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ORIGINAL RESEARCH ARTICLE

Antibiotic or gastric acid inhibitor use during pregnancy and postpartum depression: Population-based cohort study

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Abstract

Introduction: Postpartum depression is one of the most common non-obstetric postnatal complications. As the microbiome (and gut–brain axis) as well as inflammation may be involved in the mechanism, we aimed to assess if antibiotic or gastric acid inhibition use during pregnancy affects the risk of postpartum depression (clinical diagnosis and/or antidepressant use up to 1 year after childbirth).

Material and Methods: This population-based cohort study used first singleton pregnancy resulting in a live birth in Sweden from 2006 to 2016. Women with history of depression were excluded. Multivariable logistic regression models were used to assess the impact of antibiotics and gastric acid inhibitors and other risk factors, presented as odds ratios (ORs) with 95% confidence intervals (CI).

Results: Overall, 29% of all 10 666 women with postpartum depression were exposed to antibiotics and 6.2% to gastric acid inhibitors, compared to, respectively, 21% and 3.2% of 613 205 women without postpartum depression. Antibiotic use during pregnancy was associated with postpartum depression (OR 1.43, 95% CI 1.37–1.49), particularly for quinolones and other antibacterials (including nitroimidazole derivatives). Gastric acid inhibition was associated with an even higher risk than antibiotics (OR 2.04, 95% CI 1.88–2.21). Both antibiotics and gastric acid inhibitors suggested higher risk with increased dose in a dose–response analysis.

Conclusions: The use of antibiotics and gastric acid inhibition drugs during pregnancy appeared to be associated with a higher risk of postpartum depression. However, it is important to consider that other predisposing factors could contribute to this increased risk, even after excluding individuals with a history of depression.

KEYWORDS
anti-acids, antibiotics, gastric acid inhibition, microbiome, multiple logistic regression, postnatal depression, pregnancy

Abbreviations: ATC, Anatomical Therapeutic Chemical; BMI, body mass index; CI, confidence interval; DDD, defined daily dose; ICD-10, International Classification of Diseases, Tenth Revision; OR, odds ratio.

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1 | INTRODUCTION

Postpartum depression refers to the occurrence of a non-psychotic depressive episode with peripartum onset and is one of the most common postnatal complications. Symptoms of depression occur in approximately one-sixth of all pregnancies based on a meta-analysis of 565 studies,[1] and in 12% of postpartum individuals when based on diagnostic interviews.[2] The worst cases result in suicide, a leading cause of maternal mortality in developed countries.[3–5] The cognitive, social, and emotional development of the child may also be affected, with an important impact on the whole family.[6]

Identified risk factors for postpartum depression can be broadly categorized into obstetric and perinatal factors such as poor childbirth outcomes, psychosocial factors, and sociodemographic characteristics.[3,7,8] The strongest predictor for postpartum depression, however, has been found to be a history of postpartum or other depression.[3,7] In recent years, biological depression pathways have been investigated. Major depression, outside of pregnancy, has been associated with increased pro-inflammatory activity and a dysbiotic gut microbiome.[9,10] Pregnancy studies point to diverse and complex links among the microbiome, an altered immune response, and perinatal mood.[11,12] A powerful bidirectional gut–brain axis seems to regulate interactions between the gut microbiota and the central nervous system and is thought to participate in the regulation of immune, central nervous system, and endocrinological processes.[5,12,13] As changes in the composition of the microbiome during pregnancy can persist into the postnatal period, factors contributing to this dysbiosis may consequently result in dysregulation of the gut–brain axis.[14]

Antibiotics and non-antibiotic prescription drugs have a notable impact on the overall composition and functioning of the intestinal microbiome, explaining approximately 20% of the variation in population level.[15–17]

Antibiotics are the most commonly prescribed drugs during pregnancy, with an estimated 20%–25% of women using antibiotics during pregnancy, responsible for 80% of prescription drugs during pregnancy.[18] During pregnancy, most common indications include urinary (e.g., asymptomatic bacteriuria), skin, and upper and lower airway infections, while they may also be prescribed in case of preterm labor, intrapartum fever, and prevention of neonatal Group B streptococcus.[19,20] In Sweden, approximately 10% of women received antibiotics during each trimester according to 2007 data,[21] yet data on indications are not recorded on a nationwide level in the Prescribed Drug Registry. Recent studies have already shown an increased risk between antibiotic use and depressive symptoms outside pregnancy,[22,23] as highlighted in a recent literature review.[24] Yet, we only identified one small study ($n=124$) investigating the association between peripartum antibiotics and postpartum depression, also suggesting an association.[14]

Previous studies suggest a larger impact of proton pump inhibitors on the microbiome composition than antibiotics,[16,25] but little research has been done on how gastric acid inhibitors during pregnancy affect the risk of postpartum depression.

Key message

Our Swedish population-based cohort study shows that the use of antibiotics or gastric acid inhibitors during pregnancy is associated with an increased risk of postpartum depression.

By using the Swedish health registries, we aimed to explore this association in more depth, also looking at different antibiotic types, gastric acid inhibitors, and trimester of exposure.

2 | MATERIAL AND METHODS

2.1 | Study design and data

The study cohort included all women who delivered a live singleton infant in Sweden between January 1, 2006, and December 31, 2016, as described earlier.[26] The terminology "women" was defined based on the biological sex, not gender identity. Information on maternal characteristics, maternal and neonatal outcomes, and prescribed drug use was collected. To avoid issues with correlated data, only information on the first childbirth during the study period for each woman was included in the main analyses. Furthermore, women with a history of depression were excluded from the cohort. Patients with antidepressant prescriptions prior to the postpartum period were assumed to be continuing care and therefore not considered to have postpartum depression and were, therefore, excluded from the cohort, as well as women with any depression diagnosis during or prior to pregnancy in the Patient or Medical Birth Registry. The data used in this study were collected from the high-quality nationwide Swedish registers, including the Medical Birth Register, the Prescribed Drug Register, the Patient Register (In- and Specialist Outpatient care, excluding primary care), and the Causes of Death Register (to assess loss to follow-up and maternal suicide), linked by the unique personal identification number assigned to each individual residing in Sweden.[27–32]

2.2 | Exposures

The use of at least one prescribed systemic antibiotic during pregnancy was defined and categorized according to the Anatomical Therapeutic Chemical (ATC) Classification of the World Health Organization: J01 (systemic antibiotics) complemented with P01AB (nitroimidazole derivatives). Subgroup analyses grouped all antibiotics as follows: J01A: tetracyclines; J01B: amphenicols; J01C: B-lactam antibacterials, penicillins; J01D: other B-lactam antibacterials; J01E: sulfonamides and trimethoprim; J01F: macrolides, lincosamides, and streptogramins; J01G: aminoglycoside antibacterials; J01M: quinolones; J01R: combinations of antibacterials; J01X: other antibacterials (including P01AB); and A02B: drugs for peptic

ulcer and gastro-esophageal reflux disease (GERD). The timing of exposure was estimated from the date the drug was dispensed in relation to the date of the last menstrual period. Any antibiotic or gastric acid inhibitor use during pregnancy was defined as at least one prescription during pregnancy, while the pre-conception period (90 days prior to conception) was also assessed when evaluating period of exposure. Dispensed drugs were assumed to be taken by the mothers, and antibiotics are not available over the counter in Sweden. Number of prescriptions and days of use (estimated by the number of defined daily doses [DDDs] per package) were used to assess a potential dose response.[33] It should be noted that gastric acid inhibitors are available over the counter in Sweden, at a higher price compared to prescriptions.

2.3 | Outcomes

Postpartum depression was defined based on International Classification of Diseases, Tenth Revision (ICD-10) diagnoses of depression as recorded in the Patient Registry (F53, F32, F33, F34, F38, and F39), or the occurrence of antidepressant drug prescriptions (ATC code N06A) within the 12 months following delivery, aligned with prior research.[7] As all ambulatory prescriptions are recorded in the Prescribed Drug Registry, and antidepressants are on prescription only, the validity of this variable is very high.[32] (Intended) suicide in the year following delivery was also used as an indicator for postpartum depression based on the cause of death reported in the Death Registry. Women were followed from the date of delivery until postpartum depression, death, or 12 months following the date of delivery, whichever came first.

2.4 | Covariates

Potential risk factors for postpartum depression[8-11] were a priori selected and included maternal, demographic, and psychosocial characteristics: maternal age (as categories, <25, 25–34, and ≥35), maternal country of birth (Nordic or not), body mass index (BMI (weight (kg)/height (m)^2), as categories (<18.5, 18.5–24.9, 25–29.9, and ≥30)), cohabitation status, tobacco consumption (smoking and snuff [smokeless tobacco]), comorbidities (thyroid disease, hypertensive disease, and diabetes), and pregnancy-related characteristics (parity, history of stillbirth/miscarriage, assisted reproduction, mode of delivery, preterm birth, labor complications, birthweight [low, normal, or macrosomia [>4599 g]], low Apgar score at 5 min [<7/10], neonatal death, congenital malformations, and trimester of exposure).

2.5 | Statistical analyses

Multiple logistic regression was used to assess the association between antibiotics or gastric acid inhibitors and postpartum depression while adjusting for other risk factors. Associations were presented as odds ratios (OR) with 95% confidence intervals (CIs). In order to build a parsimonious and well-fitting model, purposeful selection was performed. Univariable analysis was initially conducted to assess associations between each variable and the outcome. Variables not found to be significant ($p < 0.25$) were consequently removed, and a multivariable model with the remaining predictors was then fit. Predictors not found to be significant ($p < 0.05$) were then removed one by one (backward) and the models were compared using a likelihood-ratio test ($p < 0.05$) to subsequent models. A final model was used for multivariable analysis including both antibiotics and gastric acid inhibitors as exposures and all identified risk factors.

Analyses were stratified by period of exposure, parity, maternal age, and antibiotic class, as exposures, using the risk factors identified above in a multivariable model. Dose–response analyses were based on the number of prescriptions and estimated number of days exposed.

Furthermore, interaction analyses regarding antibiotic and antiacid consumption were performed using log-likelihood ratio tests, as well as population attributable fractions (PAF) using crude values.

All analyses were conducted with R version 3.6.1. Missing values were recategorized as the absence of a characteristic, or an extra category was created since otherwise too many individuals would be excluded with complete-case analyses (7% missingness for BMI). Imputing missing values was not computationally feasible due to the size of the cohort.

3 | RESULTS

Of the 623 871 women in the final cohort, 21% ($N = 132\,441$) were exposed to at least one systemic antibiotic during pregnancy and 3.3% ($N = 20\,279$) to gastric acid inhibitors. The prevalence of postpartum depression was 1.7% ($N = 10\,666$; Table 1). Women with postpartum depression were more likely to be younger, Nordic, and tobacco consumers, and twice as likely to use gastric acid inhibitors (6.2% vs. 3.2%). They also had a higher prevalence of pregnancy-related problems (Table 1), such as low or high birthweight, low Apgar score, and congenital malformations.

Younger age, not cohabiting with the father, tobacco consumption, and cesarean section were more common among antibiotic users than non-users, as well as the use of gastric acid inhibitors which was almost twice as prevalent (5.0% vs. 2.8%; Table S1).

3.1 | Antibiotic use during pregnancy

The three most common groups of antibiotics were penicillins, other antibacterials, and non-penicillin beta-lactam antibiotics, prescribed in, respectively, 20.9%, 8.8%, and 4.1% of women with postpartum depression; and 15.3%, 5.7%, and 2.6% of women without a postpartum depression (Table 2). Antibiotic use seemed to be similar in all exposure periods in all women. Respectively, 19.0% and 14.7% of

TABLE 1 Characteristics of the cohort without and with postpartum depression.

Characteristic	No postpartum depression *N* (%)	Postpartum depression *N* (%)
Total = 623 871	613 205 (98.3)	10 666 (1.7)
Antibiotic use	129 323 (21.1%)	3118 (29.2%)
Gastric acid inhibitors	19 616 (3.2%)	663 (6.2%)
Maternal age, years		
<25	106 045 (17.3%)	2386 (22.4%)
25–34	388 333 (63.3%)	6217 (58.3%)
≥35	118 827 (19.4%)	2063 (19.3%)
Mother's country of birth		
Nordic	446 714 (72.8%)	8327 (78.1%)
Non-Nordic	165 479 (27.0%)	2321 (21.8%)
Data missing	1012 (0.2%)	18 (0.2%)
Maternal body mass index, kg/m^2		
<18.5	15 160 (2.5%)	317 (3.0%)
18.5–24.9	351 431 (57.3%)	5771 (54.1%)
25–29.9	138 445 (22.6%)	2401 (22.5%)
≥30	63 803 (10.4%)	1337 (12.5%)
Data missing	44 366 (7.2%)	840 (7.9%)
Cohabiting with father		
Yes	545 476 (89.0%)	9166 (85.9%)
Data missing	27 732 (4.5%)	530 (5.0%)
Tobacco consumption		
Yes	41 611 (6.8%)	1422 (13.3%)
Data missing	37 868 (6.2%)	802 (7.5%)
Thyroid disease		
No	601 476 (98.1%)	10 421 (97.7%)
Hyperthyroidism	403 (0.1%)	4 (0.0%)
Hypothyroidism	11 326 (1.8%)	241 (2.3%)
Hypertensive disease		
No or missing	590 126 (96.2%)	10 208 (95.7%)
Essential Hypertension	2742 (0.4%)	53 (0.5%)
Preeclampsia	20 337 (3.3%)	405 (3.8%)
Diabetic disease		
No	602 767 (98.3%)	10 444 (97.9%)
Diabetes mellitus	3870 (0.6%)	95 (0.9%)
Gestational diabetes	6568 (1.1%)	127 (1.2%)
Historical stillbirth/miscarriage		
Yes	116 514 (19.0%)	2265 (21.2%)
Assisted reproduction		
Yes	21 667 (3.5%)	396 (3.7%)
Parity		
1	408 151 (66.6%)	6840 (64.1%)
2	125 794 (20.5%)	2394 (22.4%)
≥3	79 260 (12.9%)	1432 (13.4%)
Mode of delivery		
Vaginal	511 954 (83.5%)	8450 (79.2%)
Elective C-section	37 354 (6.1%)	875 (8.2%)
Acute C-Section	63 897 (10.4%)	1341 (12.6%)
Preterm birth (<37 weeks)		
Yes	31 008 (5.1%)	677 (6.3%)
Labor complications		
Yes	301 106 (49.1%)	5297 (49.7%)
Birthweight		
Low (<2500 g)	21 570 (3.5%)	476 (4.5%)
Normal	572 647 (93.4%)	9830 (92.2%)
Macrosomia (>4500 g)	18 191 (3.0%)	337 (3.2%)
Data missing	797 (0.1%)	23 (0.2%)
Apgar 5 min (<7/10)		
Yes	7902 (1.3%)	213 (2.0%)
Data missing	2375 (0.4%)	42 (0.4%)
Neonatal death (0–27 days)		
Yes	796 (0.1%)	63 (0.6%)
Congenital malformation		
Yes	21 864 (3.6%)	446 (4.2%)

women with and without postpartum depression received a single prescription (Table 2). Overall, 2.4% of antibiotic users developed postpartum depression, compared to 1.5% of non-users (Table S1). Antibiotic use was strongly associated with postpartum depression (OR 1.43, 95% CI 1.37–1.49), with the risk being highest for quinolones (OR 1.52, 95% CI 1.11–2.02) and other antibacterials (OR 1.48, 95% CI 1.39–1.59; Table 3).

Exposure during the different exposure periods resulted in similar risks (between OR = 1.35 in the third trimester and OR = 1.45 in the second trimester; Table 3).

When estimating cumulative dose, the risk for postnatal depression remained similar (ranging from $OR_{5.0-9.0}$ 1.38, 95% CI [1.28–1.49] to $OR_{>15}$ 1.48, 95% CI [1.39–1.57]), but when looking at number of prescriptions, the risk increased with increasing number of prescriptions, being highest for ≥4 (OR 1.81, 95% CI [1.55–2.10]; Figure 2).

3.2 | Gastric acid inhibitors during pregnancy

Exposure was similar during all trimesters, with 3.8% of women who had postpartum depression receiving one prescription, compared to 2.2% of those who did not (Table 2).

TABLE 2 Antibiotic and gastric acid inhibitors use in women with and without postpartum depression, by antibiotic class, dose, and trimester.

	Total	No postpartum depression	Postpartum depression
Exposure	***N* (%)**	***N* (%)**	***N* (%)**
Total	623 871 (100%)	613 205 (98.3%)	10 666 (1.7%)
Any antibiotic	132 441 (21.2%)	129 323 (21.1%)	3118 (29.2%)
Antibiotic class			
Tetracyclines	3615 (0.6%)	3515 (0.6%)	100 (0.9%)
Amphenicols	0 (0%)	0 (0%)	0 (0%)
β-lactam antibacterials, penicillins	95 765 (15.4%)	93 535 (15.3%)	2230 (20.9%)
Other β-lactams antibacterials	16 455 (2.6%)	16 021 (2.6%)	434 (4.1%)
Sulfonamides and trimethoprim	2272 (0.4%)	2213 (0.4%)	59 (0.6%)
Macrolides, lincosamides, and streptogramins	5092 (0.8%)	4969 (0.8%)	123 (1.2%)
Aminoglycoside antibacterials	12 (0.0%)	11 (0.0%)	1 (0.0%)
Quinolones	1622 (0.3%)	1577 (0.3%)	45 (0.4%)
Combinations of antibacterials	0 (0%)	0 (0%)	0 (0%)
Other antibacterials[a]	35 946 (5.8%)	35 007 (5.7%)	939 (8.8%)
Dose distribution (exposure to any antibiotic during entire pregnancy)			
Cumulative dose in days (DDD), categorized			
<5	22 502 (3.6%)	21 982 (3.6%)	520 (4.9%)
5.0–9.0	34 234 (5.5%)	33 463 (5.5%)	771 (7.2%)
10.0–14.0	26 290 (4.2%)	25 684 (4.2%)	606 (5.7%)
≥15	49 381 (7.9%)	48 161 (7.9%)	1220 (11.4%)
No. of prescriptions, categorized			
1	92 349 (14.8%)	90 327 (14.7%)	2022 (19.0%)
2	26 215 (4.2%)	25 542 (4.2%)	673 (6.3%)
3	8120 (1.3%)	7878 (1.3%)	242 (2.3%)
≥4	5733 (0.9%)	5553 (0.9%)	180 (1.7%)
Exposure period (exposure to any antibiotics per period)			
Pre-pregnancy (−90 days)	51 631 (8.3%)	50 380 (8.2%)	1251 (11.7%)
1st trimester	51 560 (8.3%)	50 300 (8.2%)	1260 (11.8%)
2nd trimester	56 433 (9.0%)	54 992 (9.0%)	1441 (13.5%)
3rd trimester	49 743 (8.0%)	48 566 (7.9%)	1177 (11.0%)
Dose distribution (exposure to any gastric acid inhibitors during entire pregnancy)			
Cumulative dose in days (DDD), categorized			
<28	4834 (0.8%)	4698 (0.8%)	136 (1.3%)
28–38	5362 (0.9%)	5190 (0.8%)	172 (1.6%)
38–90	4940 (0.8%)	4800 (0.8%)	140 (1.3%)
≥90	5073 (0.8%)	4859 (0.8%)	214 (2.0%)
No. of prescriptions, categorized			
1	14 138 (2.3%)	13 736 (2.2%)	402 (3.8%)
2	3638 (0.6%)	3491 (0.6%)	147 (1.4%)
3	1308 (0.2%)	1252 (0.2%)	56 (0.5%)
≥4	1133 (0.2%)	1076 (0.2%)	57 (0.5%)
Exposure period (exposure to any gastric acid inhibitors per period)			
Pre-pregnancy (−90 days)	7900 (1.3%)	7605 (1.2%)	295 (2.8%)
1st trimester	9951 (1.6%)	9637 (1.6%)	314 (2.9%)
2nd trimester	8265 (1.3%)	7955 (1.3%)	310 (2.9%)
3rd trimester	7044 (1.1%)	6769 (1.1%)	275 (2.6%)

Abbreviation: DDD, defined daily dosage.

[a]This group comprises antibacterials not classified in the preceding groups, including nitroimidazole antibiotics.

TABLE 3 The association among maternal antibiotics, gastric acid inhibitors, and postpartum depression, expressed by adjusted odds ratios and their 95% confidence intervals, by class of antibiotic.

	OR	95% CI
Antibiotic exposure		
Any antibiotic use	1.43	1.37–1.49
Antibiotic class		
Tetracyclines	1.45	1.18–1.76
β-lactam antibacterials, penicillins	1.36	1.30–1.43
Other β-lactam antibacterials	1.46	1.32–1.60
Sulfonamides and trimethoprim	1.41	1.07–1.80
Macrolides, lincosamides, and streptogramins	1.22	1.01–1.46
Quinolones	1.52	1.11–2.02
Other antibacterials	1.48	1.39–1.59
Antibiotic exposure period		
Pre-pregnancy (−90 days)	1.37	1.29–1.46
1st trimester	1.38	1.30–1.47
2nd trimester	1.45	1.37–1.53
3rd trimester	1.35	1.27–1.43
Gastric acid inhibitors (ATC: A02B)	2.04	1.88–2.21
Gastric acid inhibitors exposure period		
Pre-pregnancy (−90 days)	2.14	1.89–2.40
1st trimester	1.89	1.68–2.12
2nd trimester	2.17	1.93–2.44
3rd trimester	2.26	2.00–2.56

Note: Adjusted for: maternal age, mother's country of birth, maternal BMI, parity, cohabitation with father, tobacco consumption, thyroid disease, historical stillbirth/miscarriage, mode of delivery, preterm birth (<37 w), Apgar 5 min (<7), neonatal death (0–27 days), and congenital malformations. Bolded values indicate significance at 5% alpha level.

Abbreviations: ATC, Anatomical Therapeutic Chemical; BMI, body mass index.

The use of gastric acid inhibitors during pregnancy was strongly associated with postpartum depression (OR 2.04, 95% CI 1.88–2.21; Table 3). Both cumulative dose and number of prescriptions suggested a dose response, with the highest number associated with the largest risk (Figure 2).

Furthermore, no interaction was found between antibiotic and gastric acid inhibitor consumption ($p = 0.6$).

3.3 | Other risk factors for postpartum depression

Maternal age, BMI, country of birth, parity, cohabitation with the father, tobacco consumption, thyroid disease, historical stillbirth/miscarriage, mode of delivery, preterm birth, Apgar score, neonatal death, and congenital malformations were all associated with postpartum depression in the univariable analysis and therefore included in the multivariable models.

In the multivariable model (Figure 1), tobacco consumption (OR 1.88, 95% CI 1.77–1.99) and neonatal death (OR 3.28, 95% CI 2.46–4.32) showed the strongest association with postpartum depression. On the other hand, being born outside of Nordic countries (OR 0.71, 95% CI 0.68–0.74) was associated with a lower risk of postpartum depression.

3.4 | Population attributable fraction (PAF)

Assuming a prevalence of 21% for antibiotics and 3.3% for gastric acid inhibitors, the calculated PAF was 10.2% for antibiotics and 3.1% for gastric acid inhibitors. This implies that, if this relationship were to be causal, one-tenth of all postpartum depression cases might be attributed to antibiotics consumption (or the underlying indication).

3.5 | Sensitivity analysis

To investigate the effect of women with prescribed antidepressants in our cohort on the analysis, as they might have gotten it for a different indication of depression, we ran the same multivariable models for both antibiotics and gastric acid inhibitors, but only on women who had a depression diagnosis (excluding those with antidepressants prescribed postpartum). Similar, although slightly lower, ORs were found for both antibiotics (OR 1.31, 95% CI 1.20–1.44) and gastric acid inhibitors (OR 1.70, 95% CI 1.42–2.01).

4 | DISCUSSION

Our Swedish population-based cohort study shows that the use of antibiotics or gastric acid inhibitors during pregnancy is associated with an increased risk of postpartum depression. The results seem consistent in all subgroup analyses, and a dose–response relationship was present for both antibiotics and gastric acid inhibitors. Quinolones and other antibacterials were associated with the highest risk of postpartum depression.

One of the biggest strengths of this study is the population-based design with national coverage, limiting the risk of selection bias. Although this cohort was large, including approximately over 600 000 singleton pregnancies, power was still limited for some antibiotics subclasses, of which some are contraindicated during pregnancy. As antibiotics are only available on prescription, and all included prescriptions have been dispensed, the risk of misclassification of antibiotic exposure should be limited to lack of compliance and in-hospital use, and some medically unsupervised use. Although high, the 21% antibiotic use in the present cohort seems to be in line with the literature.[18] On the other hand, gastric acid inhibitors are available over the counter in Sweden, which causes some misclassification. However, we can speculate that patients with more severe symptoms, as well as long-term users, may tend to have prescriptions for their medication. Other potential misclassifications

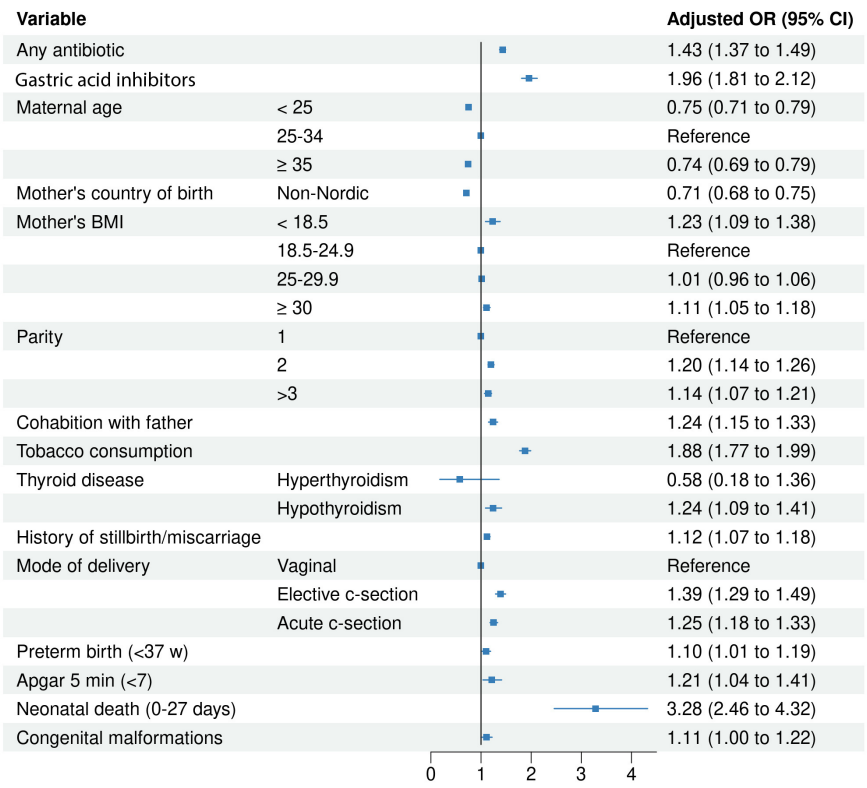

FIGURE 1 Risk factors for postnatal depression. Multivariable logistic regression model presented as odds ratios (ORs) with 95% confidence intervals (CIs). Model adjusted for maternal age, BMI, country of birth, parity, cohabitation with father, tobacco habits, antibiotics during pregnancy, gastric acid inhibitors during pregnancy, thyroid disease, historical stillbirth/miscarriage, delivery mode, preterm birth, Apgar score at 5 min, infant death, and congenital malformations.

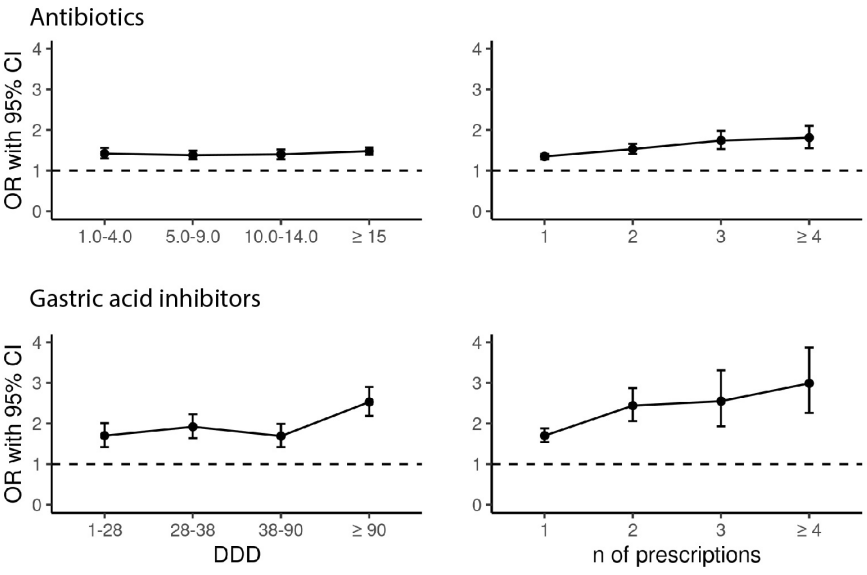

FIGURE 2 Dose–response curve showing the predicted probability of postpartum depression by (left) number of days (based on the defined daily dosage per package [DDD]) and (right) number of prescriptions for antibiotics (top row) and gastric acid inhibitors (bottom row).

are individuals who do not have diagnosed postpartum depression or used antidepressants for other indications than depression. However, our analysis shows that if we exclude women who got antidepressants prescribed but were not diagnosed with depression, the results remain similar. Additionally, those with unrecorded history of miscarriage might be misclassified, as early miscarriages are less likely to be recorded in medical records. Additionally, the registries do not have exact date of birth but only birth month which could cause misclassification of age groups, and do not include information on delivery-associated medications, such as antibiotics in relation to cesarean section.

Other variables including employment status and social support may have affected the risk of postnatal depression. Sweden has a widely accessible and state-supported system of parental support which therefore is expected to have less impact on the risk of postnatal depression than in other countries where maternal- and child support is more restricted. Furthermore, all pregnant women in Sweden are eligible to receive highly standardized antenatal care for free, including screening for postpartum depression during a postdelivery follow-up. Therefore, access to healthcare should not have majorly influenced our findings. As the existing ICD-10 classifications for postpartum mental disorders are strict

(only if onset is within 6 weeks, not elsewhere classified), we used a broader range of diagnostic codes further completed with the use of antidepressants. Nevertheless, less severe cases are likely to be underdiagnosed and underreported. The overall prevalence of diagnosed postpartum depression was 1.7% in this study, which is low compared to the global symptom prevalence of 17% as reported in a recent meta-analysis (14% in Northern Europe),[1] which can partially be explained by the exclusion of women with a history of depression, the use of register data (as compared with survey data), but it might also indicate that not all individuals are detected and diagnosed.[34] However, our numbers correspond to other large population-based studies.[7,35,36] Therefore, our findings are nevertheless expected to be generalizable to countries with similar (antenatal) antibiotic prescription practices and similar prevalence of diagnosed postpartum depression.

Indications for prescribed drug use are not included in the Prescribed Drug Registry and could therefore not be assessed in this paper. However, for this study only de novo prescriptions were included, and the majority of cases should then constitute postpartum depression. Although postpartum depression has been associated with increase in pro-inflammatory markers,[37] the knowledge about infections that lead to antibiotic prescription and postpartum depression is still scarce. Confounding by indication could not be ruled out, particularly among women exposed to many antibiotic prescriptions, as some inflammatory conditions could potentially increase depressive symptoms.[38] It is important to note that the association between somatic and mental health conditions could be bidirectional and the direction of causality can therefore be difficult to establish. For example, births that end in acute cesarean sections can often be traumatic physically and mentally and therefore result in an association with both antibiotics and postpartum anxiety or depression. The results also point to the importance of inquiring about mental health in somatic care, as the overlap between somatic and mental disorders should not be overlooked. Additionally, screening for mental health problems could be improved for postpartum women[39] and since there is a large proportion of women who are depressed during pregnancy, women who often also suffer from nausea and other somatic conditions, it is also important to correctly diagnose and support those women at higher risk.[40]

Only 3.3% of women used gastric acid inhibitors in the present cohort, of which approximately half are proton pump inhibitors.[41] Our findings suggest that gastric acid inhibitors may have a more important impact on postpartum depression than antibiotics. This could be related to a longer exposure period, making it the most important modifiable risk factor assessed in our study.

It seems increasingly likely that antibiotics and other drugs used during pregnancy do affect the (long-term) health of the mother and her offspring, and a dysbiotic gut and altered inflammatory response seem to be an increasingly plausible underlying pathway.[23] The effects of antibiotics on the composition of the microbiota can last for periods ranging from weeks to very long term, or even indefinitely.[42,43] Therefore, the pre-conception period was also included in the analysis, which also showed an association with postpartum depression. Rational prescribing may therefore contribute to reduced risk of postpartum depression and other long-term consequences of a dysbiotic gut and overconsumption of drugs. Additionally, more attention to mental health screening is needed postpartum to diagnose and help those women at higher risk. The overall benefit of antibiotic use during pregnancy is questionable for several common indications including asymptomatic bacteriuria.[20,44,45] Therefore, overprescribing of antibiotics should be addressed, taking into account antimicrobial resistance, the short- and long-term cost–benefit and potential changes of the microbiome, and consequent health effects.[18,44,45]

5 | CONCLUSION

Antibiotic use during pregnancy, as well as use of gastric inhibition drugs, were associated with the occurrence of postpartum depression. This association was shown also for women receiving only a single prescription. Especially for women exposed to many antibiotic prescriptions, the confounding by indication could not be ruled out. Although the results cannot prove causality, these findings point to the involvement of the gut–brain axis alongside the importance of infections and the immune system in the etiology of postpartum depression. Furthermore, these results support that individuals using these drugs during pregnancy may benefit from alertness toward postpartum depression for early diagnosis and treatment.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design of the study. Nele Brusselaers acquired the data and is the guarantor of the study. Njeri Kamau, Romina Fornesand, and Unnur Gudnadottir performed the data cleaning. Njeri Kamauand and Unnur Gudnadottir analyzed the data under supervision of Robin Bruyndonckx and Nele Brusselaers. All authors interpreted the data. Njeri Kamau and Nele Brusselaers drafted the manuscript, which was critically revised for important intellectual content by all other authors. All authors have given their final version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

ETHICS STATEMENT

The study was approved by the Regional Ethics Committee in Stockholm (2017/2423-31) on January 17, 2018, without informed consent because of the registry-based data; and conducted in accordance with the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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