OPEN ACCESS

Maternal treatment with selective serotonin reuptake inhibitors during pregnancy and delayed neonatal adaptation: a population-based cohort study

Marie-Coralie Cornet [1], Yvonne W Wu,[1,2] Heather Forquer,[3] Lyndsay A Avalos,[3] Achyuth Sriram,[4] Aaron W Scheffler,[5] Thomas B Newman,[1,5] Michael W Kuzniewicz [1,3,4]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/archdischild-2023-326049).

[1]Department of Pediatrics, University of California San Francisco, San Francisco, California, USA
[2]Department of Neurology, University of California San Francisco, San Francisco, California, USA
[3]Division of Research, Kaiser Permanente Northern California, Oakland, California, USA
[4]Department of Pediatrics, Kaiser Permanente Northern California, Oakland, California, USA
[5]Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, California, USA

Correspondence to
Dr Marie-Coralie Cornet, Department of Pediatrics, University of California San Francisco, San Francisco, CA 94143, USA;
marie-coralie.cornet@ucsf.edu

Received 5 July 2023
Accepted 2 November 2023
Published Online First 29 November 2023

Check for updates

To cite: Cornet M-C, Wu YW, Forquer H, *et al*. *Arch Dis Child Fetal Neonatal Ed* 2024;**109**:F294–F300.

ABSTRACT

Objective Selective serotonin reuptake inhibitor (SSRI) use is common in pregnancy. It is associated with delayed neonatal adaptation. Most previous studies have not adjusted for the severity of maternal mental health disorders or examined the impact of SSRI type and dosage. We examined whether treatment with SSRIs in late pregnancy (after 20 weeks) is associated with delayed neonatal adaptation independent of maternal depression and anxiety.

Design, setting and patients Retrospective population-based birth cohort of 280 090 term infants born at 15 Kaiser Permanente Northern California hospitals, 2011–2019. Individual-level pharmacy, maternal, pregnancy and neonatal data were obtained from electronic medical records.

Exposure Dispensed maternal SSRI prescription after 20 weeks of pregnancy.

Main outcome measures Delayed neonatal adaptation defined as a 5 min Apgar score ≤5, resuscitation at birth or admission to a neonatal intensive care unit for respiratory support. Secondary outcomes included each individual component of the primary outcome and more severe neonatal outcomes (pulmonary hypertension, hypoxic-ischaemic encephalopathy and seizures).

Results 7573 (2.7%) infants were exposed to SSRIs in late pregnancy. Delayed neonatal adaptation occurred in 11.2% of exposed vs 4.4% of unexposed infants (relative risk 2.52 (95% CI 2.36 to 2.70)). After multivariable adjustment, there was an association between SSRI exposure and delayed neonatal adaptation (adjusted OR 2.14 (95% CI 1.96 to 2.32)). This association was dose dependent. Escitalopram and fluoxetine were associated with the highest risk of delayed neonatal adaptation.

Conclusions Infants exposed to SSRIs have increased risks of delayed adaptation in a type and dose-dependent relationship, pointing toward a causal relationship.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In the USA, 4–6% of mothers are prescribed selective serotonin reuptake inhibitors (SSRIs) during pregnancy. SSRI use during pregnancy is associated with neonatal adaptation syndrome. Neonatal adaptation syndrome encompasses a wide range of different clinical presentations.

WHAT THIS STUDY ADDS

⇒ Low-dose sertraline exposure is associated with a doubling in the odds of delayed neonatal adaptation independent of maternal mental health diagnoses. The odds of delayed adaptation increase with increasing doses of SSRI and are higher for neonates on other types of SSRIs than sertraline.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study quantifies the additional risks of delayed adaptation in neonates exposed to SSRIs at various doses and types. It provides data for parents and providers to discuss SSRI treatment during pregnancy and the management of infants after birth.

INTRODUCTION

Depression and anxiety affect one in five pregnant individuals,[1] and a quarter of them are treated with selective serotonin reuptake inhibitors (SSRIs).[2] The frequency of SSRI treatment during pregnancy increased by one-third in the last decade in the USA.[2]

In making decisions regarding treatment for prenatal depression and anxiety, clinicians and women must consider the benefits of treatment as well as potential adverse effects. Unfortunately, the adverse effects of SSRI exposure in utero are poorly quantified.[3] Some studies have shown in utero SSRI exposure to be associated with delayed neonatal adaptation[4 5] manifested by lower Apgar scores,[6 7] respiratory distress[8–10] and persistent pulmonary hypertension of the newborn[11 12] leading to higher neonatal intensive care unit (NICU) admission rates.[4 13] Transient, self-limited symptoms such as abnormal tone,[14–17] jitteriness and irritability[18] have also been described. The risk of more severe neurological conditions such as hypoxic-ischaemic encephalopathy (HIE)[19] and seizures[20 21] is unclear.

Past studies are limited by small sample size,[5 10 16 19] ascertainment bias of both exposure and outcome of interest,[4 5 17 19] reliance on administrative databases[8 9] and the inability to differentiate the adverse effects of SSRIs themselves from the impact of maternal anxiety and depression on

neonatal outcomes.[9 10 22 23] Data on the relationship between the type and dose of SSRI treatment and adverse outcome are also needed. We conducted a population-based cohort study of mother–infant dyads, to evaluate the relationship between maternal SSRI treatment and delayed neonatal adaptation, adjusting for maternal depression and anxiety, and evaluating the impact of SSRI dosage and type.

METHODS

Study population and setting

This cohort study included infants born at ≥37 weeks' gestational age at 15 Kaiser Permanente Northern California (KPNC) hospitals between 1 November 2011 and 31 July 2019, whose mothers received prenatal care in KPNC. We excluded infants with congenital anomalies or genetic abnormalities. KPNC is an integrated healthcare system serving over 4.6 million members, representing approximately 40% of the insured population in Northern California. The sociodemographic distribution of the KPNC membership is broadly similar to the Northern California population, though the extremes of the income distribution are under-represented.[24]

Exposure

The primary exposure was any maternal SSRI dispensing by a KPNC pharmacy during late pregnancy, that is, after 20 weeks' gestation.[25] We identified all maternal dispensing for SSRIs (ie, sertraline, fluoxetine, citalopram, escitalopram, paroxetine, dapoxetine, vortioxetine and fluvoxamine) during pregnancy. KPNC pharmacies provide more than 96% of prescription medications to their members.[26] For each prescription, we collected dispensation date, daily dosage and number of pills dispensed. We converted SSRI prescriptions into sertraline equivalent dosage using previously published conversion factors.[27] We categorised SSRI doses into four categories with clinically meaningful cut-offs at 50, 100 and 150 mg/day of sertraline equivalent.

Covariates

We ascertained maternal inpatient and outpatient International Classification of Diseases (ICD) diagnoses of depression and anxiety during pregnancy (online supplemental file 1) from existing KPNC databases.[28] We classified the severity of depression symptoms using each mother's maximal Patient Health Questionnaire–9 (PHQ-9) score as follows: none or mild (0–9), moderate (10–14), moderate to severe (15–19), severe (20–27).[29] We extracted demographic and clinical data from existing databases[30]: birth year; maternal age, self-reported race/ethnicity and parity; state-subsidised insurance, quartile of neighbourhood deprivation index; maternal type 2 diabetes, chronic hypertension and obesity (pre-pregnancy body mass index ≥30); mode of delivery, infant sex, birth weight and gestational age. In KPNC, universal urine drug screening is a component of the prenatal evaluation; we defined a positive pregnancy toxicology screen as the presence of methadone, cocaine, amphetamine or opiates and separately assessed exposure to cannabinoids based on urine screen. Finally, we examined maternal dispensing for non-SSRI antidepressants and antipsychotics at any time during pregnancy (online supplemental file 2).

Outcomes

Delayed neonatal adaptation, the primary composite outcome, was defined as the presence of at least one of the following: 5 min Apgar score ≤5; positive pressure ventilation or intubation during delivery room resuscitation; or admission to the NICU with respiratory distress requiring invasive or non-invasive ventilation (including high-flow nasal cannula ≥2 L/min) during the birth hospitalisation. Secondary outcomes included each individual component of the primary composite outcome and more severe neonatal outcomes: persistent pulmonary hypertension of the newborn (ICD-9 747.83; ICD-10 P29.3 or treatment with nitric oxide), culture-proven neonatal sepsis, HIE (ICD-9 768.5–768.7 or 768.9; ICD-10 P21.0 or P91.6; or diagnosis of HIE based on chart abstraction), seizures (ie, electrographic seizures or focal-clonic events[31]) based on chart review of all infants with a seizure diagnosis (ICD-9 779.0, ICD-10 P90) or who received an antiepileptic medicine before day 3 after birth, treatment with therapeutic hypothermia, length of hospital stay greater than 90th percentile for mode of delivery (57 hours for vaginal delivery; 94 hours for caesarean delivery) and transfer to another hospital for higher level of care.

Statistical analysis

We calculated unadjusted relative risks and 95% CIs for our primary and secondary outcomes, comparing infants exposed and unexposed to SSRIs using X^2. We used multiple logistic regression to evaluate the adjusted association between SSRI exposure and our primary and secondary outcomes. Our final model included clinically relevant covariates, which could not be mediators or colliders, associated with both exposure to SSRI and our primary composite outcome, with an unadjusted p value of <0.10 (online supplemental file 3). Marginal adjusted risk differences and 95% CIs for our primary and secondary outcomes were calculated based on the same multiple logistic regression models.[32] All regression models used robust variance estimates using the clustered sandwich estimator, which accounts for the clustering of births within hospitals. Secondary analyses evaluated the associations between type and doses of SSRI using the same multiple logistic regression model described above. The rates of delayed neonatal adaptation vary by mode of delivery, infant sex and gestational age. In our main analysis, we did not adjust for those variables as they could be in the pathway between SSRI exposure and adverse outcome. However, we performed a stratified sensitivity analysis to assess their differential effect. We further performed two sensitivity analyses: one including each substance use from the toxicology screen as individual covariates and the other one removing maternal mental health diagnoses from the covariate list. Analyses were performed using Stata, V.17 (StataCorp, College Station, Texas, USA).

RESULTS

Of 280 682 infants born at ≥37 weeks' gestation, we excluded 592 with congenital or genetic abnormalities. Among 280 090 infants in the final study cohort, 7573 (2.7%) were exposed to SSRIs in late pregnancy. Maternal characteristics associated with SSRI treatment are described in table 1. Depression or anxiety during pregnancy was reported in 12% of the population, and an additional 5% had a maximum PHQ-9 score ≥10, indicating the presence of depressive symptoms.

Delayed neonatal adaptation occurred in 11.2% of exposed infants and 4.4% of the unexposed (relative risk 2.52 (95% CI 2.36 to 2.70)). After adjustment using multivariable logistic regression (table 2), SSRI exposure remained associated with delayed adaptation (adjusted OR (aOR) 2.14 (95% CI 1.96 to 2.32)). After accounting for SSRI exposure, maternal anxiety remained weakly associated with delayed neonatal adaptation (aOR 1.38 (95% CI 1.29 to 1.48)), but neither a maternal diagnosis of depression nor depression severity scores were associated

Table 1 Maternal characteristics of mothers treated and not treated with selective serotonin reuptake inhibitors (SSRIs) in late pregnancy

	SSRI in late pregnancy			
	Yes (N=7573)		No (N=272 517)	
	N	%	N	%
Demographic characteristics				
Maternal race/ethnicity				
White	4771	63.0	101 006	37.0
Hispanic	1525	20.1	70 677	25.9
Asian/Pacific Islander	456	6.0	68 211	25.0
Black	414	5.5	17 286	6.3
Multiracial or other	331	4.4	11 420	4.2
Missing	76	1.0	3917	1.4
State-subsidised insurance	1225	16.2	26 541	9.7
Neighbourhood deprivation index				
1st tercile (least deprived)	2584	34.1	91 165	33.5
2nd tercile	2726	36.0	90 545	33.3
3rd tercile (most deprived)	2258	29.8	90 568	33.3
Maternal age ≥35 (years)	1911	25.2	55 753	20.5
Nulliparous	2735	36.1	114 953	42.2
Maternal comorbidities				
Anxiety diagnosis during pregnancy	4244	56.0	18 248	6.7
Depression diagnosis during pregnancy	5325	70.3	18 983	7.0
Maximum PHQ-9 score				
0–9	4036	53.3	217 607	79.9
10–14	1339	17.7	16 653	6.1
15–19	963	12.7	4997	1.8
20–27	782	10.3	2053	0.8
Not performed	453	6.0	31 207	11.5
Non-SSRI antidepressant/antipsychotic	621	8.2	1946	0.7
Positive pregnancy toxicology screen*	323	4.3	2359	0.9
Cannabinoid use	797	10.5	13 778	5.1
Obesity (pre-pregnancy BMI ≥30)	2364	31.2	56 209	20.6
Type 2 diabetes	134	1.8	3089	1.1
Gestational diabetes	875	11.6	31 643	11.6
Chronic hypertension	427	5.6	9469	3.5

*Methadone, cocaine, amphetamine or opiates on any toxicology screen during pregnancy.
BMI, body mass index; PHQ-9, Patient Health Questionnaire–9.

with delayed neonatal adaptation. In sensitivity analysis, stratifying by mode of delivery, gestational age and infant sex, exposed infants in all strata had a 3.7–6.6% increased absolute risk of delayed neonatal adaptation compared with unexposed infants (online supplemental file 4). On sensitivity analysis, including each substance used from the toxicology screen as individual covariates or removing maternal mental health diagnoses from the covariate list did not change the results (online supplemental file 5).

Exposure to SSRIs was associated with all individual components of the composite primary outcome (table 3). We did not find a statistically significant association between SSRI exposure and pulmonary hypertension nor treatment with nitric oxide. While there was an association between SSRI exposure and HIE on univariable analysis, this association was not significant after adjusting for confounders (aOR 1.45 (95% CI 0.86 to 2.44)). Similarly, there was an association between SSRI exposure and treatment with therapeutic hypothermia (aOR 1.55 (95% CI 1.00 to 2.38)) of borderline statistical significance. There was no association between SSRI exposure and neonatal seizures (table 3). Neonates exposed to SSRI had longer hospital stays and were more likely to be transferred to a higher level of care facility (aOR 1.44 (95% CI 1.15 to 1.81); table 3).

Types and doses of SSRI prescriptions are described in table 4. Sertraline was the most common SSRI prescribed (70.2% of all infants). While ranges of sertraline equivalent exposure were similar for all SSRI types, the distribution varied among types. There was a dose–response relationship between sertraline equivalent daily dose and delayed neonatal adaptation (test for trend $p<0.001$; table 5). All SSRI types were associated with increased odds of delayed neonatal adaptation. When stratified by dose, all other types of SSRI were associated with increased odds of delayed neonatal adaptation compared with sertraline (table 5). In the subgroup of 865 mothers who discontinued SSRI between 20 and 30 weeks of gestation, the risk of delayed neonatal adaptation was not increased compared with unexposed mothers (OR 0.99 (95% CI 0.68 to 1.44)).

DISCUSSION

In this large population-based cohort with detailed maternal, pregnancy and neonatal information, exposure to SSRIs in

Table 2 Multivariable ORs for delayed neonatal adaptation among 280 090 term infants born in KPNC, 2011–2019

	Adjusted ORs*	95% CI	P value
SSRI exposure	2.14	1.96 to 2.33	<0.001
Maternal race/ethnicity			
White	1.00	Ref	
Hispanic	0.85	0.78 to 0.91	<0.001
Asian/Pacific Islander	0.87	0.77 to 0.99	0.03
Black	1.18	1.07 to 1.29	0.001
Multiracial, other	0.91	0.84 to 0.98	0.01
Missing	1.18	1.03 to 1.35	0.01
State-subsidised insurance	1.13	1.02 to 1.25	0.02
Maternal age ≥35 years old	1.25	1.17 to 1.34	<0.001
Nulliparous	1.98	1.87 to 2.11	<0.001
Anxiety during pregnancy	1.38	1.29 to 1.48	<0.001
Depression during pregnancy	1.00	0.94 to 1.07	0.95
Maximum PHQ-9 score ≥10			
No to mild (0–9)	1.00	Ref	
Moderate (10–14)	1.00	0.95 to 1.05	0.88
Moderate to severe (15–19)	0.91	0.83 to 0.99	0.03
Severe (20–27)	0.90	0.80 to 1.02	0.10
Not performed	1.00	0.91 to 1.11	0.97
Non-SSRI antidepressant/antipsychotic	1.36	1.16 to 1.59	<0.001
Positive pregnancy toxicology screen†	1.43	1.26 to 1.63	<0.001
Cannabinoid use	1.18	1.08 to 1.28	<0.001
Obesity (pre-pregnancy BMI ≥30)	1.33	1.26 to 1.40	<0.001
Type 2 diabetes	1.76	1.53 to 2.02	<0.001
Chronic hypertension	1.38	1.23 to 1.55	<0.001

*The adjusted ORs are derived from a multivariate multiple logistic regression model with robust error variance accounting for the clustering of births within hospitals adjusting for all variables in the table.
†Methadone, cocaine, amphetamine or opiates on any toxicology screen during pregnancy.
BMI, body mass index; KPNC, Kaiser Permanente Northern California; PHQ-9, Patient Health Questionnaire–9; SSRI, selective serotonin reuptake inhibitor.

late pregnancy was associated with a doubling in the odds of delayed neonatal adaptation after adjusting for maternal anxiety and depression. The strength of the association between SSRI exposure and delayed neonatal adaptation was dose and type dependent.

Mothers exposed to SSRIs in our cohort not only had higher rates of mental health diagnoses but higher rates of obesity, diabetes, hypertension and advanced age, which are all risk factors for delayed neonatal adaptation. We also found that maternal anxiety, but not depression, was independently associated with higher odds of delayed neonatal adaptation. The pathophysiology underlying the role of maternal anxiety on neonatal outcomes is unclear and deserves further investigation.

Neonatal adaptation syndrome was first described with fluoxetine exposure in 1996.[33] Its definition varies among studies[4 34] and can include delayed neonatal adaptation, respiratory distress and transient neurological abnormalities such as jitteriness, tremors and irritability.[4 5] In this study, we focused on delayed neonatal adaptation as an increased need for neonatal respiratory support in the first minutes, hours or days after birth. We did not examine transient neurological signs because they do not require intervention and are not reliably documented for all infants. In contrast with some previous studies,[19 20] we did not find an association between SSRI exposure and HIE or seizures. The absence of association between SSRI exposure and seizures is consistent with a recent Swedish study.[21] In contrast, a meta-analysis reported a fivefold increased risk of seizures with SSRI exposure. However, our study used a more stringent seizure definition based on recent guidelines,[31] requiring documentation of electrographic seizures or focal clonic or tonic movements, thus avoiding misclassification of non-epileptic movements as seizures.

There were borderline increased odds of treatment with therapeutic hypothermia. Similarly, a case–control study reported infants treated with therapeutic hypothermia were five times more likely to be exposed to SSRIs.[19] The increased risk of therapeutic hypothermia may be due to the overlap in symptomatology between delayed neonatal adaptation caused by SSRI exposure and mild HIE, leading to treatment with therapeutic hypothermia.[35] While the symptoms infants exposed to SSRIs may exhibit can mirror mild HIE, they are not due to disrupted blood and oxygen supply and may not benefit from therapeutic hypothermia.

There was a trend toward an increased risk of pulmonary hypertension that did not reach statistical significance. After adjusting for other risk factors, more than 3000 infants would have to be exposed to SSRI for one additional case of pulmonary hypertension. Two meta-analyses reported an association between late SSRI exposure and pulmonary hypertension,[4 36] but did not adjust for maternal characteristics. A previous large study[11] that similarly adjusted their analysis for maternal depression and anxiety also found no association. These findings highlight the need to adjust for maternal characteristics when assessing causality.

Adverse neonatal effects from prenatal SSRI exposure must be balanced against the benefits of maternal mental health treatment to both the mother and the infant.[37] Among pregnant individuals, suicide resulting from undertreated mental health disorders

Table 3 Associations between late SSRI exposure and adverse neonatal outcomes

	No SSRI N=272 517		SSRI N=7573		Unadjusted RR*	Adjusted OR†	Risk difference	Number needed to harm‡
	N	%	N	%	RR (95% CI)	OR (95% CI)	% (95% CI)	N (95% CI)
Delayed neonatal adaptation	12 078	4.4	847	11.2	2.52 (2.34 to 2.71)	2.14 (1.96 to 2.33)	4.5 (3.6 to 5.4)	22 (18 to 28)
5 min Apgar ≤5	1215	0.45	105	1.4	3.11 (2.51 to 3.85)	2.40 (1.93 to 2.99)	0.6 (0.4 to 0.9)	160 (116 to 263)
Positive pressure ventilation during neonatal resuscitation	7826	2.9	625	8.2	2.87 (2.62 to 3.15)	2.47 (2.22 to 2.76)	3.9 (3.1 to 4.7)	26 (21 to 32)
Intubation at birth	736	0.27	31	0.41	1.52 (1.03 to 2.22)	1.53 (1.08 to 2.16)	0.1 (0.0 to 0.3)	715 (360 to 10 000)
Admission for respiratory support	6299	2.3	396	5.2	2.26 (2.04 to 2.51)	1.80 (1.65 to 1.95)	1.8 (1.3 to 2.2)	56 (45 to 75)
Admission to neonatal intensive care unit	16 169	5.9	760	10.0	1.69 (1.54 to 1.85)	1.47 (1.33 to 1.62)	2.5 (1.6 to 3.3)	40 (29 to 61)
Mechanical ventilation	506	0.19	32	0.42	2.28 (1.62 to 3.21)	1.90 (1.24 to 2.90)	0.17 (0.02 to 0.31)	580 (320 to 5000)
Persistent pulmonary hypertension	298	0.11	10	0.13	1.21 (0.71 to 2.04)	1.21 (0.66 to 2.22)	0.02 (−0.06 to 0.10)	>1000
Proven neonatal sepsis	70	0.03	3	0.04	1.54 (0.48 to 4.95)	1.44 (0.50 to 4.11)	0.01 (−0.03 to 0.05)	>2000
Hypoxic-ischaemic encephalopathy	446	0.16	20	0.26	1.61 (1.06 to 2.45)	1.45 (0.86 to 2.43)	0.07 (−0.05 to 0.2)	>500
Therapeutic hypothermia	349	0.13	18	0.24	1.86 (1.22 to 2.81)	1.54 (1.00 to 2.36)	0.07 (−0.02 to 0.16)	>625
Seizures	234	0.09	7	0.09	1.08 (0.58 to 1.99)	0.95 (0.47 to 1.92)	0.00 (−0.06 to 0.05)	>2000
Prolonged length of stay§	26 998	9.9	1025	13.5	1.37 (1.28 to 1.45)	1.14 (1.08 to 1.21)	1.2 (0.65 to 1.8)	83 (56 to 155)
Transferred for higher level of care	1174	0.43	63	0.83	1.93 (1.48 to 2.52)	1.44 (1.15 to 1.81)	0.19 (0.00 to 0.38)	>260

*The unadjusted RR is the risk of developing adverse outcome among SSRI-exposed infants compared with the risk in non-exposed infants, calculated using Poisson regression with robust error variance accounting for the clustering of births within hospitals.
†The adjusted ORs are derived from a multivariate multiple logistic regression model with robust error variance accounting for the clustering of births within hospitals adjusting for maternal age, race/ethnicity, state-subsidised insurance, nulliparity; anxiety or depression during pregnancy, maximal PHQ-9 score, non-SSRI antidepressant/antipsychotic, positive pregnancy toxicology screen; chronic hypertension, type 2 diabetes and infant sex.
‡The number needed to harm is valid under the assumption of causality.
§Prolonged length of stay was defined as a length of stay greater than p90 for the mode of delivery (57 hours for vaginal delivery and 94 hours for caesarean section).
PHQ-9, Patient Health Questionnaire–9; RR, relative risk; SSRI, selective serotonin reuptake inhibitor.

is a leading cause of death.[38] Untreated depression and anxiety are associated with low birth weight, prematurity and need for NICU admission.[39] SSRIs are considered an effective treatment for maternal depression and anxiety during pregnancy, although efficacy has not been evaluated with a randomised controlled trial. Assuming causality, treatment of 22 pregnant individuals with SSRIs would result in one additional case of delayed neonatal adaptation, treatment of 40 individuals would incur one additional NICU admission and treatment of more than 500 individuals would result in one additional case of mechanical ventilation, pulmonary hypertension or HIE.

The dose–response relationship between SSRI exposure and delayed neonatal adaptation points toward a causal relationship; however, the mechanism is unclear. Placental transfer of SSRIs is substantial, suggesting a possible direct toxic effect on the fetal lungs and central nervous system.[40] Increased levels of 5-hydroxytryptamine in the fetus could alter respiratory maturation or adaptation to the extrauterine environment, leading to neonatal respiratory distress.[5] However, plasma levels of SSRIs in affected newborns do not correlate with symptom severity.[5 40] In our study, while all SSRI types were associated with delayed adaptation, citalopram, fluoxetine and escitalopram were associated with higher risks than sertraline. When exposure was discontinued before 30 weeks, there was no increased risk of delayed neonatal adaptation, suggesting a time-dependent mechanism. Further studies are needed to understand the mechanism behind this differential safety profile.

Strengths of this study include the large population, high-quality assessment of SSRI exposure and maternal mental health diagnoses, and ability to adjust for confounders. One limitation of our study is that mothers may have received SSRI prescriptions outside of KPNC or may not have taken the dispensed medication; this non-differential misclassification of exposure would bias our results toward the null. Although we adjusted for PHQ-9 scores, some residual confounding by the severity of depression or anxiety may persist. It is unlikely that large-scale studies will have more detailed information regarding depression severity. We did not evaluate the effect of sudden discontinuation versus continuous SSRI exposure after birth via breast milk. While this may affect the timing or duration of neurological symptoms, it would not affect delayed neonatal adaptation at birth. Finally, the study was limited to short-term neonatal outcome of SSRI exposure and it is important to evaluate any long-term neurological sequelae.

Table 4 Dose of sertraline equivalent among each different type of SSRI

	Total (n/%)	<50 mg/day (n/%)	50–<100 mg/day (n/%)	100–<150 mg/day (n/%)	≥150 mg/day (n/%)
Sertraline monotherapy	5161 (68)	1414 (27)	2338 (45)	922 (18)	487 (9)
Fluoxetine monotherapy	982 (13)	593 (60)	295 (30)	66 (7)	28 (3)
Citalopram monotherapy	825 (11)	558 (68)	248 (30)	14 (2)	5 (1)
Escitalopram monotherapy	382 (5)	49 (13)	176 (46)	140 (37)	17 (4)
Combination of SSRI	168 (2)	81 (48)	60 (36)	19 (11)	8 (5)

Monotherapy with other SSRI types (paroxetine, dapoxetine, vortioxetine and fluvoxamine; N=55) was excluded due to small numbers.
SSRI, selective serotonin reuptake inhibitor.

Table 5 Association between SSRI dose and type and delayed neonatal adaptation

	N	Adjusted ORs*	95% CI	P value
SSRI type				
No SSRI	Reference			
Sertraline monotherapy	5161	1.89	1.74 to 2.05	<0.001
Citalopram monotherapy	825	2.29	1.91 to 2.76	<0.001
Fluoxetine monotherapy	982	2.59	2.03 to 3.31	<0.001
Escitalopram monotherapy	382	3.86	3.01 to 4.95	<0.001
Two or more SSRIs	168	2.21	1.30 to 3.75	0.003
SSRI dose				
No SSRI	271 076	Reference		
<50 mg/day sertraline equivalent	2710	1.64	1.46 to 1.85	<0.001
50–99 mg/day sertraline equivalent	3146	2	1.74 to 2.29	<0.001
100–149 mg/day sertraline equivalent	1167	3.01	2.45 to 3.69	<0.001
>150 mg/day sertraline equivalent	550	3.79	2.95 to 4.86	<0.001
SSRI type and dose				
Low dose (<50 mg/day sertraline equivalent)				
Sertraline monotherapy	1.414	Reference		
Citalopram monotherapy	558	1.47	1.05 to 2.07	0.025
Fluoxetine monotherapy	593	1.64	1.10 to 2.46	0.016
Escitalopram monotherapy	49	1.71	0.77 to 3.83	0.19
Two or more SSRIs	81	1.71	0.75 to 3.92	0.20
Medium dose (50–<100 mg/day sertraline equivalent)				
Sertraline monotherapy	2338	Reference		
Citalopram monotherapy	248	1.84	1.21 to 2.81	0.004
Fluoxetine monotherapy	295	1.73	1.20 to 2.50	0.006
Escitalopram monotherapy	176	2.15	1.25 to 3.70	0.003
Two or more SSRIs	60	1.77	0.85 to 3.68	0.12
High-dose treatment† (≥100 mg/day sertraline equivalent)				
Sertraline monotherapy	1409	Reference		
Citalopram monotherapy	19	0.91	0.36 to 2.27	0.83
Fluoxetine monotherapy	94	2.03	1.25 to 3.28	0.004
Escitalopram monotherapy	157	1.98	1.35 to 2.89	<0.001
Two or more SSRIs	27	0.43	0.82 to 2.35	0.33

Mothers on other SSRIs (paroxetine, dapoxetine, vortioxetine and fluvoxamine; N=55) were excluded from the analysis due to small numbers.
*The adjusted ORs are derived from a multivariate multiple logistic regression model with robust error variance accounting for the clustering of births within hospitals adjusting for maternal age, race/ethnicity, state-subsidised insurance, nulliparity; anxiety or depression during pregnancy, maximal PHQ-9 score, non-SSRI antidepressant/antipsychotic, positive pregnancy toxicology screen, cannabinoid use; chronic hypertension, type 2 diabetes and obesity.
†Mothers on the two highest dose categories were combined given low numbers.
PHQ-9, Patient Health Questionnaire–9; SSRI, selective serotonin reuptake inhibitor.

CONCLUSION

In utero exposure to SSRIs during late pregnancy was associated with increased odds of delayed neonatal adaptation. This association was independent of maternal mental health and was dose and type dependent. SSRI exposure was not associated with increased odds of pulmonary hypertension, HIE or seizures. These data may guide parents and physicians in the shared decision-making balancing the benefits and risks of treatment with various doses and types of SSRI during pregnancy. It may also guide paediatricians and neonatologists caring for an increasing number of exposed infants.

Contributors M-CC, YWW, HF and AWS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design—M-CC, LAA, TBN, YWW and MWK. Acquisition, analysis or interpretation of data—M-CC, LAA, AS, HF, TBN, AWS, YWW and MWK. Drafting of the manuscript—M-CC, YWW and MWK. Critical revision of the manuscript for important intellectual content—M-CC, LAA, AS, HF, TBN, AWS, YWW and MWK. Statistical analysis—M-CC, AWS and TBN. Obtained funding—M-CC, YWW and LAA. Administrative, technical or material support—HF. Supervision—MWK, TBN and YWW.

Funding This study was funded by a Thrasher Early Career Award, the UCSF Newborn Brain Research Innovation award, grants R01HD099216 (PI: YWW), R01HD101483 (PI: LAA) and K23HD109684 (PI: M-CC) from the NICHD.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The University of California San Francisco and the Kaiser Foundation Research Institute Institutional Review Boards approved this study (IRB #1045-1276201).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets generated for this study are stored at the KPNC Division of Research. Deidentified data can be provided upon reasonable request to the corresponding author, and with permission from the KPNC Institutional Review Board.

ORCID iDs
Marie-Coralie Cornet http://orcid.org/0000-0001-5233-0800
Michael W Kuzniewicz http://orcid.org/0000-0002-3271-2999

REFERENCES

1 Lee AM, Lam SK, Sze Mun Lau SM, *et al*. Prevalence, course, and risk factors for Antenatal anxiety and depression. *Obstet Gynecol* 2007;110:1102–12.
2 Andrade SE, Reichman ME, Mott K, *et al*. Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering Liveborn infants and other women of child-bearing age within the U.S. *Arch Womens Ment Health* 2016;19:969–77.
3 Molenaar NM, Kamperman AM, Boyce P, *et al*. Guidelines on treatment of perinatal depression with antidepressants: an international review. *Aust N Z J Psychiatry* 2018;52:320–7.
4 Grigoriadis S, VonderPorten EH, Mamisashvili L, *et al*. The effect of Prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. *J Clin Psychiatry* 2013;74:e309–20.
5 Oberlander TF, Misri S, Fitzgerald CE, *et al*. Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. *J Clin Psychiatry* 2004;65:230–7.
6 Malm H, Sourander A, Gissler M, *et al*. Pregnancy complications following Prenatal exposure to SSRIs or maternal psychiatric disorders: results from population-based National register data. *AJP* 2015;172:1224–32.
7 Ross LE, Grigoriadis S, Mamisashvili L, *et al*. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA Psychiatry* 2013;70:436.
8 Bandoli G, Chambers CD, Wells A, *et al*. Prenatal antidepressant use and risk of adverse neonatal outcomes. *Pediatrics* 2020;146.
9 Nörby U, Forsberg L, Wide K, *et al*. Neonatal morbidity after maternal use of antidepressant drugs during pregnancy. *Pediatrics* 2016;138.
10 Ulbrich KA, Zumpf K, Ciolino JD, *et al*. Acute delivery room resuscitation of neonates exposed to selective serotonin reuptake inhibitors. *The Journal of Pediatrics* 2021;232:103–108.
11 Huybrechts KF, Bateman BT, Palmsten K, *et al*. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. *JAMA* 2015;313:2142–51.
12 Masarwa R, Bar-Oz B, Gorelik E, *et al*. Prenatal exposure to selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and risk for persistent pulmonary hypertension of the newborn: a systematic review, meta-analysis, and network meta-analysis. *Am J Obstet Gynecol* 2019;220:51.
13 Marks C, Silvola R, Teal E, *et al*. Comparing newborn outcomes after Prenatal exposure to individual antidepressants: A retrospective cohort study. *Pharmacotherapy* 2021;41:907–14.
14 Levinson-Castiel R, Merlob P, Linder N, *et al*. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. *Arch Pediatr Adolesc Med* 2006;160:173.
15 de Vries NKS, van der Veere CN, Reijneveld SA, *et al*. Early neurological outcome of young infants exposed to selective serotonin reuptake inhibitors during pregnancy: results from the observational SMOK study. *PLoS ONE* 2013;8:e64654.
16 Desaunay P, Dolladille C, Chrétien B, *et al*. Neonatal hypotonia following in utero exposure to antidepressant drugs. *J Pediatr* 2022;245:222–6.
17 Boucher N, Bairam A, Beaulac-Baillargeon L. A new look at the neonate's clinical presentation after in utero exposure to antidepressants in late pregnancy. *J Clin Psychopharmacol* 2008;28:334–9.
18 Forsberg L, Navér L, Gustafsson LL, *et al*. Neonatal adaptation in infants prenatally exposed to antidepressants--clinical monitoring using neonatal abstinence score. *PLoS ONE* 2014;9:e111327.
19 Neo DT, Nuss E, Hacker MR, *et al*. Prenatal selective serotonin reuptake inhibitors and therapeutic hypothermia for suspected hypoxic ischemic encephalopathy. *J Perinatol* 2020;40:640–5.
20 Uguz F. The use of antidepressant medications during pregnancy and the risk of neonatal seizures: A systematic review. *J Clin Psychopharmacol* 2019;39:479–84.
21 Wiggs KK, Sujan AC, Rickert ME, *et al*. Maternal serotonergic antidepressant use in pregnancy and risk of seizures in children. *Neurology* 2022;98:e2329–36.
22 Dowse E, Chan S, Ebert L, *et al*. Impact of perinatal depression and anxiety on birth outcomes: A retrospective data analysis. *Matern Child Health J* 2020;24:718–26.
23 Jarde A, Morais M, Kingston D, *et al*. Neonatal outcomes in women with untreated Antenatal depression compared with women without depression: A systematic review and meta-analysis. *JAMA Psychiatry* 2016;73:826.
24 Davis AC, Voelkel JL, Remmers CL, *et al*. Comparing Kaiser Permanente members to the general population: implications for Generalizability of research. *Perm J* 2023;27:87–98.
25 Chambers CD, Hernandez-Diaz S, Van Marter LJ, *et al*. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354:579–87.
26 Strom BL. Pharmacoepidemiology. 7 March 2006.
27 Hayasaka Y, Purgato M, Magni LR, *et al*. Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. *J Affect Disord* 2015;180:179–84.
28 Young-Wolff KC, Sarovar V, Tucker L-Y, *et al*. Association of depression, anxiety, and trauma with Cannabis use during pregnancy. *JAMA Netw Open* 2020;3:e1921333.
29 Flanagan T, Avalos LA. Perinatal obstetric office depression screening and treatment: implementation in a health care system. *Obstet Gynecol* 2016;127:911–5.
30 Escobar GJ, Fischer A, Kremers R, *et al*. Rapid retrieval of neonatal outcomes data: the Kaiser Permanente neonatal minimum data set. *Qual Manag Health Care* 1997;5:19–33.
31 Ropper AH, Yozawitz E. Neonatal seizures. *N Engl J Med* 2023;388:1692–700.
32 Norton EC, Miller MM, Kleinman LC. Computing adjusted risk ratios and risk differences in STATA. *Stata J* 2013;13:492–509.
33 Chambers CD, Johnson KA, Dick LM, *et al*. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996;335:1010–5.
34 Kautzky A, Slamanig R, Unger A, *et al*. Neonatal outcome and Adaption after in utero exposure to antidepressants: A systematic review and meta-analysis. *Acta Psychiatr Scand* 2022;145:6–28.
35 Chalak L, Latremouille S, Mir I, *et al*. A review of the conundrum of mild hypoxic-ischemic encephalopathy: Current challenges and moving forward. *Early Human Development* 2018;120:88–94.
36 Ng QX, Venkatanarayanan N, Ho CYX, *et al*. Selective serotonin reuptake inhibitors and persistent pulmonary hypertension of the newborn: an update meta-analysis. *J Womens Health* 2019;28:331–8.
37 Hussain-Shamsy N, Somerton S, Stewart DE, *et al*. The development of a patient decision aid to reduce decisional conflict about antidepressant use in pregnancy. *BMC Med Inform Decis Mak* 2022;22.
38 Susanna T, Gyan C, Fanny N, *et al*. Pregnancy-related deaths: data from maternal mortality review committees in 36 US States, 2017–2019. In: *Services UDoHaH*. Atlanta, GA, 2022.
39 Jahan N, Went TR, Sultan W, *et al*. Untreated depression during pregnancy and its effect on pregnancy outcomes: A systematic review. *Cureus* 2021;13.
40 Rampono J, Simmer K, Ilett KF, *et al*. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry* 2009;42:95–100.