Journal of Affective Disorders 339 (2023) 502–510

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Antidepressant continuation and adherence in pregnancy, and risk of antenatal hospitalization for unipolar major depressive and/or anxiety disorders

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ARTICLE INFO

Keywords:
Antidepressant
Maternal mental health
Pregnancy
Adherence
Unipolar depressive disorder
Anxiety

ABSTRACT

Background: Knowledge about the effectiveness of antidepressants in pregnancy is limited. We aimed to evaluate the association of antidepressant continuation in pregnancy and adherence with the risk of antenatal hospitalization for depression/anxiety.

Methods: In a population-based study based on the healthcare databases of the Lombardy region, Italy (2010–2020), we included 17,033 live-birth pregnancies within 16,091 women with antidepressant use before pregnancy. Antidepressant exposure was classified as continued in pregnancy versus discontinued proximal to pregnancy. Outcome measure was antenatal hospitalization for depression/anxiety. Propensity score matching analysis was performed to control for measured confounding. Stratification by pre-pregnancy antidepressant adherence based on the proportion of days covered (PDC) with antidepressants served to address confounding by disease severity. We applied 60 days lag-time for antidepressant exposure to minimize the risk of protopathic bias.

Results: There were 362 (2.1 %) antenatal hospitalizations for depression/anxiety. Among the matched pairs, the cumulative incidence was 3.5 (continued antidepressant) versus 2.1 (discontinued antidepressant) per 1000 person-months, yielding a hazard ratio (HR) of 1.76 (95 % confidence interval (CI): 1.34–2.33)). The HR declined to the null (1.02, 95 % CI: 0.62–1.69) in the stratified analysis of pregnancies with moderate-high adherence pre-pregnancy. Moderate-high adherence in pregnancy was associated with 85 % greater risk of the antenatal outcome, but the HR decreased with the 60 days lag-time (HR: 1.40, 95 % CI: 0.79–2.50).

Limitations: Lack of information regarding antidepressant dosage.

Conclusion: We found no difference in risk for antenatal hospitalization for depression/anxiety with antidepressant continuation or higher adherence in pregnancy, relative to discontinuation or lower adherence.

1. Background

Major depressive and anxiety disorders are common perinatal psychiatric illnesses, and they often coexist (Falah-Hassani et al., 2017). These disorders increase the risk of a spectrum of negative outcomes in the offspring, and pose debilitating consequences for mothers and their children (Suri et al., 2014). In moderate to severe cases, antidepressant treatment may be required. Up to 10 % of women in the US and 1–3 % in Europe fill at least one prescription for antidepressant medication during pregnancy (Molenaar et al., 2020). Pregnancy, however, remains a major driver for antidepressant discontinuation, dosage modification and/or poor adherence (Lupattelli et al., 2015; Petersen et al., 2011).

The decision-making about antidepressants in pregnancy involves weighing the possible risk of in-utero drug exposure to the child against the benefit to the woman; for the latter, however, the evidence is limited and unclear (Bayrampour et al., 2020). A recent population-based study (Liu et al., 2022) found that antidepressant discontinuation during pregnancy, but not before, was associated with a 25 % increased risk for

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https://doi.org/10.1016/j.jad.2023.07.066
Received 18 January 2023; Received in revised form 18 June 2023; Accepted 14 July 2023
Available online 16 July 2023

any psychiatric admission, relative to continuation throughout pregnancy. This risk was more modest than previously reported in clinical settings for relapse of major depression specifically (Cohen, 2006). However, another study (Swanson et al., 2015) reported a higher risk of hospitalization for depression with antidepressant continuation in early pregnancy relative to discontinuation, highlighting the critical issue of confounding by maternal disease severity.

In a population of pregnancies with antidepressant dispensations in the year pre-pregnancy, we sought to determine the association between antidepressant *continuation* in pregnancy and risk for antenatal hospitalization for unipolar major depressive and/or anxiety disorders relative to *discontinuation* proximal to pregnancy. To better understand this association by the extent of treatment, we compared the above maternal outcome between pregnancies with moderate-high versus low antidepressant adherence. We assessed antenatal hospitalization for unipolar major depressive and/or anxiety disorders as proxy outcome of more severe maternal mental health status.

2. Methods

2.1. Setting

Data were retrieved from the healthcare utilization databases of Lombardy, a region of Italy that accounts for about 16 % (almost ten million) of its population. Italy has a universal health care system covered by the National Health Service (NHS). In Lombardy, an automated system of databases associated with NHS was established since 1997 to collect a variety of information, including outpatient and inpatient clinical diagnosis at public or private hospitals, filled drug prescriptions in community pharmacies, specialist visits, and diagnostic exams. A specific automated system concerning outpatient specialist mental healthcare collects data from the regional Department of Mental Health accredited by the NHS. Finally, a database reporting the Certificates of Delivery Assistance (CeDAP) is consistently managed in all Italian regions. CEDAP provides detailed information on the mother's socioeconomic status, as well as medical information on pregnancy, childbirth, and child presentation at delivery. The unique personal identification code allows linkage across all databases within each region for all beneficiaries of the NHS, including pregnancy-child dyads (Cantarutti et al., 2017). To preserve privacy, each identification code

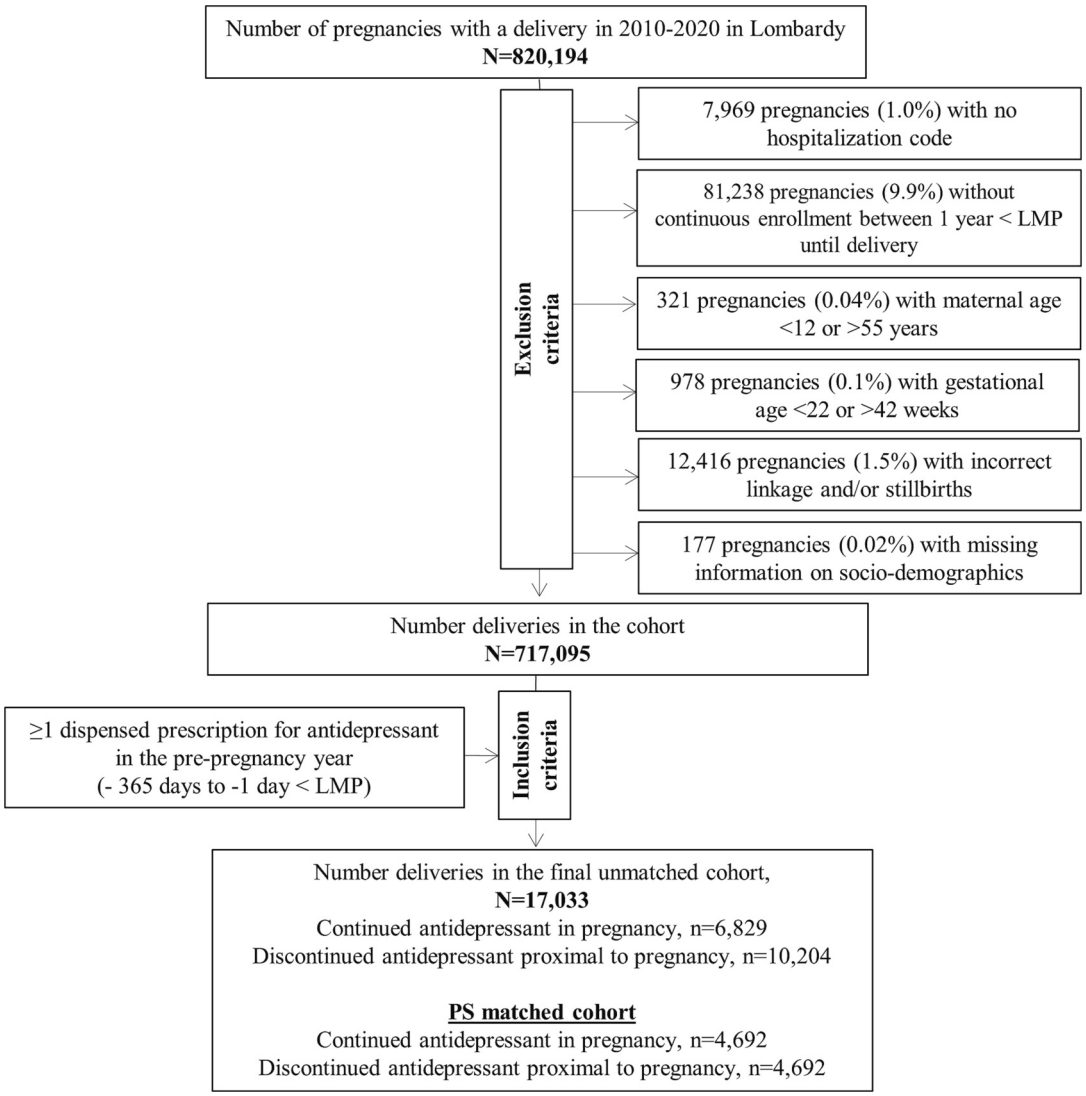

Fig. 1. Flowchart of exclusion ad inclusion criteria to achieve the final cohort.
Abbreviations: LMP = last menstrual period; PS = propensity score.

was automatically de-identified, the inverse process being allowed only to the Regional Health Authority on request from judicial authorities.

2.2. Cohort selection

Using the CeDAP database, we identified all live-birth pregnancies in Lombardy between 2010 and 2020 among women who were beneficiaries of NHS and resident in Lombardy, had age 12–55 years at delivery, and had 22 to 42 weeks of gestation, based on the date of the last menstrual period (LMP) ascertained via maternal report or ultrasound. Additional exclusion criteria are shown in Fig. 1. We further limited the cohort to pregnancies with at least one antidepressant prescription filled in the pre-pregnancy year (365 days < LMP). Because individuals can migrate between regions in Italy, we required that all pregnancies had continuous coverage in the databases from at least one year before LMP through delivery.

2.3. Antidepressant exposure

The drug prescription database provided information on the type and date of dispensed antidepressant prescriptions. Drugs are classified using Anatomical Therapeutic Chemical (ATC) Classification System as selective serotonin reuptake inhibitors (SSRIs, ATC code N06AB), serotonin-norepinephrine reuptake inhibitors (SNRIs, ATC codes N06AX16, N06AX17, N06AX21, N06AX23), and other antidepressants (ATC N06A except SSRI/SNRI). Among the pregnancies with at least one antidepressant dispensed in the year pre-pregnancy, we defined the following groups: (i) *continued* antidepressant in pregnancy, i.e. with ≥1 antidepressant dispensation between LMP and delivery, or in the 30 days window prior to LMP provided that the number of defined daily doses (DDDs) dispensed overlapped with LMP date, assuming intake of 1 DDD per day; (ii) *discontinued* antidepressant proximal to pregnancy, i.e. with ≥1 antidepressant dispensations before LMP but not during pregnancy.

Because the *continued* antidepressant group included pregnancies with different degrees of treatment length and a varying number of prescription fills, we additionally defined (i) moderate-high antidepressant adherence, i.e., having a proportion of days covered (PDC) by antidepressant treatment >0.60; and (ii) low adherence, defined as PDC ≤ 0.60 (Adhikari et al., 2019). This exposure definition served to better address the role of continuity of antidepressant treatment in pregnancy. The PDC was calculated based on days of gestational length for each pregnancy and expressed the fraction of days covered by antidepressant day supply (assuming intake of 1 DDD/day) before the outcome (Martin et al., 2009). A PDC of 0.60 was used as the cut-off value to reflect the real-world degree of adherence (Adhikari et al., 2019). Because a PDC of 0.80 is often considered as a cut-off value for high adherence (Martin et al., 2009), we also compared pregnancies having high antidepressant adherence (>0.80) to those with moderate-low (≤0.80).

2.4. Outcome

Our outcome was any hospitalization with a recorded diagnosis of unipolar major depressive and/or anxiety disorders from LMP to delivery (see ICD-9 codes in eTable 1). We examined these two disorders because anxiety is an important symptom in perinatal women with severe illness (Putnam et al., 2017). As done in prior studies, we choose the severe event of hospitalization as a proxy outcome of more severe mental health status (Liu et al., 2022; Swanson et al., 2015). Because there is substantial heterogeneity in depression symptoms severity and clinical manifestations depending on the timing of onset (pregnancy vs. postpartum) (Putnam et al., 2017), our outcome was specific to the pregnancy period.

2.5. Maternal covariates

We considered a set of confounders measured in the year pre-pregnancy, including (i) history of psychiatric (e.g., depression, anxiety, bipolar disorder, schizophrenia, substance dependence, sleep disorder) and other conditions (e.g., diabetes, hypertension, epilepsy), based on inpatient and outpatient specialist diagnostic codes; (ii) filled prescriptions of benzodiazepines, antipsychotics, antiepileptic, and non-steroidal anti-inflammatory drugs; and (iii) use of healthcare services (i.e., hospitalization for any reason) and the number of all filled prescriptions (excluding antidepressants) as a proxy of access to medical care. Additional confounders measured at LMP included age, nationality, marital status, parity, employment, educational attainment, and previous miscarriage. All factors were ascertained in CeDAP, hospital discharge registry, or the drug prescription database (see eTable 2 for diagnostic and ATC codes).

2.6. Statistical analysis

An Intention-to-Treat (ITT) approach was used in the main analysis. We fitted extended Cox proportional hazard models to estimate the unadjusted and adjusted hazard ratio (HR) and its 95 % confidence interval (CI) for the examined associations. Antidepressant was modelled as a time-dependent exposure (cf. eFig. 1), which allows a re-definition of exposure status during the follow-up. This results in separate observational records for exposed pregnancies. For instance, a pregnancy is considered exposed only from the period following the actual date of antidepressant fill, and as unexposed from the LMP date and up to the time of actual antidepressant filling or outcome onset (i.e., the end of follow-up time). Adjusted HRs were obtained using a time-dependent propensity score (PS) matching procedure (Zhang et al., 2020). First, we estimated for each pregnancy the probability of *continued* antidepressants using Cox regression, given the set of confounders. Second, pregnancies with a *continued* and *discontinued* antidepressant were 1:1 matched on their PS (±0.1) and LMP (±2 days) using the nearest neighbour and sequential matching algorithm (Austin, 2014). Pairs in the continuing and discontinuing groups accumulated person-time of follow-up from the index date (i.e., the exposure date for continuers) until the outcome of interest or delivery, whichever came first. The distribution of maternal covariates by exposure status was compared before and after the PS matching; balance was considered satisfactory when the standardized mean difference was <0.1 (Austin, 2014). To make the *continued* and *discontinued* more comparable in terms of antidepressant treatment history pre-pregnancy after the PS matching, we stratified our analyses by low (PDC ≤ 0.60) and moderate-high (PDC > 0.60) antidepressant adherence in the year pre-pregnancy.

2.7. Lag-time analysis

Antidepressants may be resumed as a result of unmeasured psychiatric symptom worsening in women before any hospitalization is detected (Arfè and Corrao, 2016); this could produce a paradoxical positive exposure-outcome association. To minimize this risk of protopathic bias, we considered current antidepressant dispensation with lag-times of 60 days preceding the outcome (Tamim et al., 2007). We chose 60 days based on prior work and the pharmacological properties of antidepressants (Yonkers et al., 2011). As the lag-time precludes the possibility of observing antidepressant exposure in women who experienced the outcome early (i.e., within a period shorter than the investigated lag-time), analyses were restricted to pregnancies with a sufficient available time window.

2.8. Adherence analysis

Adjusted HRs were obtained from a 1:1 PS matching procedure (Austin, 2018); logistic regression was used to estimate the probability

of having a moderate-high or high adherence in pregnancy versus low or moderate-low, as the exposure was as time-fixed. Then, a 1:1 match on their PS ± 0.1 and LMP ± 2 days using the nearest neighbour matching algorithm without replacement was adopted (Austin, 2018). Pairs in the moderate-high or high adherence and comparator groups accumulated person-time of follow-up from the LMP until the outcome of interest or delivery, whichever came first. Finally, Cox regression was fit to estimate adjusted HRs.

2.9. Sensitivity and sub-group analysis

To limit the risk of exposure misclassification, we conducted an as-treated (AS) analysis censoring the follow-up of the matching pairs when antidepressant treatment was resumed in those pregnancies previously categorized as discontinuers (eFig. 1). Finally, we investigated associations by specific antidepressant classes (i.e., SSRI and SNRI), and refined the outcome definition to hospitalization for unipolar major

Table 1
Baseline characteristics of the final cohort by antidepressant treatment status in pregnancy in the unadjusted and matched analysis. Data are number (%) unless stated otherwise.

Characteristics	Unadjusted			Matched[†]		
	Continued antidepressants	*Discontinued* antidepressants	*S.M.D.* in %	*Continued* antidepressants	*Discontinued* antidepressants	*S.M.D.* in %
	(N = 6829)	(N = 10,204)		(N = 4692)	(N = 4692)	
Maternal comorbidity and health factors in the year prior to pregnancy[§]						
Pre-pregnancy antidepressant PDC ≥ 60 %[¥]	2527 (37.0)	694 (6.8)	0.78	1726 (36.8)	758 (16.2)	0.48
Depression and/or Anxiety	649 (9.5)	604 (5.9)	0.13	400 (8.5)	283 (6.0)	0.1
Hypertension	17 (0.3)	13 (0.1)	0.03	1 (0.02)	4 (0.09)	−0.03
Diabetes	26 (0.4)	13 (0.1)	0.05	0 (0)	2 (0.04)	−0.03
Obesity or overweight	17 (0.3)	25 (0.3)	0	11 (0.2)	9 (0.2)	0
Dyslipidemia	3 (0)	2 (0)	0.01	–	–	–
Migraine/headache	29 (0.4)	56 (0.6)	−0.02	17 (0.4)	21 (0.4)	0
Sleep disorder	1 (0)	1 (0)	0	0 (0)	1 (0.02)	0.06
Preeclampsia	5 (0.1)	6 (0.1)	0	4 (0.1)	3 (0.1)	0
Epilepsy	6 (0.1)	7 (0.1)	0.01	2 (0.0.04)	3 (0.0.06)	0
Bipolar disorder	19 (0.3)	10 (0.1)	0.04	2 (0.04)	2 (0.04)	0
Personality disorder	78 (1.1)	64 (0.6)	0.05	19 (0.4)	18 (0.4)	0
Neuropathic, non-neuropathic, and other pains	56 (0.8)	97 (1.0)	−0.01	35 (0.8)	43 (0.9)	−0.01
Other psychiatric disorders	34 (0.5)	37 (0.4)	0.02	15 (0.3)	14 (0.3)	0
Psychosis	6 (0.1)	10 (0.1)	0	2 (0.04)	1 (0.02)	0.01
Schizophrenia	6 (0.1)	1 (0)	0.04	–	–	–
Adjustment disorder	6 (0.1)	9 (0.1)	0	1 (0.02)	1 (0.02)	0
Substance dependence	39 (0.6)	43 (0.4)	0.02	14 (0.3)	10 (0.2)	0.02
Pregnancy information[∫]						
Prior miscarriages	1914 (28.0)	2953 (28.9)	−0.02	1282 (27.3)	1290 (27)	0
Multiple births	87 (1.3)	180 (1.8)	−0.04	45 (1)	54 (1.1)	−0.01
Primiparity	3180 (46.6)	4973 (48.7)	−0.04	2198 (46.9)	2185 (46.6)	0
Maternal sociodemographic[∫]						
Age in years, mean (SD)	34 ± 5.2	33 ± 5.3	0.18	33.8 ± 4.7	33.8 ± 4.8	0
Foreign nationality	802 (11.7)	1892 (18.5)	−0.19	407 (8.7)	397 (8.5)	0
Unmarried	2786 (40.8)	4012 (39.3)	0.03	1848 (39.4)	1873 (39.9)	−0.01
Unemployed	2185 (32.0)	3387 (33.2)	−0.03	1369 (29.2)	1365 (29)	0
Educational attainment						
Low	2075 (30.4)	3371 (33.0)	−0.06	1385 (29.5)	1344 (28.6)	0.02
Intermediate	3130 (45.8)	4604 (45.1)	0.01	2173 (46.3)	2189 (46.7)	0
High	1624 (23.8)	2229 (21.8)	0.05	1134 (24.2)	1159 (24.7)	−0.01
Other medication in the year pre-pregnancy[§,*]						
Benzodiazepines	65 (1.0)	44 (0.4)	0.06	13 (0.3)	12 (0.3)	0
Antipsychotics	392 (5.7)	299 (2.9)	0.14	76 (1.6)	81 (1.7)	0
Antiepileptic	509 (7.5)	523 (5.1)	0.1	199 (4)	192 (4.1)	0.01
NSAIDs	558 (8.2)	973 (9.5)	−0.05	379 (8)	356 (7.6)	0.04
Healthcare utilization in the year pre-pregnancy[§]						
Hospitalization, for any reason	1275 (18.7)	1858 (18.2)	0.01	798 (17)	768 (16.4)	0.02
No. of distinct prescription drugs in pregnancy, excluding antidepressants						
None	1378 (20.2)	2167 (21.2)	−0.03	1005 (21.4)	1076 (22.9)	−0.03
1	1894 (27.7)	2768 (27.1)	0.01	1364 (29.1)	1337 (28.5)	0.03
≥2	3557 (52.1)	5269 (51.6)	0.01	2323 (49.5)	2279 (48.5)	0.06

Abbreviations: S.M.D. = Standardize Mean Difference; NSAID = non-steroidal anti-inflammatory drugs.

[†] Time-dependent propensity score (PS) matching. The PS was estimated by Cox proportional hazard regression model, regressing time-to-exposure on time-fixed covariates.

[§] Maternal covariates, concomitant psychotropic and analgesic medication, and healthcare utilization variables were measured in the one year before LMP.

[¥] The Pre-pregnancy antidepressant PDC was not included as a covariate in the PS calculation.

[*] Antipsychotics include medications with ATC code N05A, whereas antiepileptics include N03A with exclusion of clonazepam.

[∫] Data related to the current pregnancy (multiple births and parity). Data related to prior pregnancies (prior miscarriages).

depressive disorders or anxiety disorders only. All analyses were also stratified according to the pre-pregnancy antidepressant adherence. Because women with history of hospitalization for major depressive or anxiety disorders may be a high-risk patient group for readmission during pregnancy, we stratified our association measures by history of hospitalization for unipolar major depressive and/or anxiety disorders in the five years prior to LMP. We replicated the analysis including only one pregnancy per woman.

All analyses were performed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, North Carolina).

3. Results

The study included 17,033 pregnancies within 16,091 women with antidepressant fills in the pre-pregnancy year. Of these, 6829 (40.1 %) *continued* antidepressant during pregnancy, mainly SSRIs; few pregnancies were on polytherapy (eTable 3). A substantial number of pregnancies (3689/6829: 54.0 %) in the *continued* group were on antidepressant treatment only until the first trimester of pregnancy (eTable 4). After PS-matching, the cohort included 4692 pairs. Table 1 shows maternal baseline characteristics by antidepressant *continuation*

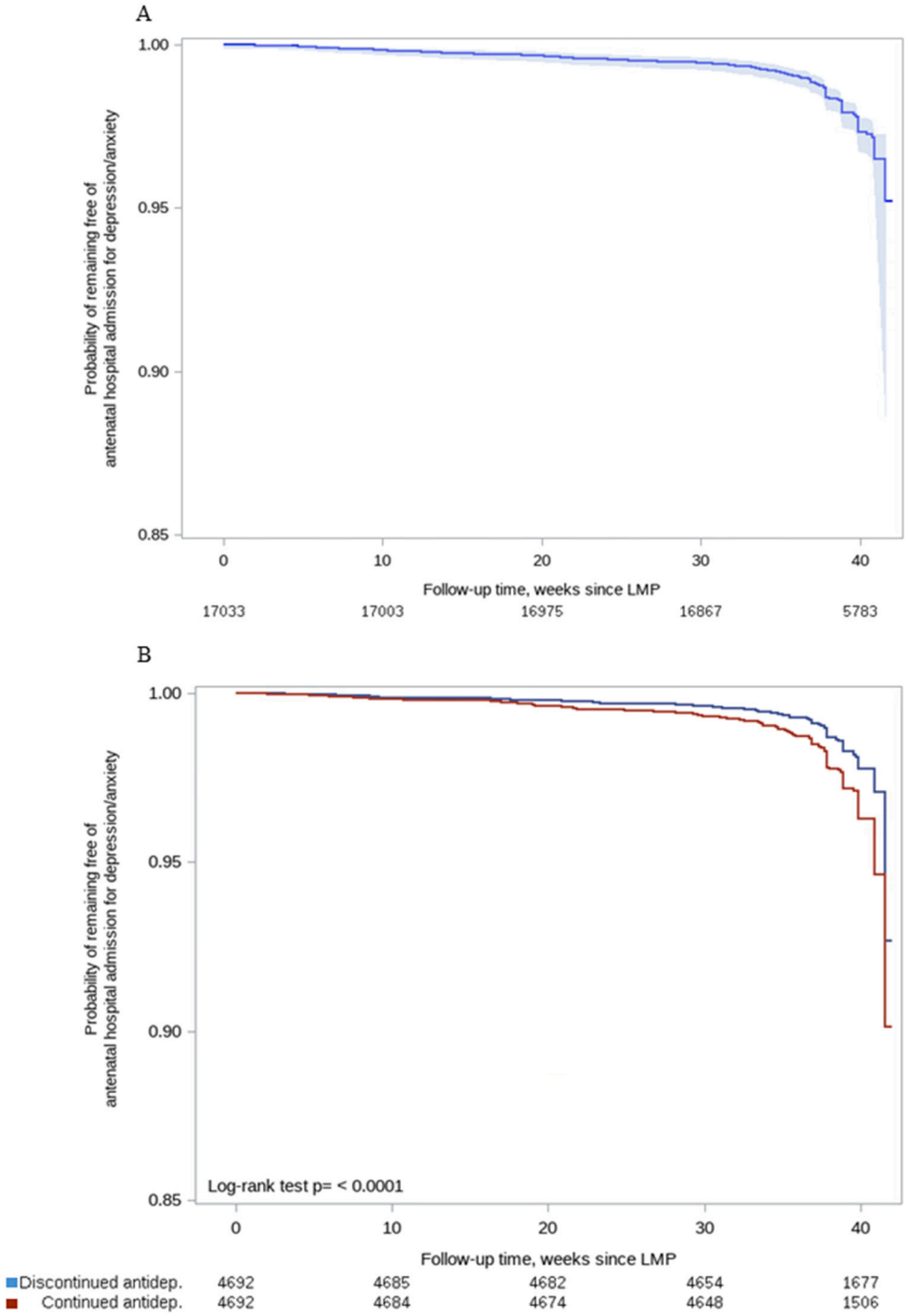

Fig. 2. (Panel A) Unadjusted survival probability of remaining free of antenatal hospitalization for unipolar major depressive and/or anxiety disorders; (Panel B) adjusted survival probability of remaining free of antenatal hospitalization for unipolar major depressive and/or anxiety disorders by antidepressant exposure in the PS-matched cohort.

and *discontinuation*, in the unadjusted and PS-matched cohort. There was satisfactory balance in the distribution of covariates after applying the PS-matching, except for moderate-high antidepressant adherence pre-pregnancy; this remained 36.8 % in the *continued* group and 16.2 % in the *discontinued* group.

There were 362 (2.1 %) antenatal hospitalizations for unipolar major depressive and/or anxiety disorders, where of 10 % were given in psychiatric wards, 87 % in gynecology/obstetric wards, and the remaining 3 % in other wards. The majority of hospitalizations were for both disorders concurrently (266/362, 73.5 %) and occurred in late pregnancy. Fig. 2 shows the survival probability of remaining free of this antenatal outcome overall (panel A) and by exposure status in the PS-matched cohort (panel B). Among the matched pairs, the adjusted cumulative incidence of the maternal outcome was 3.5 versus 2.1 per 1000 person-months in the *continued* and *discontinued* groups, respectively.

Fig. 3 shows the unadjusted and adjusted HRs with 95 % CI for the main, sub-group, and sensitivity analyses. In the PS-matched ITT analysis, the HR was 1.76 (95 % CI: 1.33–2.34) with antidepressant *continuation*, relative to *discontinuation* proximal to pregnancy. In the stratified analysis among pregnancies with moderate-high antidepressant adherence pre-pregnancy, the HR decreased to the null (HR: 1.02, 95 % CI: 0.62–1.69) for any antidepressant as well as for SSRI exposure specifically. When refining the outcome definition to hospitalization for unipolar major depressive disorders, the HR was 1.71 (95 % CI: 1.22–2.38) with antidepressant *continuation*, relative to *discontinuation* proximal to pregnancy, and decreased to 1.10 (95 % CI: 0.63–1.90) among pregnancies with moderate-high antidepressant adherence pre-pregnancy (Fig. 3). When we considered only anxiety as outcome of interest, the HR was 2.13 (95 % CI: 0.96–4.70) with antidepressant *continuation*. The risk is driven by the association found in women with low antidepressant adherence pre-pregnancy (HR: 3.48; 95 % CI: 1.24–9.75); however, we did not find any association in those women with moderate-high antidepressant adherence pre-pregnancy (Fig. 3).

Of the 6829 pregnancies with *continued* antidepressant, 1528 (22.4 %) had a moderate-high antidepressant adherence. Of these, 999 (65.4 %) had a moderate-high adherence also pre-pregnancy (eTable 5). In the 1485 PS-matched pairs, the adjusted HR for the maternal outcome was 1.85 (95 % CI: 1.28–2.67) with moderate-high adherence relative to low (Table 2), and decreased to 1.40 in the lag-time analysis.

Results of the analysis restricted to one pregnancy per woman (data not shown) did not deviate from the main results. The adjusted HR for antidepressant *continuation* relative to *discontinuation* proximal to pregnancy was 2.09 (95 % CI: 0.68–6.41) among women with history of hospitalization for depression/anxiety in the five years prior to LMP, and 1.71 (95 % CI: 1.28–2.28) among women with no such history. In the lag-time analysis, the HR was 1.73 (95 % CI: 0.47–6.40) and 1.73 (95 % CI: 1.26–2.38), respectively in the two strata.

4. Discussion

In this population-based study, the risk of antenatal hospitalization for unipolar major depressive and/or anxiety disorders was similar among women who *continued* antidepressant in pregnancy compared to those who *discontinued* proximal to pregnancy. In absolute terms, the risk remained low in both groups. This null association was evident in the stratified analysis where both the *continued* and *discontinued* group had moderate-high antidepressant adherence pre-pregnancy, and specifically for SSRIs. The stratification approach made the exposure groups more comparable in terms of antidepressant treatment history before pregnancy, and possibly reduced confounding by psychiatric illness severity at baseline. It is important to note that we only examined a severe and specific mental health outcome, and whether this could be improved by antidepressant treatment in pregnancy. Assessing less severe mental health outcomes using healthcare utilization databases alone remains challenging (Swanson et al., 2015). Given the known risks of confounding by indication and mental illness severity, and limitations with use of healthcare utilization data, we cannot rule out that the lack of benefit of antidepressant treatment on maternal mental health outcomes could be explained by systematic biases. The effectiveness of antidepressant treatment on the broader spectrum of psychiatric disorders, clinical depressive symptoms or other patient-reported outcomes during the entire perinatal period, remains a topic of research.

Few and inconsistent findings exist in relation to the effectiveness of antidepressant treatment in pregnancy, and different timings of discontinuation (before or during pregnancy) have been examined (Bayrampour et al., 2020; Berard et al., 2019; Liu et al., 2022; Yonkers et al., 2011). When comparing *continued* antidepressant versus *discontinuation* proximal to pregnancy, the magnitude of our observed risk for antenatal hospitalization for unipolar major depressive and/or anxiety disorders was smaller than what previously reported for a publicly insured US population (Swanson et al., 2015). Women discontinuing antidepressants before pregnancy are a heterogeneous group in terms of pregnancy planning, comorbidity, and not least psychiatric illness severity (Trinh et al., 2022). Our point estimate in fact decreased to the null in those pregnancies with moderate-high antidepressant adherence pre-pregnancy, which is likely less prone to confounding and in line with

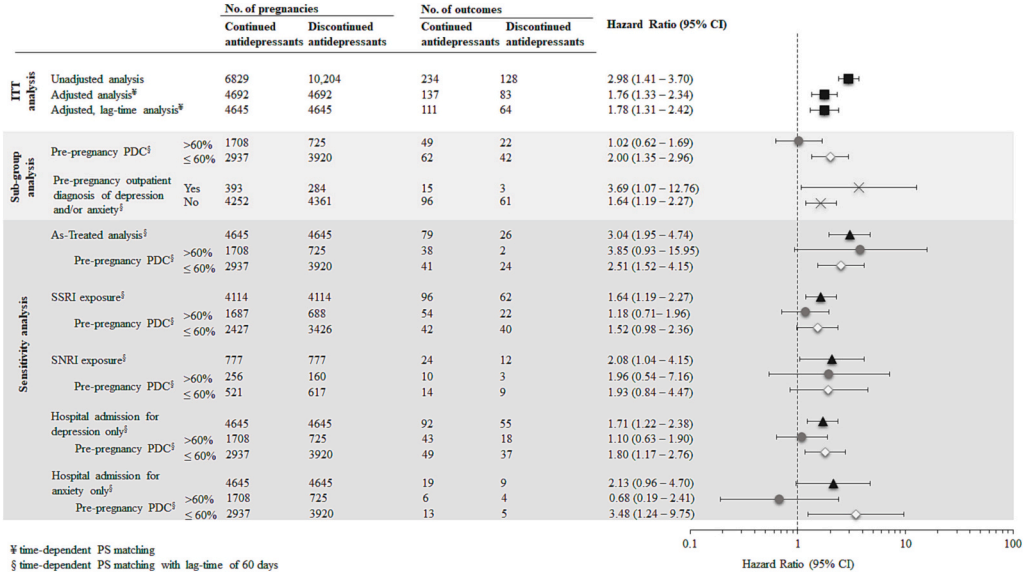

Fig. 3. Association between *continued* antidepressant in pregnancy and antenatal hospitalization for unipolar major depressive and/or anxiety disorders in main, sub-group, and sensitivity analyses.
Abbreviations: PDC = proportion of days covered; PS = propensity score; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin–norepinephrine reuptake inhibitors; ITT = Intention-to-Treat.

Table 2
Association between moderate-high antidepressant adherence in pregnancy (PDC > 60 % or 80 %) and antenatal hospitalization for unipolar major depressive and/or anxiety disorders.

	No. of pregnancies		No. of outcomes		Hazard ratio	(95 % CI)
	Moderate-high adherence, PDC > 60 %	Low adherence, PDC ≤ 60 %	Moderate-high adherence, PDC > 60 %	Low adherence, PDC ≤ 60 %		
Unadjusted	1528	5110	79	153	1.45	(1.12–1.87)
Adjusted analysis[§]	1485	1485	77	46	1.85	(1.28–2.67)
Adjusted analysis, lag-time 60 days[§]	724	724	26	21	1.40	(0.79–2.50)

	High adherence, PDC > 80 %	Low adherence, PDC ≤ 80 %	High adherence, PDC > 80 %	Low adherence, PDC ≤ 80 %	Hazard ratio	(95 % CI)
Unadjusted	800	5839	49	184	1.44	(1.11–1.86)
Adjusted analysis[§]	797	797	48	19	2.85	(1.67–4.86)
Adjusted analysis, lag-time 60 days[§]	334	334	10	5	2.21	(0.75–6.48)

Abbreviations: PDC = proportion of days covered.
[§] Time-fixed propensity score (PS) matching.

two other studies (Swanson et al., 2015; Yonkers et al., 2011). Our results remained consistent when we examined the distinct risks for antenatal hospitalization for unipolar major depressive disorders or anxiety disorders.

Among the pregnancies with *continued* antidepressant use, we did not observe a link between moderate-high adherence and reduced risk for the examined maternal outcome. The reduction of our effect estimate in the 60 days lag-time analysis however underlines the issue of protopathic bias in observational drug effectiveness research (Tamim et al., 2007). Using the PDC as a measure of adherence in pregnancy might be too approximate, as the dispensed antidepressant day supply fails to capture information on possible dosage adjustments over the course of gestation. Berard et al. reported that women who did not modify the antidepressant dosage during pregnancy had greater depressive symptoms in late pregnancy than women who did not use antidepressants (Berard et al., 2019). It is possible that the interplay between hormonal changes and serotonin availability, and the increased antidepressant metabolism, make this medication less effective in pregnant women (Schoretsanitis et al., 2020). Inadequate antidepressant dose-adjustment or woman-initiated dose reductions will inevitably have poor or no benefit on maternal outcomes.

The decision-making about antidepressant treatment in pregnancy is complex for both women and clinicians. Intrauterine exposure to antidepressants does not substantially increase the risk of congenital anomalies and negative developmental outcomes in offspring, albeit a moderate risk for poor neonatal adaptation and persistent pulmonary hypertension of the new-born cannot be excluded (Spigset and Nordeng, 2016). Our findings add to the limited evidence about the effectiveness of antidepressants in pregnancy, and underline the need of further research determining the effects of antidepressant dose adjustment or initiation in pregnancy on the broader spectrum of psychiatric severity and clinical symptom typology.

4.1. Strengths and limitations

The study is population-based and of large sample size, thereby sufficiently powered to appreciate the association of interest. We minimized the risk of protopathic bias, applied more advanced methods to control for measured confounding, and considered antidepressants as time-dependent exposure. To better understand the risk of exposure misclassification, we conducted an AS analysis, and used PDC as a measure of adherence. We also conducted multiple sub-analysis to assess the effectiveness of individual antidepressant classes. Our outcome measure was specific to major depressive/anxiety disorders as well as to unipolar depression or anxiety alone, and specific to the antenatal period. To make the exposure groups more comparable in terms of antidepressant treatment history pre-pregnancy and address residual confounding by psychiatric illness severity after PS matching, we stratified our analysis by maternal prepregnancy adherence level and psychiatric admission history.

Several limitations need mentioning. Our exclusion criteria limit generalizability of our findings to teen pregnancies, those with <22 gestational weeks and stillbirths. Residual and unmeasured confounding by alcohol abuse, smoking habit, illicit drugs, maternal psychiatric history, and disease severity before pregnancy as well as at the time of antidepressant continuation or discontinuation, cannot be ruled out. However, as women with more severe symptoms likely have a higher baseline risk of relapse, this source of bias may underestimate the protective effect of the antidepressant. The study lacked information on antidepressant dosage and could not estimate the effectiveness of antidepressants on psychiatric outcomes less severe than hospitalization. Our data also did not cover diagnosis in primary care setting whereas most patients with mental illnesses are treated and followed-up with general practitioners. Our main outcome measure included hospitalization for both unipolar depression and anxiety disorders, which may have different evolutionary trajectories during pregnancy; however, the results for the individual disorders alone remained consistent with those of the main analysis. The majority of hospitalisations for unipolar depression and/or anxiety disorders were in gynecology/obstetric wards, only 10 % in psychiatric wards; however, in the Italian healthcare system, the specialist obstetric unit follows up closely pregnant women. Our sample was small when examining effect estimates for antidepressant adherence, and no stratified analysis by pre-pregnancy PDC could be done. Because we assumed that drug dispensing corresponded to drug consumption, exposure misclassification is possible. Our definition of *continued* antidepressants in pregnancy was heterogeneous, as women filling single or multiple antidepressant prescriptions would be grouped together. To overcome this limitation, we further employed PDC as a measure of antidepressant treatment coverage in pregnancy and compared pregnancies with different degrees of treatment adherence. We excluded pregnancies with missing data on sociodemographics; however, the proportion was 1 % at the highest.

5. Conclusions

In this population-based study in Lombardy region, Italy, there was no difference in risk for antenatal hospitalization for unipolar major depressive and/or anxiety disorders between women who *continued* antidepressants in pregnancy compared to those who *discontinued* this treatment proximal to pregnancy after considering multiple sources of

confounding and biases. The risk of this maternal outcome did not differ by levels of antidepressant adherence in pregnancy. Our findings are limited by the possibility that women with more severe psychiatric illness and thereby most in need of antidepressant treatment are the ones who continued treatment and were more adherent. We cannot preclude a possible benefit of antidepressant continuation in pregnancy on other psychiatric dimensions throughout the perinatal period, as well as on less severe outcomes than hospitalization. Additional studies addressing maternal psychiatric outcomes following the necessary antidepressant dose-adjustment during pregnancy are necessary to better aid clinical practice.

Ethics

According to the rules from the Italian Medicines Agency (available at: http://www.agenziafarmaco.gov.it/sites/default/files/det_20marzo2008.pdf), retrospective studies without direct contact with patients do not need written consent to process personal data when they are used for research aims.

CRediT authorship contribution statement

Conception of study: A.L and A.C.
Data access and approval: A.C.
Design of study: A.L, G.C, F.R, N.T, A.C.
Data management: C.G., F.R.
Data analysis: C.G., F.R.
Drafting of the manuscript: A.L and A.C.
Revising of the manuscript: G.C, C.G, F.R, N.T.
Final approval of the version to be published: all authors.

Funding

This project, Nhung Trinh and Angela Lupattelli, are supported by the Norwegian Research Council (NRC, grant no. 288696). The project was also funded by a grant from the Italian Ministry of the Education, University and Research: (i) 'Fondo d'Ateneo per la Ricerca' portion, year 2020 (grant number 2020-ATE-0541). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of competing interest

The authors have no conflict of interest to declare. We affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of any organization or company.

Data availability

Data may be obtained from a third party and are not publicly available.

Acknowledgments

We thank Simone Vigod, Xiaoqin Liu and Trine Munk-Olsen for providing critical feedback on this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.07.066.

References

Adhikari, K., Patten, S.B., Lee, S., Metcalfe, A., 2019. Adherence to and persistence with antidepressant medication during pregnancy: does it differ by the class of antidepressant medication prescribed? Can. J. Psychiatr. 64, 199–208. https://doi.org/10.1177/0706743718802809.

Arfè, A., Corrao, G., 2016. The lag-time approach improved drug-outcome association estimates in presence of protopathic bias. J. Clin. Epidemiol. 78, 101–107. https://doi.org/10.1016/j.jclinepi.2016.03.003.

Austin, P.C., 2014. A comparison of 12 algorithms for matching on the propensity score. Stat. Med. 33, 1057–1069. https://doi.org/10.1002/sim.6004.

Austin, P.C., 2018. Assessing covariate balance when using the generalized propensity score with quantitative or continuous exposures. Stat. Methods Med. Res. https://doi.org/10.1177/0962280218756159, 962280218756159.

Bayrampour, H., Kapoor, A., Bunka, M., Ryan, D., 2020. The risk of relapse of depression during pregnancy after discontinuation of antidepressants: a systematic review and meta-analysis. J. Clin. Psychiatry 81. https://doi.org/10.4088/JCP.19r13134.

Berard, A., Sheehy, O., Zhao, J.P., Chambers, C., Roth, M., Bozzo, P., Johnson, D., Kao, K., Lavigne, S., Wolfe, L., Quinn, D., Dieter, K., 2019. Impact of antidepressant use, discontinuation, and dosage modification on maternal depression during pregnancy. Eur. Neuropsychopharmacol. 29, 803–812. https://doi.org/10.1016/j.euroneuro.2019.06.007.

Cantarutti, A., Merlino, L., Giaquinto, C., Corrao, G., 2017. Use of antidepressant medication in pregnancy and adverse neonatal outcomes: a population-based investigation. Pharmacoepidemiol. Drug Saf. 26, 1100–1108. https://doi.org/10.1002/pds.4242.

Cohen, L.S., 2006. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 295, 499. https://doi.org/10.1001/jama.295.5.499.

Falah-Hassani, K., Shiri, R., Dennis, C.-L., 2017. The prevalence of antenatal and postnatal co-morbid anxiety and depression: a meta-analysis. Psychol. Med. 47, 2041–2053. https://doi.org/10.1017/S0033291717000617.

Liu, X., Molenaar, N., Agerbo, E., Momen, N.C., Rommel, A.S., Lupattelli, A., Bergink, V., Munk-Olsen, T., 2022. Antidepressant discontinuation before or during pregnancy and risk of psychiatric emergency in Denmark: a population-based propensity score-matched cohort study. PLoS Med. 19, e1003895 https://doi.org/10.1371/journal.pmed.1003895.

Lupattelli, A., Spigset, O., Björnsdóttir, I., Hämeen-Anttila, K., Mårdby, A.-C., Panchaud, A., Juraski, R.G., Rudolf, G., Odalovic, M., Drozd, M., Twigg, M.J., Juch, H., Moretti, M.E., Kennedy, D., Rieutord, A., Zagorodnikova, K., Passier, A., Nordeng, H., 2015. Patterns and factors associated with low adherence to psychotropic medications during pregnancy: a cross-sectional, multinational web-based study. Depress Anxiety 32, 426–436. https://doi.org/10.1002/da.22352.

Martin, B.C., Wiley-Exley, E.K., Richards, S., Domino, M.E., Carey, T.S., Sleath, B.L., 2009. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. Ann. Pharmacother. 43, 36–44. https://doi.org/10.1345/aph.1K671.

Molenaar, N.M., Bais, B., Lambregtse-van den Berg, M.P., Mulder, C.L., Howell, E.A., Fox, N.S., Rommel, A.-S., Bergink, V., Kamperman, A.M., 2020. 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. J. Affect. Disord. 264, 82–89. https://doi.org/10.1016/j.jad.2019.12.014.

Petersen, I., Gilbert, R.E., Evans, S.J.W., Man, S.-L., Nazareth, I., 2011. Pregnancy as a major determinant for discontinuation of antidepressants: an analysis of data from the Health Improvement Network. J. Clin. Psychiatry 72, 979–985. https://doi.org/10.4088/JCP.10m06090blu.

Putnam, K.T., Wilcox, M., Robertson-Blackmore, E., Sharkey, K., Bergink, V., Munk-Olsen, T., Deligiannidis, K.M., Payne, J., Altemus, M., Newport, J., Apter, G., Devouche, E., Viktorin, A., Magnusson, P., Penninx, B., Buist, A., Bilszta, J., O'Hara, M., Stuart, S., Brock, R., Roza, S., Tiemeier, H., Guille, C., Epperson, C.N., Kim, D., Schmidt, P., Martinez, P., Di Florio, A., Wisner, K.L., Stowe, Z., Jones, I., Sullivan, P.F., Rubinow, D., Wildenhaus, K., Meltzer-Brody, S., Postpartum Depression: Action Towards Causes and Treatment Consortium, 2017. Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. Lancet Psychiatry 4, 477–485. https://doi.org/10.1016/S2215-0366(17)30136-0.

Schoretsanitis, G., Spigset, O., Stingl, J.C., Deligiannidis, K.M., Paulzen, M., Westin, A.A., 2020. The impact of pregnancy on the pharmacokinetics of antidepressants: a systematic critical review and meta-analysis. Expert Opin. Drug Metab. Toxicol. 16, 431–440. https://doi.org/10.1080/17425255.2020.1750598.

Spigset, O., Nordeng, H., 2016. Safety of psychotropic drugs in pregnancy and breastfeeding. In: Spina, E., Trifirò, G. (Eds.), Pharmacovigilance in Psychiatry. Springer International Publishing, Cham, pp. 299–319. https://doi.org/10.1007/978-3-319-24741-0_15.

Suri, R., Lin, A.S., Cohen, L.S., Altshuler, L.L., 2014. Acute and long-term behavioral outcome of infants and children exposed in utero to either maternal depression or antidepressants: a review of the literature. J. Clin. Psychiatry 75, e1142–e1152. https://doi.org/10.4088/JCP.13r08926.

Swanson, S.A., Hernandez-Diaz, S., Palmsten, K., Mogun, H., Olfson, M., Huybrechts, K.F., 2015. Methodological considerations in assessing the effectiveness of antidepressant medication continuation during pregnancy using administrative data. Pharmacoepidemiol. Drug Saf. 24, 934–942. https://doi.org/10.1002/pds.3798.

Tamim, H., Monfared, A.A., LeLorier, J., 2007. Application of lag-time into exposure definitions to control for protopathic bias. Pharmacoepidemiol. Drug Saf. 16, 250–258. https://doi.org/10.1002/pds.1360.

Trinh, N.T.H., Nordeng, H.M.E., Bandoli, G., Eberhard-Gran, M., Lupattelli, A., 2022. Antidepressant and mental health care utilization in pregnant women with depression and/or anxiety: an interrupted time-series analysis. J. Affect. Disord. 308, 458–465. https://doi.org/10.1016/j.jad.2022.04.101.

Yonkers, K.A., Gotman, N., Smith, M.V., Forray, A., Belanger, K., Brunetto, W.L., Lin, H., Burkman, R.T., Zelop, C.M., Lockwood, C.J., 2011. Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? Epidemiology (Cambridge, Mass.) 22, 848–854. https://doi.org/10.1097/EDE.0b013e3182306847.

Zhang, Z., Li, X., Wu, X., Qiu, H., Shi, H., written on behalf of AME Big-Data Clinical Trial Collaborative Group, 2020. Propensity score analysis for time-dependent exposure. Ann. Transl. Med. 8, 246. https://doi.org/10.21037/atm.2020.01.33.