Acta Psychiatrica Scandinavica

Received: 4 November 2021 | Accepted: 30 January 2022

DOI: 10.1111/acps.13409

ORIGINAL ARTICLE

Acta Psychiatrica Scandinavica WILEY

Antidepressant use during pregnancy and risk of adverse neonatal outcomes: A comprehensive investigation of previously identified associations

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Funding information
This study is supported by the National Institute of Mental Health (NIMH) (R01MH122869). Dr Liu is also supported by the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 891079. Dr Munk-Olsen is also supported by iPSYCH, the Lundbeck Foundation Initiative for Integrative Psychiatric Research (R155-2014-1724), the Lundbeck Foundation (R313-2019-569), AUFF NOVA (AUFF-E 2016-9-25), and Fabrikant Vilhelm Pedersen og Hustrus Legat. The funders of the study had no role in study design, data analysis, data interpretation, writing, or submission for publication.

[Correction added on 18 March 2022, after first online publication: The first sentence of Methods in the abstract and Table 2 has been corrected.]

Abstract

Objective: Prenatal antidepressant use is widespread. Observational studies have investigated the neonatal effects of prenatal antidepressant exposure with inconclusive results. We aimed to comprehensively investigate the associations between prenatal antidepressant exposure and the most commonly studied adverse neonatal outcomes: preterm birth, birthweight, poor neonatal adaptation, persistent pulmonary hypertension of the neonate (PPHN), neonatal admission and congenital malformations.

Methods: We included 45,590 singletons (born 1997-2015) whose mothers used antidepressants within one year before pregnancy. Children were categorised into two groups: continuation (antidepressant use before and during pregnancy) or discontinuation (antidepressant use before but not during pregnancy). We applied random-effects logistic and linear regressions, adjusting for covariates.

Results: After adjusting for confounders, prenatal antidepressant exposure was associated with a 2.3 day (95% CI −2.9; −2.0) decrease in gestational age and a 51 g (95% CI −62g; −41 g) decrease in birthweight. The continuation group was at increased risk for moderate-to-late preterm birth (32–37 weeks) (aOR = 1.43; 95%CI 1.33; 1.55), moderately low birthweight (1500–2499 g) (aOR = 1.28; 95%CI 1.17; 1.41), postnatal adaptation syndrome (aOR = 2.59; 95%CI 1.87; 3.59) and neonatal admission (aOR = 1.52; 95%CI 1.44; 1.60) compared to the discontinuation group.

Conclusion: Prenatal antidepressant exposure was associated with small decreases in gestational age and birthweight, as well as higher risk for moderate-to-late preterm birth, moderately low birthweight, neonatal admission and postnatal adaptation syndrome. No differences in risk were found for PPHN, or congenital malformations. The causality of the observed associations cannot be established due to the potential for unmeasured residual confounding linked to the underlying disease.

KEYWORDS
antidepressants, low birthweight, neonatal outcomes, perinatal depression, preterm birth

1 | INTRODUCTION

Depression and anxiety during pregnancy and after delivery impact around 12% of new mothers worldwide.[1] Children of individuals who suffered from depression during pregnancy have an increased risk of being born preterm and with low birthweight.[2] Maternal perinatal depression can also lead to behavioural, emotional, cognitive and motor problems in early childhood.[3] Antidepressants are the first-line treatment for depression and anxiety,[4] with many patients using them long-term as maintenance treatment to prevent relapse.[5] Therefore, antidepressant use during pregnancy is widespread, with prevalence estimates ranging between 2% and 13%.[6] Yet, antidepressants cross the placenta and the blood-brain barrier[7] and, out of fear for the potential negative consequences to their child, approximately 50% of pregnant individuals decide to discontinue their antidepressants before or during pregnancy.[8] Numerous observational studies have investigated the effects of prenatal exposure to antidepressants, albeit with inconclusive results. Some studies have found maternal antidepressant use to be associated with increased risks for preterm delivery,[9] low birthweight,[9] poor neonatal adaptation,[10] persistent pulmonary hypertension of the neonate (PPHN)[11] and congenital malformations;[12] while other studies did not find these increased risks or observed only modest effects.[13-15] Several of these studies failed to adjust for important confounders, such as smoking, maternal mental illness or other associated chronic conditions. Furthermore, few sought to assess the effects of antidepressant exposure against exposure to untreated maternal depression, i.e., confounding by indication.[16]

Most research indicates that prenatal antidepressant exposure is associated with preterm birth (<37 weeks gestation) and gestational age at birth.[17] A meta-analysis of 28 studies (N = 3,063,499) found that prenatal antidepressant exposure increases the risk of preterm birth by ~70% (relative risk [RR] = 1.69, 95% CI = 1.52; 1.88).[9] Another meta-analysis of 41 observational studies

Significant Outcomes

- Antidepressant exposure during any point in pregnancy was associated with modest decreases in gestational age of ~2 days and in birthweight of ~51 g.
- Antidepressant exposure during any point in pregnancy was also associated with increased risk for moderate-to-late preterm birth (32–37 weeks), moderately low birthweight (1500–2499 g), postnatal adaptation syndrome and neonatal admission.
- Continuing antidepressant treatment in pregnancy did not increase the risk for the most severe neonatal outcomes, including being born extremely preterm (<28 weeks), very preterm (28–32 weeks), very low birthweight (<1500 g), small for gestational age or with congenital malformations.

Limitations

- Unmeasured confounding, particularly confounding by indication cannot be ruled out. Registers do not contain information on disorder severity, and it is conceivable that individuals who continue antidepressant use throughout one pregnancy have more severe symptoms than in another episode during another pregnancy or compared with individuals who discontinue.
- Prescription data were used to define antidepressant exposure. Some patients may fill prescriptions without actually taking the antidepressants, leading to potential exposure misclassification.
- While our sample size is large, some subgroup analyses are based on a small number of cases.

(N = 5,335,547) suggested that the effects of antidepressants on gestational age may be related to the timing of exposure.[18] Controlling for confounding factors (e.g. maternal age, smoking, alcohol use and previous preterm birth), the authors found that third trimester antidepressant exposure (OR = 1.96; 95% CI = 1.62; 2.38), but not exposure in the first trimester (OR = 1.16; 95% CI = 0.92;1.4), was associated with preterm birth.[18] However, heterogeneity across studies in all three meta-analyses was large, indicating that the variability of the results across the included studies was high. Moreover, the meta-analyses found evidence of possible publication bias, suggesting that studies with negative findings may not have been published.[9] Lastly, most studies compared children exposed to antidepressants in utero with unexposed children, thus failing to properly address confounding by indication.[18]

Evidence for an association between prenatal antidepressant exposure and birthweight remains inconclusive. One meta-analysis of 15 studies (N = 3,001,041) found that prenatal exposure to antidepressants was associated with low birthweight (<2500 g) (RR = 1.44; 95% CI = 1.21; 1.70), although heterogeneity across studies was significant.[9] Another meta-analysis of 20 studies (N = 1,438,994) reported that birthweight was decreased in children prenatally exposed to antidepressants compared with unexposed children (mean difference [MD] = −74 g; 95% CI = −117 g; −31 g).[19] Yet, when children prenatally exposed to antidepressants were compared with children prenatally exposed to maternal depression (six studies, N = 165,268), the mean difference was close to zero (MD = −0.10 g; 95% CI = −0.16 g; −0.03 g), with high precision and little heterogeneity.[19]

Low-strength evidence seems to provide support for an association between exposure to antidepressants during pregnancy and overall occurrence of poor neonatal adaptation (PNA). Although definitions vary, symptoms of PNA include agitation and restlessness, irritability, insomnia, hypoglycaemia, hypothermia, respiratory distress, altered muscle tone, convulsions/seizures and feeding problems. The reported incidence of PNA among infants prenatally exposed to antidepressants ranges from 5% to 85%, with the variability possibly explained by different studies applying different definitions.[20] According to a meta-analysis of eight observational studies (N = 959 infants), PNA is more likely to occur in neonates prenatally exposed to antidepressants than unexposed neonates (OR = 5.07; 95% CI = 3.25; 7.90).[20] A more recent meta-analysis comparing infants prenatally exposed to antidepressants compared with healthy controls (N = 23,231 exposed infants), showed increased risk for convulsions (OR = 3.25; 95% CI = 1.76; 6.02); hypoglycaemia (OR = 1.65; 95% CI = 1.53; 1.78), respiratory problems (OR = 1.96; 95% CI = 1.80; 2.14), temperature dysregulation (OR = 1.75; 95% CI = 1.20; 2.55) and feeding problems (OR = 2.25; 95% CI = 1.08; 4.69).[10] However, few studies in this field sufficiently control for bias, including confounding due to indication, disease-related moderators, socioeconomic status, ethnicity, somatic health or other known risk factors for adverse neonatal outcome.[10]

Multiple studies have found a link between antidepressant use during late pregnancy (i.e. third trimester) and a small absolute increase of persistent pulmonary hypertension of the newborn (PPHN), a potentially fatal condition that occurs in ~2 per 1000 live births in the general population.[21] However, research has yielded conflicting results which may reflect differences in methodology, particularly a failure to address confounding by indication.[11] The most recent meta-analysis of 11 observational studies compared children who were prenatally exposed to antidepressants during any trimester (n = 156,978) with unexposed children (n = 6,923,872).[11] The incidence of PPHN in exposed and unexposed children was 2.9 in 1000 and 1.8 in 1000, respectively. The number needed to harm was 1000, meaning that antidepressants were associated with one additional case of PPHN for every 1000 children prenatally exposed to antidepressants and 1000 unexposed children. The risk of PPHN was greater in the children prenatally exposed to antidepressants than unexposed children (OR = 1.82, 95% CI = 1.31; 2.54). However, heterogeneity across studies was high, and confounding by indication has not yet been addressed.[11]

Prenatal exposure to antidepressants may further be associated with admission to the neonatal intensive care unit (NICU).[22] In a recent meta-analysis, admission to the NICU was analysed in 13 highly heterogeneous studies (n = 22,396 exposed infants). The meta-analysis revealed a higher risk of NICU admission in infants prenatally exposed to antidepressants compared with unexposed infants (OR = 1.74; 95% CI = 1.43; 2.11), as well as to infants born to depressed but untreated mothers (OR = 2.64; 95% CI = 1.58; 4.40).[10]

Most research indicates that antidepressants as a group are not teratogenic.[23-29] However, the risk of congenital malformations in exposed children has been the subject of discussion and controversy.[12] A recent meta-analysis of 29 cohort studies (N = 9,085,954) found that prenatal antidepressant exposure was associated with an increased risk of overall major congenital anomalies (MCAs) (RR = 1.11; 95% CI = 1.03; 1.19) and congenital heart defects (CHD) (RR = 1.24; 95% CI = 1.11; 1.37) compared with the general population. However, when the analysis was restricted to children of women with a psychiatric diagnosis (MCAs: RR = 1.04; 95% CI = 0.95; 1.13; CHD: RR = 1.06; 95% CI = 0.90; 1.26), no significantly increased risk was observed.[12]

In summary, none of the aforementioned associations are supported by convincing evidence, although suggestive evidence exists for some, including for the association with preterm birth. Conflicting findings may be the result of varying study designs, exposure times, and a failure to address confounding factors such as lifestyle factors, socioeconomic factors, and confounding by indication.[14]

1.1 | Aims of the study

The aim of the current prospective population-based register study was to conduct a comprehensive investigation of the associations between prenatal antidepressant exposure and the most commonly investigated adverse neonatal outcomes[30]: gestational age, preterm birth, low birthweight and small for gestational age (SGA), poor neonatal adaptation, persistent pulmonary hypertension of the neonate (PPHN), neonatal admission and congenital malformations, controlling for important confounding factors.

2 | METHODS

2.1 | Study population

We carried out a population-based cohort study using data from the Danish national registers.[31] All residents in Denmark are assigned a unique identification number in the Danish Civil Registration System,[32] which permits accurate linkage of individual-level data. We first identified 1,158,082 liveborn singletons born during 1997–2015 from the Danish National Medical Birth Registry.[33] We excluded 16,248 children who had missing or unrealistic gestational age or birthweight data (gestational age <154 or >315 days; birthweight <300 or >6400 g), and 3319 children with chromosomal abnormalities (the International Classification of Diseases, 10th revision (ICD-10) codes: Q90–Q99). We included a total of 1,138,515 children born to 665,051 mothers (Figure 1). Throughout this paper, we refer to pregnant and birthing individuals as 'mothers' for fluency and unambiguity while acknowledging that not all pregnant and birthing individuals choose this label. The study was approved by the Danish Data Protection Agency. No informed consent is required for purely register-based studies on the basis of encrypted data in accordance with the legislation in Denmark. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human participants/patients were approved by the Danish Data Protection Agency. By Danish law, no informed consent is required for a register-based study using anonymised data.

2.2 | Antidepressant exposure during pregnancy

Information on antidepressant use during pregnancy was retrieved from the Danish National Prescription Registry.[34] This register includes a record of all prescriptions dispensed in Denmark since 1995. For each prescription, it contains anatomical therapeutic chemical (ATC) classification codes, the number of defined daily doses per package, the number of packages dispensed and the dispensing date. The ATC code for selective serotonin reuptake inhibitors (SSRIs) is N06AB; for non-SSRI antidepressants, the ATC codes are N06AA, N06AF, N06AG and N06AX. The start of antidepressant use was indicated by the dispensing date of the first relevant prescription. We defined antidepressant use during pregnancy as at least one prescription dispensed on any date from one month before pregnancy until delivery. The start of pregnancy was ascertained using gestational age. This was primarily based on the first- or second-trimester ultrasound scan; however, when no ultrasound data were available, the first day of the mother's last menstrual period was used.[33] To capture recent episodes, we included antidepressant prescriptions dispensed from one year up to one month before pregnancy. Children were categorised into four mutually exclusive groups according to maternal redemption of an antidepressant prescription from one year to one month before pregnancy (referred to as 'before pregnancy') and/or during pregnancy (Figure 1): (i) unexposed, with no maternal antidepressant use before or during pregnancy; (ii) discontinuation, with use before but not during pregnancy; (iii) continuation, with use both before and during pregnancy and (iv) new user, with use only during pregnancy (Figure 1).

2.3 | Outcomes of interest

Our primary outcomes included extremely preterm birth (gestational age <28 weeks), very preterm birth (28–32 weeks), moderate-to-late preterm birth (32–37 weeks), very low birthweight (<1500 g), moderately low birthweight (1500–2499 g), small for gestational age (i.e. a birthweight below the 10th percentile of birthweight by gestational age and sex), persistent pulmonary hypertension of the neonate (PPHN), neonatal admission, postnatal adaptation syndrome and congenital malformations. We derived data on gestational age, birthweight and sex of the

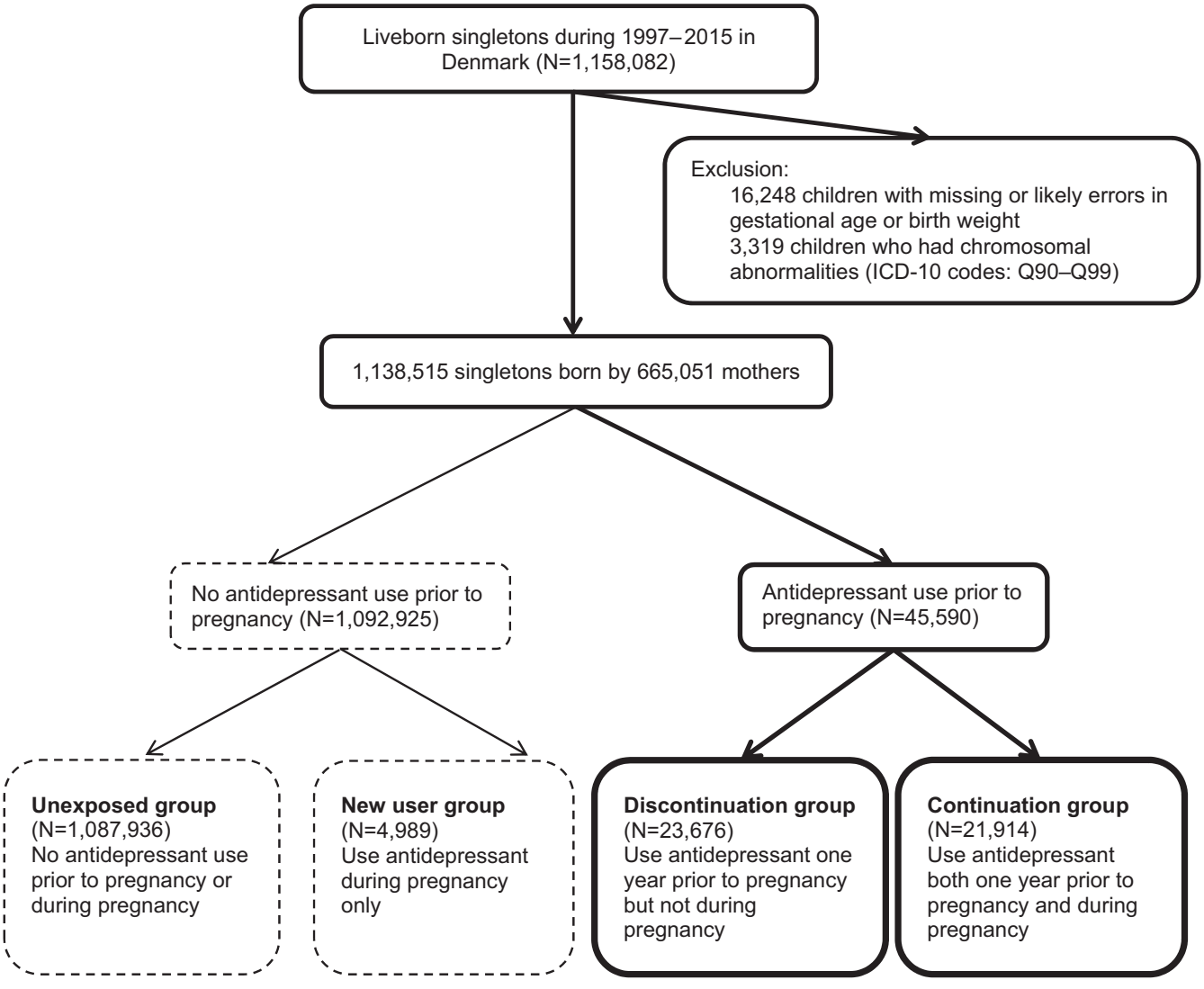

FIGURE 1 Flow chart illustrating the identification of the study population

child from the Danish Medical Birth Registry. Information on postnatal adaptation syndrome, PPHN, neonatal admission and congenital malformations was obtained from the Danish National Patient Registry.[35] The registry contains data on inpatients since 1977; since 1995, outpatient and emergency visits are also included. Children were considered to have postnatal adaptation syndrome if they had an inpatient, outpatient or emergency hospital treatment with an ICD-10 code of P96.1. PPHN was defined as a hospital contact, with ICD-10 codes of P29.3 or I27.0, within seven days of birth. We defined neonatal admission as an inpatient contact within the first 28 days, excluding contacts with the ICD-10 codes Z38 (liveborn infants according to the place of birth and type of delivery) or Z76 (persons encountering health services in other circumstances, mainly healthy person accompanying sick person). Congenital malformations, excluding chromosomal abnormalities, were determined by 1 year of age, including all singular and combined structural defects, syndromes, sequences and associations, such as cardiovascular defects, neural tube defects, hypospadias and epispadias (ICD-10 codes Q00–Q89, excluding minor malformations according to the EUROCAT Guide 1.4) treated in the hospitals.

2.4 | Potential confounders

We considered a broad range of potential confounders related to maternal characteristics in our analyses using directed acyclic graphs (see Appendix S1): psychiatric history at delivery retrieved from the Danish Psychiatric Central Research Register[36] (ICD-8 codes 290–315; ICD-10 codes F00–F99); age at delivery (<25 years, 25–34 years, ≥35 years); primiparity (yes/no); inpatient and outpatient psychiatric treatment from one year before pregnancy until delivery (yes/no); prescriptions for other psychotropic drugs (ATC codes N05 and N06 excluding N06A)

during pregnancy (from one month prior to pregnancy until delivery; yes/no); prescriptions for antiepileptic drugs (ATC code N03) during pregnancy (yes/no); number of non-psychiatric hospital visits during pregnancy (0–1, 2–3 or ≥4); smoking during pregnancy (yes/no); marital status (married or cohabiting, single, divorced, widowed); highest education (mandatory education, above mandatory education) and calendar year of delivery (1997–2000, 2001–05, 2006 or 2011–15). Data on these covariates came from the registers mentioned above and from Statistics Denmark's registers on socioeconomic status.[37]

2.5 | Statistical analysis

Analyses were performed in Stata, version 16.0 (Stata Corp, College Station, TX) and SAS, version 9.4. We used random-effects logistic regression to estimate the odds ratios (ORs) and absolute risk differences of adverse birth outcomes (categorical outcomes), as well as their 95% confidence intervals (CIs) with robust standard error estimation and mother's identity as a cluster variable, adjusting for the above-mentioned covariates.[38,39] We also calculated the attributable fraction of antidepressants as the proportionate increase in the risk of adverse neonatal outcomes among the antidepressant exposure group using the following formula: (p (outcome = 1|expo = 1) – p (outcome = 1|expo = 0))/p (outcome = 1|expo = 1). Random-effects generalised linear regression was employed to estimate the mean difference (β) of birthweight and gestational age (continuous outcomes).[38,39] The comparisons were made between children in the antidepressant continuation group and children in the antidepressant discontinuation group. The rationale for this analysis is that individuals who discontinue antidepressants should be more comparable with individuals who continue antidepressants than individuals who never used antidepressants. This comparison group should control for some of the impact of the underlying psychiatric disorders. Data were missing in 7.0% of the participants for one or more potential confounders. We applied 20 imputations using the Markov Chain Monte Carlo technique for imputing missing values.[40]

To examine whether the associations between antidepressant exposure and adverse birth outcomes depended on the timing of exposure, we divided the exposure window into three groups based on the last menstrual period: (i) first trimester only (one month before pregnancy to 90 days after last menstrual period); (ii) second or third trimester only (91 to 180 days after last menstrual period or 181 days after last menstrual period to childbirth) and (iii) more than one trimester. We considered a child to be exposed to antidepressants during a particular exposure window if the dispensing date fell within the window or if the number of days prescribed overlapped with that window. To study whether the associations varied with different classes of antidepressant, we categorised antidepressant treatment into (i) SSRIs only, (ii) non-SSRIs only and (iii) both SSRIs and non-SSRIs. Types of preterm birth (extremely preterm, very preterm, moderate-tolate preterm and full-term birth), and types of low birthweight (very low birthweight, moderately low birthweight and healthy birthweight) were included as nominal variables where full-term birth and birthweight >2500 g where considered the reference variables, respectively.

3 | RESULTS

Of the 1,138,515 children included in the study, 45,590 children born to mothers who used antidepressants in the year before pregnancy were included in the analyses (4.0% of the total sample). Among them, 21,914 were born to mothers who continued antidepressant treatment during pregnancy (1.9% of the total sample); 75.0% ($n = 16{,}429$) of these mothers used SSRI monotherapy, 16.9% ($n = 3700$) used non-SSRI antidepressant monotherapy and 8.1% ($n = 1785$) used both SSRI and non-SSRI antidepressants. Mothers who continued antidepressants during pregnancy were older, more likely to have a psychiatric history, more likely to have had inpatient- or outpatient-psychiatric treatment, and more likely to redeem other psychotropic and antiepileptic prescriptions during pregnancy. Table 1 lists the psychiatric and demographic characteristics of the study population.

3.1 | Antidepressant exposure at any time during pregnancy

The mean gestational age of children in the continuation and discontinuation group was 274.6 days (SD = 14.0) and 277.3 days (SD = 13.5) respectively. The mean birthweight for the continuation was 3403 g (SD = 589); for the discontinuation group, it was 3468 g (SD = 588). Antidepressant exposure during pregnancy was associated with a decrease in gestational age of 2.3 days (95% CI: −2.9; −2.0) and in birthweight of 51 g (95% CI: −62; −41).

The risks for several adverse birth outcomes were higher in the continuation group than the discontinuation group: adjusted OR (aOR) = 1.43 (95% CI: 1.33; 1.55) for moderate-to-late preterm birth (32–37 weeks); aOR = 1.28 (95% CI: 1.17; 1.41) for moderately low birthweight (1500–2499 g); aOR = 1.52 (95% CI: 1.44; 1.60) for neonatal admission and aOR = 2.59 (95% CI: 1.87; 3.59) for postnatal adaptation syndrome. Continuing

TABLE 1 Characteristics of study population according to maternal antidepressant use before and during pregnancy. Values are numbers (percentages) unless stated otherwise

Characteristics	Antidepressant continuation group ($N = 21,914$)		Antidepressant discontinuation group ($N = 23,676$)	
	n	%	*n*	%
Maternal age at delivery, years				
<25	2939	13.4	4354	18.4
25–34	13,710	62.6	14,841	62.7
≥35	5265	24.0	4481	18.9
Primiparity	9937	45.3	10,812	45.7
Maternal psychiatric history at delivery	11,106	50.7	7910	33.4
Maternal inpatient psychiatric treatment from 1 year before pregnancy to delivery	1124	5.1	697	2.9
Maternal outpatient psychiatric treatment from 1 year before pregnancy to delivery	5728	26.1	3662	15.5
Psychotropic prescriptions during pregnancy	3398	15.5	1352	5.7
Antiepileptic prescriptions during pregnancy	927	4.2	326	1.4
Number of maternal non-psychiatric hospital visits during pregnancy				
0–1	4301	19.6	4749	20.1
2–3	9644	44.0	10,497	44.3
≥4	7969	36.4	8430	35.6
Maternal smoking during pregnancy				
Yes	6186	28.2	6650	28.1
No	14,833	67.7	15,688	66.3
Missing	895	4.1	1338	5.7
Maternal marital status at delivery				
Married or cohabiting	16,854	76.9	18,058	76.3
Single, divorced or widowed	5027	22.9	5555	23.5
Missing	33	0.2	63	0.3
Maternal highest education at delivery				
Mandatory education	6405	29.2	7935	33.5
Above mandatory education	15,064	68.7	15,164	64.1
Missing	445	2.0	577	2.4
Calendar year of delivery				
1997–2000	1237	5.6	2297	9.7
2001–2005	4053	18.5	5370	22.7
2006–2010	8283	37.8	7631	32.2
2011–2015	8341	38.1	8378	35.4
Sex of child				
Male	11,318	51.6	12,163	51.4
Female	10,596	48.4	11,513	48.6

(Continues)

antidepressant treatment in pregnancy did not increase the risk of the neonate being born extremely preterm (<28 weeks), very preterm (28–32 weeks), very low birthweight (<1500 g) or small for gestational age. Continuing antidepressant treatment in pregnancy also did not increase the risk for congenital malformations in the child (Table 2). The most pronounced adjusted absolute risk difference was seen for neonatal admission (6.3%, 95% CI: 6.2%; 6.4%). Antidepressant effectiveness was 22.7%, suggesting that neonatal admissions were 22.7% higher in the antidepressant exposure group than they would have been if these neonates had not been exposed to maternal antidepressants during pregnancy. The predominant reasons for neonatal admission were (i) conditions originating in the perinatal period (66.2%), (ii) medical observation and evaluation for suspected diseases and conditions (14.6%), (iii) symptoms, signs, and abnormal clinical and laboratory findings (4.6%) and (iv) congenital malformations (3.6%).

3.2 | Timing of antidepressant exposure

Exposure to antidepressants in the second or third trimester only was associated with a greater decrease in gestational age than antidepressant exposure in the first trimester only. The risks of other adverse birth outcomes did not differ by timing of exposure. However, children exposed to antidepressants in more than one trimester

TABLE 2 Crude and adjusted odds ratio and adjusted absolute risk difference of adverse birth outcomes among children born to mothers with continuous antidepressant use, compared with mothers with discontinuous antidepressant use

Birth outcomes	Continuation group ($N = 21,914$)[a] Mean (SD)	Discontinuation group ($N = 23,676$)[a] Mean (SD)	Crude analysis β (95% CI)	Adjusted analysis β (95% CI)	aAbsolute risk difference % (95% CI)
Gestational age (days)[b]	274.6 (14.0)	277.3 (13.5)	−2.7 (−2.9; −2.4)	−2.3 (−2.6; −2.0)	–
Birthweight (g)[b]	3,402.7 (589.4)	3,468.1 (587.6)	−66.1 (−76.9; −55.3)	−51.3 (−62.2; −40.5)	–
	***n* (%)**	***n* (%)**	OR **(95% CI)**	OR **(95% CI)**	**% (95% CI)**
Extremely preterm (<28 weeks)	56 (0.3)	63 (0.3)	0.99 (0.69; 1.41)	0.90 (0.61; 1.32)	0 (−0.1; 0.1)
Very preterm (28–32 weeks)	174 (0.8)	163 (0.7)	1.18 (0.96; 1.47)	1.18 (0.95; 1.47)	0.1 (−0.1; 0.3)
Moderate-to-late preterm (32–37 weeks)	1,673 (7.6)	1,251 (5.3)	1.48 (1.38; 1.60)	1.43 (1.33; 1.55)	2.1 (1.7; 2.6)
Very low birthweight (<1500 g)	178 (0.8)	192 (0.8)	1.01 (0.83; 1.24)	1.00 (0.81; 1.24)	0 (−0.2; 0.2)
Moderately low birthweight (1500–2499 g)	1,105 (5.0)	315 (3.9)	1.32 (1.21; 1.44)	1.28 (1.17; 1.41)	1.0 (0.7; 1.4)
Small for gestational age	2,500 (11.4)	2,675 (11.3)	1.04 (0.96; 1.13)	0.99 (0.91; 1.08)	−0.1 (−0.1; 0)
Postnatal adaptation syndrome	228 (1.0)	67 (0.3)	3.92 (2.89; 5.31)	2.59 (1.87; 3.59)	0.5 (0.4; 0.6)
Persistent pulmonary hypertension of the neonate	59 (0.3)	44 (0.2)	1.45 (0.98; 2.14)	1.26 (0.86; 1.87)	0.1 (0.0; 0.1)
Neonatal admission	5,907 (27.0)	4,523 (19.1)	1.67 (1.58; 1.76)	1.52 (1.44; 1.60)	6.3 (6.2; 6.4)
Congenital malformations	970 (4.4)	990 (4.2)	1.06 (0.97; 1.17)	1.03 (0.94; 1.14)	0.1 (−0.3; 0.5)

Note: OR, odds ratio; aAbsolute risk difference, adjusted absolute risk difference; Adjusted for maternal age at delivery, primiparity, maternal psychiatric history at delivery, maternal inpatient and outpatient treatment from 1 year before pregnancy to delivery, dispensing of other psychotropic prescriptions during pregnancy, dispensing of antiepileptic prescriptions during pregnancy, number of maternal non-psychiatric hospital visits during pregnancy, smoking during pregnancy, marital status at delivery, highest education at delivery, and calendar year of delivery.

[a]Values are numbers of cases (percentages) unless stated otherwise.

[b]Crude and adjusted mean differences, β-coefficients were estimated for gestational age and birth weight as continuous variables.

had the highest risk of very preterm birth, moderate-to-late preterm birth, low birthweight, neonatal admission and postnatal adaptation syndrome (Table 3).

3.3 | Type of antidepressant exposure

Children exposed to non-SSRI monotherapy had a greater decrease in gestational age and birthweight than children exposed to SSRI monotherapy. Similarly, higher risks of preterm birth, low birthweight and neonatal admission were observed for children born to mothers treated with non-SSRI monotherapy than SSRI monotherapy, with the largest difference seen for preterm birth. The aOR for very preterm birth and moderate-to-late preterm birth was 0.98 (95% CI: 0.66; 1.45) and 0.98 (95% CI: 0.84; 1.13) for SSRI monotherapy, respectively, versus 1.86 (95% CI: 1.33; 2.59) and 2.08 (95% CI: 1.84; 2.35) for non-SSRI monotherapy respectively. The risk for postnatal adaptation syndrome did not differ by type of antidepressant (Table 4).

4 | DISCUSSION

In this comprehensive prospective population-based study of the effects of intrauterine antidepressant exposure on the most commonly investigated neonatal outcomes,[30] we found that antidepressant exposure during any point in pregnancy was associated with modest decreases in gestational age (2.3 days) and birthweight (51 g). In support of previously suggestive evidence,[30] we further demonstrated higher risk for moderate-to-late preterm birth

TABLE 3 Adjusted odds ratio and absolute risk difference of adverse birth outcomes among children of mothers with continued antidepressant use, compared with mothers with discontinued antidepressant use by the timing of antidepressant exposure

	1st trimester only ($N = 4362$)[a]		2nd or 3rd trimester only ($N = 597$)[a]		More than one trimester ($N = 16,955$)	
Birth outcomes	**aOR β (95% CI)**	**aAbsolute risk difference % (95% CI)**	**aOR β (95% CI)**	**aAbsolute risk difference % (95% CI)**	**aOR β (95% CI)**	**aAbsolute risk difference % (95% CI)**
Gestational age (days)[b]	−0.1 (−0.6; −0.3)	–	−1.4 (−2.5; −0.4)	–	−3.0 (−3.3; −2.7)	–
Birth weight (g)[b]	5.1 (−13.2; 23.3)	–	−29.9 (−74.8; 15.0)	–	−70.3 (−82.2; −58.5)	–
Extremely preterm (<28 weeks)[c]	1.10 (0.60; 2.03)	0.0 (−0.2; 0.2)	–	–	0.82 (0.54; 1.24)	−0.1 (−0.2; 0.1)
Very preterm (28–32 weeks)[c]	0.98 (0.66; 1.45)	0.0 (−0.3; 0.3)	–	–	1.28 (1.02; 1.62)	0.2 (0.0; 0.3)
Moderate-to-late preterm (32–37 weeks)	0.98 (0.84; 1.13)	−0.1 (−0.8; 0.6)	1.19 (0.85; 1.66)	0.9 (−1.0; 2.9)	1.59 (1.46; 1.72)	2.8 (2.3; 3.3)
Very low birthweight (<1500 g)	0.93 (0.64;1.36)	−0.1 (−0.3; 0.2)	1.06 (0.43; 2.59)	0.0 (−0.7; 0.8)	1.02 (0.80; 1.29)	0.0 (−0.2; 0.2)
Low birthweight (1500–2499 g)	1.02 (0.86; 1.20)	0.1 (−0.6; 0.7)	1.12 (0.75; 1.68)	0.5 (−1.2; 2.1)	1.37 (1.24; 1.52)	1.4 (0.9; 1.8)
Small for gestational age	0.98 (0.85; 1.12)	−0.2 (−0.7; 0.3)	0.97 (0.68; 1.38)	−0.2 (−2.3; 1.9)	1.00 (0.91; 1.09)	0.0 (−0.1; 0.1)
Postnatal adaptation syndrome[c]	1.47 (0.88; 2.46)	0.2 (−0.1; 0.3)	–	–	2.99 (2.12; 4.22)	0.6 (0.5; 0.7)
Neonatal admission	0.99 (0.90; 1.09)	0.0 (−0.8; 0.7)	1.28 (1.03; 1.59)	3.6 (0.8; 6.3)	1.71 (1.61; 1.81)	8.3 (8.1; 8.5)
Congenital malformations	1.10 (0.94; 1.30)	−0.1 (−0.3; 0.2)	0.84 (0.54; 1.32)	−0.2 (−0.7; 0.3)	1.02 (0.92; 1.13)	0.1 (−0.1; 0.2)

Note: Children born to mothers who discontinued antidepressants were the comparison group. The numbers of cases of persistent pulmonary hypertension in neonates were too small to estimate trimester-specific effect.

OR, odds ratio; aOR, adjusted odds ratio; aAbsolute risk difference, adjusted absolute risk difference; Adjusted for maternal age at delivery, primiparity, maternal psychiatric history at delivery, maternal inpatient and outpatient treatment from 1 year before pregnancy to delivery, dispensing of other psychotropic prescriptions during pregnancy, dispensing of antiepileptic prescriptions during pregnancy, number of maternal non-psychiatric hospital visits during pregnancy, smoking during pregnancy, marital status at delivery, highest education at delivery and calendar year of delivery.

[a]1st trimester only—one month before pregnancy to 90 days after last menstrual period); 2nd or 3rd trimester only—91–180 days after last menstrual period or 181 days after last menstrual period to childbirth.

[b]Adjusted mean differences, β-coefficients were estimated for gestational age and birth weight as continuous variables.

[c]Less than 5 outcomes and thus cannot provide an accurate estimate for 2nd or 3rd exposure only.

TABLE 4 Adjusted odds ratio and absolute risk difference of adverse birth outcomes among children of mothers with continued antidepressant use, compared with mothers with discontinued antidepressant use by type of antidepressant exposure

	SSRIs only ($N = 16{,}429$)[a]		Non-SSRIs only ($N = 3700$)[a]		SSRIs and non-SSRIs ($N = 1785$)[a]	
Birth outcomes	**aOR β (95% CI)**	**aAbsolute risk difference % (95% CI)**	**aOR β (95% CI)**	**aAbsolute risk difference % (95% CI)**	**aOR β (95% CI)**	**aAbsolute risk difference % (95% CI)**
Gestational age (days)[b]	−1.8 (−2.1; −1.6)	–	−4.0 (−4.6; −3.5)	–	−3.3 (−4.0; −2.6)	–
Birthweight (g)[b]	−45.8 (57.3; −34.2)	–	−67.6 (−89.1; −46.0)	–	−73.8 (−101.7; −45.8)	–
Extremely preterm (<28 weeks)	0.82 (0.53; 1.25)	−0.1 (−0.2; 0.1)	1.31 (0.71; 2.42)	0.1 (−0.1; 0.3)	0.90 (0.35; 2.32)	−0.1 (−0.3; 0.2)
Very preterm (28–32 weeks)	1.05 (0.82; 1.34)	0.0 (−0.2; 0.2)	1.86 (1.33; 2.59)	0.5 (0.1; 0.9)	1.18 (0.68; 2.02)	0.1 (−0.3; 0.5)
Moderate-to-late preterm (32–37 weeks)	1.28 (1.18; 1.39)	1.4 (0.9; 1.9)	2.08 (1.84; 2.35)	5.0 (4.0; 6.0)	1.66 (1.39; 1.98)	3.2 (1.9; 4.5)
Very low birthweight (<1500 g)	0.95 (0.75; 1.20)	−0.1 (−0.2; 0.1)	1.27 (0.89; 1.80)	0.2 (−0.2; 0.5)	0.98 (0.57; 1.68)	0.0 (−0.5; 0.4)
Low birthweight (1500–2499 g)	1.20 (1.08; 1.32)	0.7 (0.3; 1.1)	1.61 (1.39; 1.87)	2.2 (1.4; 3.0)	1.40 (1.13; 1.74)	1.5 (0.4; 2.5)
Small for gestational age	0.99 (0.91; 1.08)	−0.1 (−0.1; 0.0)	0.97 (0.80; 1.13)	−0.2 (−0.8; 0.4)	1.04 (0.85; 1.28)	0.3 (−0.8; 1.3)
Postnatal adaptation syndrome	2.51 (1.79; 3.50)	0.5 (0.3;0.6)	3.05 (1.91; 4.87)	0.6 (0.4; 0.8)	2.48 (1.49; 4.13)	0.5 (0.2; 0.7)
Persistent pulmonary hypertension of the neonate	1.16 (0.75; 1.79)	0.0 (−0.1; 0.1)	1.57 (0.86; 2.88)	0.1 (−0.1; 0.3)	1.57 (0.72; 3.42)	0.1 (−0.1; 0.3)
Neonatal admission	1.43 (1.35; 1.51)	5.3 (5.1; 5.4)	1.85 (1.68; 2.03)	9.7 (8.7; 10.6)	1.79 (1.57; 2.03)	9.0 (7.5; 10.5)
Congenital malformations	1.01 (0.91; 1.12)	0.0 (−0.4; 0.4)	1.13 (0.95; 1.34)	0.5 (−0.2; 1.2)	1.10 (0.86; 1.40)	0.4 (−0.6; 1.4)

Note: Children born to mothers who discontinued antidepressants were the comparison group.

OR, odds ratio; aOR, adjusted odds ratio; aAbsolute risk difference, adjusted absolute risk difference; Adjusted for maternal age at delivery, primiparity, maternal psychiatric history at delivery, maternal inpatient and outpatient treatment from 1 year before pregnancy to delivery, dispensing of other psychotropic prescriptions during pregnancy, dispensing of antiepileptic prescriptions during pregnancy, number of maternal non-psychiatric hospital visits during pregnancy, smoking during pregnancy, marital status at delivery, highest education at delivery and calendar year of delivery.

[a]SSRIs only—Children born to mothers who used selective serotonin reuptake inhibitors during pregnancy. Non-SSRIs —Children born to mothers who used non-selective serotonin reuptake inhibitors during pregnancy. SSRIs and non-SSRIs—Children born to mothers who used both SSRIs and non-SSRIs during pregnancy, which could be due to switching or polytherapy.

[b]Adjusted mean differences, β-coefficients were estimated for gestational age and birth weight as continuous variables.

(32–37 weeks), moderately low birthweight (1500–2499 g), postnatal adaptation syndrome and neonatal admission. Continuing antidepressant treatment in pregnancy did not increase the risk for the most severe neonatal outcomes, including being born extremely preterm (<28 weeks), very preterm (28–32 weeks), very low birthweight (<1500 g), small for gestational age or with congenital malformations.

We suggest that the observed associations may be attributable to the severity of the underlying maternal disorders rather than intrauterine effects of the medication. Although the present register-based study does not have information on the severity of the underlying maternal disorder, analyses of timing and type of antidepressant exposure provide some insight into severity of the disorder. This idea is based on the assumptions that (i) pregnant individuals with severe symptoms are more likely to continue treatment throughout pregnancy compared with individuals with milder forms of depression and/or anxiety who may decide to discontinue antidepressant use upon learning of their pregnancy[41]; and (ii) since SSRIs are the most commonly prescribed antidepressants, treatment with non-SSRI monotherapy may be associated with drug switching due to persistent symptoms and limited or no treatment response,[42] and thus greater severity of the disorder. We found that children exposed to antidepressants in more than one trimester had the highest risk of very preterm birth (28–32 weeks), moderate-to-late preterm birth (32–37 weeks), low birthweight (1500–2499 g), neonatal admission and postnatal adaptation syndrome. Moreover, children exposed to non-SSRI monotherapy had a greater decrease in gestational age and birthweight than children exposed to SSRI monotherapy.

4.1 | Strengths and limitations of study

We examined the association between prenatal exposure to antidepressants and neonatal outcomes in a large population-based sample using a random effects model. Comparing prenatally antidepressant-exposed individuals with individuals born to mothers who discontinued antidepressants before pregnancy may not completely address confounding by indication. Yet, applying a random effects model allowed us to estimate the marginal effect of antidepressant exposure in the entire population while accounting for family-level effects. This model may provide more accurate estimates of the effects of antidepressant exposure than previous work. Moreover, ascertainment and recall biases were reduced by the independent and prospective collection of exposure and outcome data in the Danish registries. Lastly, this study investigated a comprehensive list of the most commonly investigated birth and neonatal outcomes.[30]

The following limitations must be considered. First, to define antidepressant exposure, we used prescription data. Some patients may fill prescriptions without actually taking the antidepressants, leading to potential exposure misclassification. However, this is a limitation present in all observational pharmaco-epidemiological studies. Antidepressant treatment compliance during pregnancy is high in Denmark; so, the extent of misclassification is likely to be small.[43] Second, unmeasured confounding cannot be ruled out, as in all observational studies. Third, it is currently unclear how generalisable our findings are to populations that differ from the Danish population, for example with regard to cultural diversity or genetic makeup. Fourth, although our sample size is large, some subgroup analyses are based on a small number of cases. Fifth, potential mediators, such as psychotropic and antiepileptic prescriptions, may be misclassified as covariates. However, here, we used the presence of these prescriptions as proxies for comorbid conditions, as is common in pharmaco-epidemiological research.[44,45] Moreover, we may be underestimating the effect of second and third trimester exposure on preterm birth because of immortal time bias, i.e., the error in estimating the association between the exposure and the outcome that results from the exclusion of time intervals.[46] However, it is important to note that 20,259 (94.7%) of children in our study were exposed to antidepressants in the first trimester. Therefore, the influence of immortal time bias is likely minimal in this study. Lastly, registers do not contain information on disorder severity[47] and it is conceivable that individuals who continue antidepressant use throughout one pregnancy have more severe symptoms in that pregnancy than during another pregnancy or compared with individuals who discontinue.[41] Although we aimed to limit the effects of the underlying confounding by indication (by comparing individuals who discontinue antidepressant to individuals who used antidepressants throughout pregnancy and controlling for important psychiatric confounders, e.g., psychiatric history, inpatient and outpatient psychiatric treatment, prescriptions for other psychotropic drugs), confounding by severity may still be present.

In conclusion, this large prospective population-based register study investigating a comprehensive list of the most commonly studied neonatal outcomes associated with prenatal exposure to antidepressants provides evidence for an association between prenatal antidepressant use and small decreases in gestational age and birthweight, as well as higher risk for moderate-to-late preterm birth, moderately low birthweight, neonatal admission and postnatal adaptation syndrome. The causality of the observed associations is far from established due to the probability of unmeasured residual confounding linked to the underlying

disease. Nonetheless, the potential risks related to antidepressant use during pregnancy should be explained to antidepressant-treated individuals who wish to conceive or who discover their pregnancy to allow an informed decision. Individuals may then weigh up the risks and benefits for themselves in tandem with their treating physician.

CONFLICT OF INTEREST

All authors declare that support for the submitted work as described below; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTIONS

ASR, NCM, NMM, EA, VB, TM-O, and XL conceived and designed the study. ASR drafted the manuscript. XL had full access to the data, analysed the data, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors interpreted the data and revised the manuscript critically.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13409.

DATA AVAILABILITY STATEMENT

Data are not publicly available.

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How to cite this article: Rommel A-S, Momen NC, Molenaar NM, et al. Antidepressant use during pregnancy and risk of adverse neonatal outcomes: A comprehensive investigation of previously identified associations. Acta Psychiatr Scand. 2022;00:1–13. doi:10.1111/acps.13409