices in Ontario hospitals may have

Table 2: Unadjusted and adjusted relative risk between feeding method and neonatal withdrawal

Analysis	Outcome	Feeding method	No outcome n (%)	Had outcome n (%)	Risk ratio (95% CI)	
					Unadjusted	Adjusted ^a
Primary Cohort (N = 5,079)	Neonatal Withdrawal*	Formula feeding only	1,717 (97.7)	41 (2.3)	1.0	1.0
		Breastfeeding only	3,271 (98.5)	50 (1.5)	0.66 (0.44, 1.00)	0.86 (0.56, 1.34)
	Transfer to the NICU**	Formula feeding only	1,569 (89.2)	189 (10.8)	1.0	1.0
		Breastfeeding only	3,083 (92.8)	238 (7.2)	0.67 (0.56, 0.80)	0.80 (0.66, 0.97)
Sensitivity: 3rd Trimester SSRI exposed only (N = 2,916)	Neonatal Withdrawal*	Formula feeding only	958 (96.8)	32 (3.2)	1.0	1.0
		Breastfeeding only	1,891 (98.2)	35 (1.8)	0.56 (0.35, 0.90)	0.77 (0.47, 1.28)
	Transfer to the NICU**	Formula feeding only	865 (87.4)	125 (12.6)	1.0	1.0
		Breastfeeding only	1,756 (91.2)	170 (8.8)	0.70 (0.56, 0.87)	0.83 (0.66, 1.04)
Sensitivity: Any Breastfeeding included (N = 7,420)	Neonatal Withdrawal*	Formula feeding only	1,717 (97.7)	41 (2.3)	1.0	1.0
		Any Breastfeeding	5,556 (98.1)	106 (1.9)	0.80 (0.56, 1.15)	0.96 (0.66, 1.40)
	Transfer to the NICU**	Formula feeding only	1,569 (89.2)	189 (10.8)	1.0	1.0
		Any Breastfeeding	5,112 (90.3)	550 (9.7)	0.90 (0.77, 1.06)	0.93 (0.79, 1.10)

*ICD-10 P96.1(data source: Discharge Abstract Database (DAD)).

**Combined admissions to Neonatal Intensive Care Unit (NICU) and Special Care Nursery (SCN) (data source: Discharge Abstract Database (DAD)).

^aPropensity Score weighted using IPTW with covariates adjustment for gestational age, type of birth, parity, maternal age, neighbourhood income quintiles, other antidepressants (non-SSRIs), psychotropic medications, opioid use, alcohol exposure in pregnancy, smoking at time of birth, rurality, and Elixhauser co-morbidity index.

contributed to sustaining the higher rate of exclusive breastfeeding (65.3%) observed in our study compared to the rates reported by Kieviet et al. [25] (43.3% (n = 107) breastfeeding, 18.2% (n = 45) formula feeding and 38.5% (n = 95) mixed feeding).

We hypothesized that breastfeeding might confer a significant risk reduction for newborn withdrawal given that Kieviet et al., had reported that formula-feeding newborns in their study were three times as likely to have withdrawal as compared to newborns who were breastfed or received mixed feeds (OR = 3.16, 95% CI 1.40, 7.13) [25]. The overall low rate of withdrawal signs observed in our study may be due to newborns receiving non-pharmacological support (e.g. skin-to-skin contact, rooming-in, breastfeeding), which has been reported to be effective in reducing the severity of withdrawal among opioid exposed newborns [26–28]. Formula-fed newborns in our study likely received benefits from some of these non-pharmacologic interventions, which could have partially affected our study result of no difference in risk of withdrawal by feeding method. Additionally, we defined our cohort as exposure to any SSRI, while Kieviet et al. [25, 64] included multiple medication categories (i.e. SSRIs, SNRIs, NaSSA).

Serotonergic antidepressants have different pharmacokinetic properties, and thus, they are likely to impact the exposed newborn differently after birth. Cornet et al. [54] suggested that there may be a causal relationship between type and dose of SSRI medication exposure and risk of delayed neonatal adaptation, although research is required to identify the mechanism underlying this relationship [54]. These authors did not include feeding method as a variable in their analysis; however, they acknowledged that the effect of sudden discontinuation of SSRI exposure after birth as compared with continuous exposure via breast milk was an area of investigation they did not evaluate [54].

Transfer to the Neonatal Intensive Care Unit

In our study, we found a lower risk of NICU transfers in exclusively breastfed compared with formula-fed NeoWISE. However, this finding did not persist in sensitivity analyses when examining outcomes for NeoWISE with any breastfeeding. While the maternal-newborn dyads were balanced following propensity score adjustment using IPTW minimized confounding, it is possible that conditioning on exclusive breastfeeding in our primary analysis may have

caused selection bias on our association with NICU admission. The use of exclusive breastfeeding as an exposure likely selected healthier maternal-newborn dyads for inclusion in our study, with no such conditioning on the formula-fed; these exclusively breastfed newborns would be less likely to be admitted to the NICU for any reason.

The proportion of newborns requiring NICU admission was lower in our cohort than in others. Kieviet et al. [25] found an overall NICU admission rate of 29% ($n=45/157$), with 3% of these newborns transferred due to severe symptoms of withdrawal. In contrast, Gorman et al. [65] conducted a prospective cohort study ($n=466$) of women taking SSRIs at some point during pregnancy who called a teratogen information service over a 10-year period. There was a small difference in the rate of admission to the NICU between newborns with SSRI exposure before delivery (8.6%), SSRI exposure at delivery (14.4%), and no exposure to SSRIs (8.2%) ($p=0.13$) [65]. Variations in hospital policies related to transfer to NICU may alter the frequency of this outcome.

Other potential reasons for transfer to the NICU can be proposed. In a recent systematic review and meta-analysis, exposure to in-utero serotonin reuptake inhibitors (i.e. SSRI or SNRI) was associated with an increased risk for convulsions ($OR=3.25$, $p=0.0002$), hypoglycemia ($OR=1.65$, $p < 0.0001$), temperature dysregulation ($OR=1.75$, $p=0.004$) and respiratory problems ($OR=1.96$, $p < 0.0001$) in newborns as compared to newborns born to healthy controls, defined as healthy women or women with major depressive disorder but not taking in-utero serotonergic medication [66]. Of relevance to our study, the authors also reported an increased risk of feeding problems ($OR=2.25$, $p=0.031$) [66]. Other authors have reported that in-utero SSRI exposure impacted newborn feeding as evidenced by feeding/ digestive disturbances [14], desaturation on feeding [11], and poor suck necessitating tube feeding [14]. NeoWISE in our study who received any breastfeeding may have had a similar medical complexity as formula-fed newborns and thus were at no greater risk of transfer to the NICU.

Additionally, it is possible that maternal body mass index could have moderated the observed association between feeding and NICU transfer [67]. Suk et al. reported that women with a BMI < 30 as compared with a BMI ≥ 30 had a greater odd of newborn admission to the NICU ($OR=1.39$, $p=0.045$); there was a stronger association when comparing women with a BMI ≥ 35 ($OR=1.76$, $p=0.006$) [67]. We were unable to include body mass index as a covariate due to a high level of missing data. However, we attempted to control for pre-existing maternal health issues using the Elixhauser comorbidity index which includes obesity and other diagnoses associated with elevated BMI (e.g. diabetes, hypertension).

Third-trimester SSRI exposure

There are discrepancies in the literature regarding the impact of third-trimester SSRI exposure and the risk for neonatal withdrawal, with some studies showing an association with newborn withdrawal signs [13, 39, 48, 68, 69]. In a review, third-trimester SSRIs exposure was significantly associated with an increased incidence of neonatal behavioural syndrome, which are serotonin withdrawal-like symptoms ($OR=3.0$, 95%

CI, 2.0, 4.4) [14]. Our findings do not confirm this association when relevant covariates were taken into account.

The results of our study suggest that feeding method is not associated with an increased risk of neonatal withdrawal diagnosis. This is not to discount the presence of transient neonatal behavioural signs, which should not be disregarded. The increased likelihood of irritability, crying, and sleep disturbances could be distressing to mothers, even if for a short duration, and anticipatory guidance should be provided. Given that women have reported concerns about taking medication during pregnancy and breastfeeding, health care providers have an essential role in sharing evidence-based information. Health care providers can use these findings along with the extant literature and have greater confidence to support women's preferred feeding method when counselling expectant parents about postnatal newborn care.

Strengths & limitation

Strengths of our study include the large sample size of NeoWISE compared to other cohorts; the use of a population-based cohort study design that linked multiple health administrative databases and validated registries; and IPTW of propensity scores to balance differences in baseline characteristics related to newborn feeding methods minimizing confounding bias [46].

This study has some limitations. The cohort was restricted to women on ODB as this was the only record of SSRI prescription claims in ICES. The results are likely not generalizable given that the study cohort represents less than 1% of the population of births in Ontario within the study timeframe, and thus, different effects of breastfeeding may be observed in the larger pregnancy population. The NeoWISE cohort was much younger than the general population of childbearing women in Ontario (Supplementary Table 6). Women with a lower income, a younger age, and poor mental health are at increased risk of poor breastfeeding outcomes [70]. Additional maternal and newborn characteristics associated with low rates of breastfeeding include primiparous, unmarried, low social support, maternal obesity, diabetes during pregnancy, smoking during pregnancy, cesarean birth, preterm infant, admission to the NICU, and formula supplementation in hospital [70]. Regardless of these potential barriers, we observed that the majority of mothers in our cohort of ODB recipients were either exclusively breastfeeding or mixed feeding at the time of postnatal hospital discharge.

We did not collect data on maternal mental health diagnoses or the severity of mental health concerns. SSRI medications are primarily prescribed to treat depression, as observed in other retrospective studies [56]. However, SSRIs have also been used as a first-line pharmacotherapy for many other psychiatric disorders. It is possible that NeoWISE who were exposed to SSRIs through the entire pregnancy ($n=1,636$, 32.2%) had mothers with more severe mental health concerns, and this may have influenced observed associations. Off label SSRI prescribing has been reported for binge eating disorders, body dysmorphic disorder, fibromyalgia, paraphilias, autism, and Raynaud phenomenon [71], although these are likely rare occurrences in the perinatal population.

While there were no guideline changes in medication prescribing or treatment for perinatal mental health disorders during the study timeframe, the prescribing practices of health care providers may have evolved as more information became available on the risks/benefits of various psychotropics. By using medication dispensing data, we reduced bias due to confounding by indication by selecting only pregnant women who were dispensed an SSRI medication, and we were able to conduct sensitivity analysis comparing any SSRI exposure during pregnancy versus third trimester SSRI exposure. Although we were able to identify the trimester in which the SSRI medication was dispensed by using data obtained from the ODB, it is not possible to know for certain if the mother took the medication as prescribed. Therefore, medication exposure may have been misclassification when assembling the study cohort.

Data were limited to variables that were available in health administrative databases. The specific withdrawal signs of the newborns in our study are unknown, given that a diagnostic code (P96.1) was used as the primary outcome. As a result, we have likely underestimated the incidence of withdrawal given that the P96.1 variable may have reduced sensitivity to identify newborns who are experiencing minor adverse reactions following in-utero SSRI exposure. Numerous authors have reported that some of the most common signs of withdrawal include tremors, irritability, crying, sleep disturbances, increased moro reflex [13, 14, 56, 72–74] and these are not variables in health administrative databases. Furthermore, the P96.1 diagnosis code is non-specific to SSRI exposure, so all clinicians may not use it. Currently, no variable exists in health administrative databases for SSRI exposure.

Future research

To date, past research has many limitations, including the predominant use of case review methodology, small sample sizes, self-reported adverse outcomes, and a lack of long-term follow-up [75]. Pharmacoepidemiologic studies require more robust breastfeeding data. Jordan et al. [76] emphasized the need for quality breastfeeding data in population health databases to enable pharmacoepidemiologists to explore relationships between medication exposures, breastfeeding, and short and long-term newborn outcomes. Health care providers can strive to ensure complete and accurate documentation of newborn feeding; audit and feedback cycles may be useful to demonstrate progress in this area. Additional methods of capturing newborn feeding data are warranted. A prospective cohort study design may facilitate improved data collection on essential variables such as mental health status, medication history, newborn feeding details, and neonatal behavioural/withdrawal signs. More rigorous data collection would improve surveillance and reporting of adverse outcomes, mainly to obtain a more precise estimate of the withdrawal prevalence in the NeoWISE.

Future researchers should consider creating a core outcome set of variables reflecting the most common signs of SSRI withdrawal, as has been done for in-utero opioid exposure [77]. Wang and Cosci have proposed a framework that is worth consideration [78]; transient neonatal behavioural signs, which may impact newborn feeding ability, will need to be integrated.

This promising research direction may improve the sensitivity and specificity of identifying newborns with clinically relevant withdrawal. Finally, capturing parent-reported observations in future research studies would be particularly important. Qualitative studies exploring the parental experience of caring for NeoWISE may provide insightful guidance for clinical care, particularly regarding the pre- and postnatal support women require to achieve their desired newborn feeding goals.

Conclusion

In this study, we report an overall low risk of neonatal withdrawal, and no difference in risk among breastfed compared with formula-fed NeoWISE. We also observed a possible reduced risk of transfer to the NICU in breastfed newborns. The findings of this study contribute to the extant literature, which indicates that perinatal women who take SSRI medications can be supported in their preferred newborn feeding method with the appropriate monitoring for newborn well-being. Pregnant and breastfeeding families need to receive anticipatory guidance about potential signs of withdrawal in the NeoWISE and when to seek health care after birth.

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The data set from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set 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 data set 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.

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Ethics statement

This study was approved by the Queen's Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (REB NURS-576-23).

Statement on conflicts of interest

The authors reported no conflicts of interest.

References

1. Moyer SW, Kinser PA. A comprehensive conceptual framework to guide clinical practice and research about mental health during the perinatal period. *Journal of Perinatal & Neonatal Nursing*, 35(1):46–56, 2021. <https://doi.org/10.1097/JPN.0000000000000535>
2. MacQueen GM, Frey BN, Ismail Z, Jaworska N, Steiner M, Lieshout RJV, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 6. Special populations: Youth, women, and the elderly. *Canadian Journal of Psychiatry*, 61(9):588–603, 2016. <https://doi.org/10.1177/0706743716659276>
3. Molenaar NM, Kamperman AM, Boyce P, Bergink V. Guidelines on treatment of perinatal depression with antidepressants: An international review. *Australian & New Zealand Journal of Psychiatry*, 52(4):320–7, 2018. <https://doi.org/10.1177/0004867418762057>
4. Molenaar NM, Bais B, Lambregtse-van den Berg MP, Mulder CL, Howell EA, Fox NS, et al. The international prevalence of antidepressant use before, during, and after pregnancy: A systematic review and meta-analysis of timing, type of prescriptions and geographical variability. *Journal of Affective Disorders*, 264:82–9, 2020. <https://doi.org/10.1016/j.jad.2019.12.014>
5. Forsberg L, Naver L, Gustafsson LL, Wide K. Neonatal adaptation in infants prenatally exposed to antidepressants: Clinical monitoring using neonatal abstinence score. *PloS One*, 9(11):e111327-e, 2014. <https://doi.org/10.1371/journal.pone.0111327>
6. Jefferies AL. Selective serotonin reuptake inhibitors in pregnancy and infant outcomes. *Paediatrics & Child Health*, 16(9):562–, 2018. <https://doi.org/10.1093/pch/16.9.562>
7. Perinatal Services BC. Antidepressant use during pregnancy: Considerations for newborn exposed to SSRIs. 2013.
8. Hendson L, Shah V, Trkulja S. Selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors in pregnancy: Infant and childhood outcomes. *Paediatrics & Child Health*, 26(5):321, 2021. <https://doi.org/10.1093/pch/pxab021>
9. Koren G, Finkelstein Y, Matsui D, Berkovich M. Diagnosis and management of poor neonatal adaptation syndrome in newborns exposed in utero to selective serotonin/norepinephrine reuptake inhibitors. *Journal of Obstetrics and Gynaecology Canada*, 31(4):348–50, 2009. [https://doi.org/10.1016/S1701-2163\(16\)34157-3](https://doi.org/10.1016/S1701-2163(16)34157-3)
10. Jordan S, Davies GI, Thayer DS, Tucker D, Humphreys I. Antidepressant prescriptions, discontinuation, depression and perinatal outcomes, including breastfeeding: A population cohort analysis. *PloS one*, 14(11):e0225133-e, 2019. <https://doi.org/10.1371/journal.pone.0225133>
11. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. *New England Journal of Medicine*, 335(14):1010–5, 1996. <https://doi.org/10.1056/nejm199610033351402>
12. Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics*, 129(2):e540, 2012. <https://doi.org/10.1542/peds.2011-3212>
13. Grigoriadis S, VonderPorten EH, Mamisashvili L, Eady A, Tomlinson G, Dennis CL, et al. The effect of prenatal antidepressant exposure on neonatal adaptation: A systematic review and meta-analysis. *Journal of Clinical Psychiatry*, 74(4):e309–20, 2013. <https://doi.org/10.4088/JCP.12r07967>
14. Moses-Kolko EL, Bogen D, Perel J, Bregar A, Uhl K, Levin B, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors. *JAMA*, 293(19):2372, 2005. <https://doi.org/10.1001/jama.293.19.2372>
15. Convertino I, Sansone AC, Marino A, Galiulo MT, Mantarro S, Antonioli L, et al. Neonatal adaptation issues after maternal exposure to prescription drugs: Withdrawal syndromes and residual pharmacological effects. *Drug Safety*, 39(10):903–24, 2016. <https://doi.org/10.1007/s40264-016-0435-8>

16. Clark L, Rohan A. Identifying and assessing the substance-exposed infant. *American Journal of Maternal Child Nursing*, 40(2):87-95, 2015. <https://doi.org/10.1097/NMC.0000000000000117>
17. Canadian Paediatric Society. ACoRN: Acute Care of the at-Risk Newborn. 2nd ed. New York: Oxford University Press; 2021.
18. Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. *Drug Safety*, 28(2):137-52, 2005. <https://doi.org/10.2165/00002018-200528020-00005>
19. Franz N. The effects of selective serotonin reuptake inhibitors on newborn adaptation and withdrawal symptoms: A scoping review. *Journal of Neonatal Nursing*, 29(2):235-44, 2023. <https://doi.org/10.1016/j.jnn.2022.07.004>
20. Shan F, Macvicar S, Allegaert K, Offringa M, Jansson LM, Simpson S, et al. Outcome reporting in neonates experiencing withdrawal following opioid exposure in pregnancy: A systematic review. *Trials*, 21(1) 2020. <https://doi.org/10.1186/s13063-020-4183-9>
21. Hendrick V, Stowe ZN, Altshuler LL, Mintz J, Hwang S, Hostetter A, et al. Fluoxetine and norfluoxetine concentrations in nursing infants and breast milk. *Biological Psychiatry*, 50(10):775-82, 2001.
22. Kristensen JH, Ilett KF, Hackett LP, Yapp P, Paech M, Begg EJ. Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br J Clin Pharmacol*, 48(4):521-7, 1999. <https://doi.org/10.1046/j.1365-2125.1999.00040.x>
23. Leutritz AL, van Braam L, Preis K, Gehrman A, Scherf-Clavel M, Fiedler K, et al. Psychotropic medication in pregnancy and lactation and early development of exposed children. *Br J Clin Pharmacol*, 89(2):737-50, 2023. <https://doi.org/10.1111/bcp.15533>
24. Pogliani L, Zuccotti G, Baldelli S, Cattaneo D, Pileri P, Cetin I, et al. Selective serotonin reuptake inhibitors' passage into human milk of lactating women. *Journal of Maternal-Fetal & Neonatal Medicine*, 32(18):3020-5, 2019. <https://doi.org/10.1080/14767058.2018.1455180>
25. Kieviet N, Hoppenbrouwers C, Dolman KM, Berkhof J, Wennink H, Honig A. Risk factors for poor neonatal adaptation after exposure to antidepressants in utero. *Acta Paediatrica*, 104(4):384-91, 2015. <https://doi.org/10.1111/apa.12921>
26. Grossman MR, Berkowitz AK, Osborn RR, Citarella BV, Hochreiter D, Bizzarro MJ. Evaluating the effect of hospital setting on outcomes for neonatal abstinence syndrome. *Journal of Perinatology*, 40(10):1483-8, 2020. <https://doi.org/10.1038/s41372-020-0621-5>
27. Holmes AV, Atwood EC, Whalen B, Beliveau J, Jarvis JD, Matulis JC, et al. Rooming-in to treat neonatal abstinence syndrome: Improved family-centered care at lower cost. *Pediatrics*, 137(6):e20152929-e, 2016. <https://doi.org/10.1542/peds.2015-2929>
28. Newman A, Davies GA, Dow K, Holmes B, Macdonald J, McKnight S, et al. Rooming-in care for infants of opioid-dependent mothers: Implementation and evaluation at a tertiary care hospital. *Canadian Family Physician*, 61(12):e555-e61, 2015.
29. Hale TW, Krutsch K. Hale's medications & mothers' milk™ 2023: A manual of lactational pharmacology. 20th ed: Springer; 2023.
30. Dunn S, Lanes A, Sprague AE, Fell DB, Weiss D, Reszel J, et al. Data accuracy in the Ontario birth Registry: A chart re-abstraction study. *BMC Health Serv Res*, 19(1):1001-, 2019. <https://doi.org/10.1542/peds.2015-2929>
31. Government of Ontario. Get coverage for prescription drugs 2022 [Available from: <https://www.ontario.ca/page/get-coverage-prescription-drugs#section-0>].
32. Government of Ontario. Data catalogue: Ontario Drug Benefit 2017 [Available from: <https://data.ontario.ca/dataset/ontario-drug-benefit-odb-database>].
33. Huybrechts KF, Bateman BT, Desai RJ, Hernandez-Diaz S, Rough K, Mogun H, et al. Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: Cohort study. *BMJ*, 358:j3326-j, 2017. <https://doi.org/10.1136/bmj.j3326>
34. Kocherlakota P. Neonatal abstinence syndrome. *Pediatrics*, 134(2):e547-e61, 2014. <https://doi.org/10.1542/peds.2013-3524>
35. Froggatt S, Covey J, Reissland N. Infant neurobehavioural consequences of prenatal cigarette exposure: A systematic review and meta-analysis. *Acta Paediatrica*, 109(6):1112-24, 2020. <https://doi.org/10.1111/apa.15132>
36. Froggatt S, Reissland N, Covey J. The effects of prenatal cigarette and e-cigarette exposure on infant neurobehaviour: A comparison to a control group. *EclinicalMedicine*, 28:100602, 2020. <https://doi.org/10.1016/j.eclinm.2020.100602>
37. Nakamura A, François O, Lepeule J. Epigenetic alterations of maternal tobacco smoking during pregnancy: A narrative review. *International Journal of Environmental Research and Public Health*, 18(10):5083, 2021. <https://doi.org/10.3390/ijerph18105083>
38. Bertini G, Elia S, Lori S, Dani C. Abnormal neurological soft signs in babies born to smoking mothers were associated with lower breastfeeding for first three months. *Acta Paediatrica*, 108(7):1256-61, 2019. <https://doi.org/10.1111/apa.14762>
39. Oberlander TF, Misri S, Fitzgerald CE, Kostaras X, Rurak D, Riggs W. Pharmacologic factors associated with transient neonatal symptoms following

- prenatal psychotropic medication exposure. *J Clin Psychiatry*, 65(2):230-7, 2004. <https://doi.org/10.4088/jcp.v65n0214>
40. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Medical care*, 36(1):8-27, 1998. <https://doi.org/10.1097/00005650-199801000-00004>
 41. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Medical Care*, 47(6):626-33, 2009. <https://doi.org/10.1097/MLR.0b013e31819432e5>
 42. Ontario Ministry of Health and Ministry of Long Term Care. Narcotics Monitoring System 2021 [Available from: https://www.health.gov.on.ca/en/pro/programs/drugs/ons/monitoring_system.aspx
 43. Ontario Government. Registered Persons Database (RPDB) 2017 [Available from: <https://data.ontario.ca/dataset/registered-persons-database-rpdb>.
 44. American Academy of Pediatrics Committee on Fetus Newborn, American College of Obstetricians Gynecologists Committee on Obstetric Practice, Watterberg KL, Aucott S, Benitz WE, Cummings JJ, et al. The Apgar score. *Pediatrics*, 136(4):819-22, 2015. <https://doi.org/10.1542/peds.2015-2651>
 45. ICES. Data dictionary. Library: Discharge Abstract Database (DAD) 2022 [Available from: <https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library=DAD>.
 46. 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. *Statistics in Medicine*, 34(28):3661-79, 2015. <https://doi.org/10.1002/sim.6607>
 47. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behavioral Research*, 46(3):399-424, 2011. <https://doi.org/10.1080/00273171.2011.568786>
 48. Kendall-Tackett K, Hale TW. The use of antidepressants in pregnant and breastfeeding women: A review of recent studies. *Journal of Human Lactation*, 26(2):187-95, 2010. <https://doi.org/10.1177/0890334409342071>
 49. Van den Hof MC, Smithies M, Nevo O, Oullet A. No. 375-Clinical Practice Guideline on the use of first trimester ultrasound. *J Obstet Gynaecol Can*, 41(3):388-95, 2019. <https://doi.org/10.1016/j.jogc.2018.09.020>
 50. American College of Obstetricians and Gynecologists CoOPtAloUiMtSfM-FM. Committee Opinion No 700: Methods for estimating the due date. *Obstet Gynecol*, 129(5):e150-e4, 2017. <https://doi.org/10.1097/aog.0000000000002046>
 51. Cunningham FG. Williams obstetrics. 26th ed. ed. New York, New York: McGraw Hill Medical; 2022.
 52. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: Introducing the E-value. *Annals of Internal Medicine*, 167(4):268-74, 2017. <https://doi.org/10.7326/M16-2607>
 53. Langan SM, Schmidt SA, Wing K, Ehrenstein V, Nicholls SG, Filion KB, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). *BMJ Online*, 363:k3532-k, 2018. <https://doi.org/10.1136/bmj.k3532>
 54. Cornet MC, Wu YW, Forquer H, Avalos LA, Sriram A, Scheffler AW, et al. Maternal treatment with selective serotonin reuptake inhibitors during pregnancy and delayed neonatal adaptation: A population-based cohort study. *Arch Dis Child Fetal Neonatal Ed*, 109(3):294-300, 2024. <https://doi.org/10.1136/archdischild-2023-326049>
 55. Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med*, 160(2):173-6, 2006. <https://doi.org/10.1001/archpedi.160.2.173>
 56. Ferreira E, Carceller AM, Agogu   C, Martin BZ, St-Andr   M, Francoeur D, et al. Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics*, 119(1):52-9, 2007. <https://doi.org/10.1542/peds.2006-2133>
 57. Costei AM, Kozer E, Ho T, Ito S, Koren G. Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med*, 156(11):1129-32, 2002. <https://doi.org/10.1001/archpedi.156.11.1129>
 58. Provincial Council for Maternal and Child Health & Neonatal Abstinence Workgroup. Neonatal abstinence syndrome [Clinical Practice Guideline]. Toronto, ON; 2016.
 59. Yang A, Ciolino JD, Pinheiro E, Rasmussen-Torvik LJ, Sit DKY, Wisner KL. Neonatal discontinuation syndrome in serotonergic antidepressant-exposed neonates. *J Clin Psychiatry*, 78(5):605-11, 2017. <https://doi.org/10.4088/JCP.16m11044>
 60. Hippman CLaLwaB. Maternal mental health: Is Canada doing enough? A review of maternal mental health supports across the country. 2021.
 61. World Health Organization. Protecting, promoting and supporting breastfeeding in facilities providing maternity and newborn services. 2017.
 62. Baby-Friendly Initiative Strategy Ontario. Ontario's Baby-Friendly Initiative Report, 2019. 2019 April 29, 2019.
 63. Ontario Government. Moms and babies to benefit from new breastfeeding supports: Ontario government helping

- babies get healthy start 2013, Sept 30 [Available from: <https://news.ontario.ca/en/release/27066/moms-and-babies-to-benefit-from-new-breastfeeding-supports>]
64. Kieviet N, van Keulen V, van de Ven PM, Dolman KM, Deckers M, Honig A. Serotonin and poor neonatal adaptation after antidepressant exposure in utero. *Acta Neuropsychiatrica*, 29(1):43-53, 2017. <https://doi.org/10.1017/neu.2016.30>
 65. Gorman JR, Kao K, Chambers CD. Breastfeeding among women exposed to antidepressants during pregnancy. *Journal of Human Lactation*, 28(2):181-8, 2012. <https://doi.org/10.1177/0890334411429782>
 66. Kautzky A, Slamanig R, Unger A, Höflich A. Neonatal outcome and adaption after in utero exposure to antidepressants: A systematic review and meta-analysis. *Acta psychiatrica Scandinavica*, 145(1):6-28, 2022. <https://doi.org/10.1111/acps.13367>
 67. Suk D, Kwak T, Khawar N, Vanhorn S, Salafia CM, Gudavalli MB, et al. Increasing maternal body mass index during pregnancy increases neonatal intensive care unit admission in near and full-term infants. *Journal of Maternal-Fetal & Neonatal Medicine*, 29(20):3249-53, 2016. <https://doi.org/10.3109/14767058.2015.1124082>
 68. Casper RC, Gilles AA, Fleisher BE, Baran J, Enns G, Lazzeroni LC. Length of prenatal exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants: Effects on neonatal adaptation and psychomotor development. *Psychopharmacology*, 217(2):211-9, 2011. <https://doi.org/10.1007/s00213-011-2270-z>
 69. Hendrick V, Smith LM, Suri R, Hwang S, Haynes D, Altshuler L. Birth outcomes after prenatal exposure to antidepressant medication. *Am J Obstet Gynecol*, 188(3):812-5, 2003. <https://doi.org/10.1067/mob.2003.172>
 70. Best Start Resource Centre. Populations with lower rates of breastfeeding: A summary of findings. 2015.
 71. Chu A, Wadhwa R. Selective serotonin reuptake inhibitors. StatPearls [Internet]. 2023, May 1 2024, July 30. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK554406/>.
 72. Gentile S. On categorizing gestational, birth, and neonatal complications following late pregnancy exposure to antidepressants: The prenatal antidepressant exposure syndrome. *CNS Spectrums*, 15(3):167-85, 2010. <https://doi.org/10.1017/S1092852900027449>
 73. Galbally M, Spigset O, Johnson AR, Kohan R, Lappas M, Lewis AJ. Neonatal adaptation following intrauterine antidepressant exposure: Assessment, drug assay levels, and infant development outcomes. *Pediatric Research*, 82(5):806-13, 2017. <https://doi.org/10.1038/pr.2017.156>
 74. Kieviet N, Dolman KM, Honig A. The use of psychotropic medication during pregnancy: How about the newborn? *Neuropsychiatric Disease and Treatment*, 9:1257-66, 2013. <https://doi.org/10.2147/NDT.S36394>
 75. Orsolini L, Bellantuono C. Serotonin reuptake inhibitors and breastfeeding: A systematic review. *Human Psychopharmacology*, 30(1):4-20, 2015. <https://doi.org/10.1002/hup.2451>
 76. Jordan S, Komninou S, Lopez Leon S. Where are the data linking infant outcomes, breastfeeding and medicine exposure? A systematic scoping review. *PLOS ONE*, 18(4):e0284128, 2023. <https://doi.org/10.1371/journal.pone.0284128>
 77. Kelly A. A core outcome set for neonatal opioid withdrawal syndrome. *Pediatrics*, 146(1):e20200018, 2020. <https://doi.org/10.1542/peds.2020-0018>
 78. Wang J, Cosci F. Neonatal withdrawal syndrome following late in utero exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis of observational studies. *Psychotherapy and Psychosomatics*, 90(5):299-307, 2021. <https://doi.org/10.1159/000516031>
 79. Better Outcomes Registry & Network. Data dictionary and library 2024 [Available from: <https://www.bornontario.ca/en/data/data-dictionary-and-library.aspx>.]

Abbreviations

AD:	Antidepressant
NAS:	Neonatal Abstinence Syndrome
NaSSA:	Noradrenergic and Specific Serotonergic Antidepressants
NeoWISE:	N eonates W ith I n-utero SSRI E xposure
NICU:	Neonatal Intensive Care Unit
NOWS:	Neonatal Opioid Withdrawal Syndrome
SNRI:	Serotonin and Noradrenaline Reuptake Inhibitors
SSRI:	Selective Serotonin Reuptake Inhibitor



Supplementary Table 1: Databases used to identify cohort and derive study variables*

Data source	Abbreviation	Description of data held
Ontario Drug Benefit Program	ODB	Prescription drug benefit information for persons who live in Ontario and are older than 65 years of age; under 65 years who are unemployed (receiving benefits from Ontario Works); have disabilities (receiving benefits from Ontario Disability Support Program); or have high prescription costs relative to net household income (enrolled in Trillium Drug Program).
Ontario Health Insurance Plan	OHIP	Physician claims for services provided related to diagnosing mental health concerns.
Registered Persons Database	RPDS	Personal health information on persons registered under OHIP who are eligible for the Ontario Drug Program. Data is linked to programs that deliver health services to the public such as hospital services, physicians services and drug benefits.
Better Outcomes Registry and Network	BORN	Ontario's prescribed maternal newborn registry. This is an acquired registry at ICES and captures 99% of health records for in-hospital births.**
Narcotics Monitoring System	NMS	All prescription narcotics and other controlled substances are recorded regardless of mode of payment (publicly funded drug program, private insurance, or cash). The purpose of the NMS is to help reduce misuse, addiction, unlawful activities, and deaths related to these medications. For this study we will identify dispensed opioids from the <i>Monitored Drugs List</i> .
ICES	MOMBABY	Validated database of pregnancies, pregnancy outcomes, and mother–infant linkage from these healthcare data.
Canadian Institute for Health Information-Discharge Abstract Database	DAD	Demographic and clinical information about all hospital admissions and discharges, including transfers and deaths. DX10CODE was used to identify newborns who were diagnosed with neonatal withdrawal.

*Diagnoses in these datasets are recorded using the Canadian Coding Standards for the International Statistical Classification of Diseases and Related Health Problems (hospital) and physician billing claim codes (OHIP).

**Source: Murphy MSQ, Fell DB, Sprague AE, et al. Data resource profile: Better Outcomes Registry & Network (BORN) Ontario. *Int J Epidemiol.* Nov 10 2021;50(5):1416–1417h. <https://doi.org/10.1093/ije/dyab033>

Supplementary Table 2: Secondary outcome

Variable	Source	Code	Definition
Rate of transfer to the NICU (%)	DAD	50	Special Care Unit Neonatal Intensive Care Nursing Unit Undifferentiated/ General
		51	Neonatal Intensive Care Nursing Unit Level 1
		52	Neonatal Intensive Care Nursing Unit Level 2
		53	Neonatal Intensive Care Nursing Unit Level 3
		70	Paediatric Intensive Care Nursing Unit



Supplementary Table 3: Covariates included in the propensity score

Variable	Categories
Gestational age (weeks)	< 37 (preterm) ≥37 (term)
Type of birth	Vaginal Cesarean
Parity	0 1+
Maternal age (years)	mean
Neighbourhood income quintiles	1 2 3 4 5
Other antidepressant medication exposure one year prior to/during pregnancy (non-SSRIs)	Yes No
Psychotropic medication exposure one year prior to/during pregnancy	Yes No
Any opioid use one year prior to/during pregnancy	Yes No
Alcohol exposure in pregnancy	Yes No
Smoking at time of birth	Yes No
Rurality	Yes No
Elixhauser Co-morbidity Index* (Sum of scores)	0 1 2+

*Source: van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Medical Care*. 2009;47(6):626–633. <https://doi.org/10.1097/MLR.0b013e31819432e5>

Supplementary Table 4: Type and frequencies of SSRI medication exposure

SSRI	Frequency n (%) [*]
Escitalopram	3672 (37)
Sertraline	2979 (30)
Citalopram	1612 (16)
Fluoxetine	1154 (12)
Paroxetine	448 (5)
Fluvoxamine	58 (1)
TOTAL	9,923 (101)

*Does not equal 100% due to rounding. Among the 9,014 women, a total of 9,923 SSRI exposures were identified with 909 women taking more than one medication during their pregnancy.

Supplementary Table 5: Trimester of SSRI medication exposure

Trimester of SSRI exposure	Frequency n (%)
Any exposure in pregnancy	5,079 (100)
Trimester 1	3,712 (73.1)
Trimester 2	3,088 (60.8)
Trimester 3	2,916 (57.4)
All trimesters	1,636 (32.2)

Supplementary Table 6: Distribution of maternal age at birth: comparison of NeoWISE study cohort versus general population

NeoWISE study cohort	Ontario- general population*
15–20 = 9.4%	<20 = 1.9%
20–25 = 44.1%	20–24 = 10.2 %
26–34 = 35.9%	25–29 = 26.9%
	30–34 = 37.3 %
35–49 = 10.6%	35–39 = 19.5%
	≥40 = 4.3%

*Source: Better Outcomes Registry and Network (2018). One in a Million. BORN Ontario Biennial Report 2016-2018. Ottawa, Ontario. Retrieved on July 30, 2024 from Annual and Biennial Reports - BORN Ontario p. 42.



Supplementary Figure 1: Cohort creation

