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<u>**Title Page**</u>

Antidepressant Use in Late Gestation and Risk of Postpartum Haemorrhage: A retrospective cohort study

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Short Title: Antidepressant Use and Postpartum Haemorrhage

Abbreviations: CI- confidence interval; SSRI- selective serotonin reuptake inhibitor; TCA-tricyclic antidepressant; RR-relative risk

Abstract

Objective: To investigate the association between antidepressant use in late gestation and postpartum haemorrhage (PPH).

Design: Retrospective cohort study

Setting: Tertiary teaching hospital in Adelaide, Australia

Population: A total of 30,198 women delivering between 2002 and 2008

Methods: Relative risks adjusted for maternal sociodemographics and comorbidities (aRRs) were calculated for PPH, comparing women with late-gestation exposure to antidepressants (n=558), women with a psychiatric illness but no antidepressant use (n=1,292), and women with neither antenatal exposures (n=28,348). Additional sensitivity analyses were undertaking examining associations with severe PPH, and postpartum anaemia.

Main outcome measures: The primary outcome was PPH, defined as a recorded blood loss of ≥500mL for vaginal deliveries and ≥1000mL for caesarean sections. Secondary outcomes included severe PPH (≥1,000mL blood loss, irrespective of method of delivery), and the presence of postpartum anaemia (identified from hospital medical records).

Results: Compared to unexposed controls, women exposed to antidepressants had an increased risk of PPH (aRR 1.53; 95% confidence interval 1.25-1.86), whereas no increased risk was observed for women with a psychiatric illness but no antidepressant use (aRR 1.04; 0.89-1.23). In sensitivity analyses, late gestation antidepressant exposure was associated with increased risk of severe PPH (aRR 1.84; 1.39-2.44), as well as postpartum anaemia (aRR 1.80; 1.46-2.22).

Conclusion: Exposure to antidepressants in late gestation was associated with a significantly increased risk of PPH. While potential confounding by unmeasured factors cannot be ruled out, these findings suggest a direct effect of antidepressant exposure on PPH.

Key Words: Antidepressive agents; prenatal exposure; pregnancy; selective serotonin reuptake inhibitors; postpartum haemorrhage

Introduction:

Internationally there has been a striking increase in the numbers of women exposed to antidepressants during pregnancy. In Denmark, prescribing of antidepressants during pregnancy increased from 0.2% to 3.2% from 1997 to 2010,[1] a trend mirrored in other countries such as the United States, where use increased from 2% to 7.6% from 1996 to 2005.[2] Antidepressant use has been associated with a range of adverse pregnancy outcomes, including preterm birth, persistent pulmonary hypertension of the newborn, and poor neonatal adaptation.[3-6] While some of these outcomes may be confounded by underlying maternal illness, there is a continual need to assess the benefits and safety of antidepressant use during pregnancy in an effort to guide and improve clinical care and health outcomes.

In non-pregnant adults a number of, but not all, studies have demonstrated that antidepressant use is associated with increased risks of gastrointestinal, perioperative, and other bleeding events.[7-11] This is thought to occur through an effect on the depletion of serotonin within platelets, with serotonin playing an important role in influencing the platelet – endothelial cell interaction, and platelet activation and aggregation.[12] Evidence to date is equivocal in relation to antidepressant use near delivery and risk of postpartum haemorrhage (PPH), with four studies demonstrating inconsistent findings in relation to the use of all antidepressants combined[13], or the use of serotonin and non-serotonin reuptake inhibitors investigated separately.[14-16] In addition, major differences and limitations are evident in previous studies across key methodological aspects such as sample size, outcome definitions used, and adjustment for possible confounders.[13, 15-17] Palmsten *et al*. provide the most extensive and compelling evidence regarding an increased risk of PPH following antidepressant use close to delivery.[17] Among a cohort of more than 10,000 exposed pregnancies, the largest to date, use of serotonin reuptake inhibitors near delivery was associated with a 1.47-fold increased risk (95% confidence interval 1.33 to 1.62) of PPH and

use of non-serotonin reuptake inhibitors associated with a 1.39-fold increased risk (1.07 to 1.81). As this study was undertaken among low income women enrolled in the US Medicaid program, the generalizability of these findings to other populations remains to be determined. In light of this and existing evidence, we sought to investigate the association between antidepressant use in late pregnancy and risk of primary PPH.

Methods:

Eligible Population

We undertook a retrospective cohort study involving all births in the Children, Youth and Women's Health Service (CYWHS) in South Australia between January 2002 and December 2008. Data were obtained from linkable routinely collected health administrative data within the Women's and Children's Hospital (WCH), which included the Perinatal Statistics Collection and Hospital Pharmacy Dispensing Records. Each individual's unique hospital identifier number was used to link related health records. The eligible population consisted of 30,198 pregnancies from 24,266 women.

Exposure

The WCH pharmacy dispensing records were utilised to obtain data on women dispensed an antidepressant during pregnancy. . The hospital pharmacy dispensing records have previously been validated as an indicator of late gestation exposure to antidepressants during pregnancy,[18] and have been utilised in research evaluating outcomes following antidepressant use in pregnancy [19, 20].

Women with a reported psychiatric illness during pregnancy, as identified through the Perinatal Statistics Collection, but who were not dispensed an antidepressant, served as a

disease comparitor. The unexposed control group comprised of women who were not dispensed an antidepressant and had no reported psychiatric illness during pregnancy.

Outcome

The primary outcome measure was primary PPH, defined as a blood loss of ≥ 500mL following vaginal delivery and ≥ 1000 mL following a caesarean section. Secondary outcomes included severe PPH, defined as blood loss ≥ 1000mL within 24 hours of delivery, as well as postpartum anaemia.

These outcomes were based on data routinely collected and recorded in the WCH Perinatal Statistics Collection. The Perinatal Statistics Collection involves the collection of data on the pregnancy and outcome of every live birth and late fetal death occurring at the WCH by a specially trained research midwife. Data are collected using a structured coding sheet, with data collected on maternal illnesses (e.g. pre-existing hypertension or diabetes, epilepsy, asthma and psychiatric illness), lifestyle factors (e.g. smoking), obstetric history, pregnancy complications (e.g. gestational diabetes) and newborn characteristics (e.g. birth weight). The data collected for the Perinatal Statistics Collection are checked manually for completeness and data discrepancies and then go through a series of automated validation procedures during data entry. The information in the Perinatal Statistics Collection has been previously validated and has been shown to be very reliable when compared with hospital medical records.[21]

Statistical Analysis

We compared the risk for PPH or postpartum anaemia between women with exposure to either antidepressants or psychiatric illness without antidepressant use and the unexposed group using relative risks and risk differences and their corresponding 95% confidence

intervals from generalised linear models (Poisson distribution). Models were adjusted for potential confounders and robust variances were used to account for correlations among multiple pregnancies in the same woman. Outcomes were stratified according to method of delivery to evaluate the potential for effect modification. To support the validity of our outcome definition, we also assessed the association between well-established risk factors for PPH and occurrence of PPH. Finally, we examined differences in the prevalence of known risk factors for PPH across each of the exposure groups to identify potential mediators. All analyses were performed using Stata 12.1 (Stata, College Station, TX, USA).

Results

Of the women eligible to participate in this study (n=30,198), 558 were dispensed an antidepressant (exposed), 1,292 had a reported psychiatric illness but were not dispensed an antidepressant (non-medicated psychiatric illness) and 28,348 did not have a reported psychiatric illness and were not dispensed an antidepressant during pregnancy (unexposed). All women were dispensed only one type of antidepressant (in order of frequency; SSRIs: sertraline [n=194], citalopram [n=133], paroxetine [n=57], fluoxetine [n=27], fluvoxamine [n=17], escitalopram [n=7]; SNRIs: venlafaxine [n=64]); TCAs: amitriptyline [n=29], dothiepin [n=10], imipramine [n=3], clomipramine [n=1], nortriptyline [n=1], doxepin [n=1]; other antidepressants: mirtazapine [n=13], moclobemide [n=1]). The majority of women dispensed an antidepressant had a reported psychiatric illness (n=554), with the remainder potentially using antidepressants for an alternative indication such as neuropathic pain.

Compared with unexposed women, more women in the antidepressant exposed group were older, multiparous, smokers, Caucasian, using other psychotropic medications during pregnancy, and had asthma, pre-existing diabetes or hypertension, and a previous LSCS (**Table 1**). In contrast, compared with women with a psychiatric illness but no antidepressant

use, more women in the antidepressant exposed group were older, of higher socioeconomic status, non-smokers, multiparous, using other psychotropic medications during pregnancy, and had pre-existing diabetes or hypertension.

The overall risk of PPH was 11% among unexposed women, 11% among women with a psychiatric illness but no antidepressant use, and 16% among women exposed to antidepressants (**Table 1**). The risk of severe PPH was 5% among unexposed women, 5% among women with a psychiatric illness but no antidepressant use, and 9% among women exposed to antidepressants. Compared with women without each predisposing factor, women with placenta praevia (RR 3.25; 2.85 to 3.71), prolonged labour (RR 1.42; 1.25 to 1.85), hypertensive disorders of pregnancy (RR 1.23; 1.11 to 1.35), and assisted vaginal delivery (RR 1.60; 1.47 to 1.73) had an increased risk of PPH. Following adjustment for potential confounders, antidepressant use in late pregnancy was associated with a significantly increased risk of PPH (aRR 1.53; 1.25 to 1.86), with no increased risk observed for women with a psychiatric illness but no antidepressant use (aRR 1.04; 0.89 to 1.23) (**Table 2**). This risk associated with antidepressant use remained significant irrespective of method of delivery. Additional adjustment for maternal BMI, which was recorded in approximately two thirds of pregnancies, increased the risk estimate slightly (aRR 1.66: 1.32 to 2.07).

The risk of severe PPH following antidepressant use in late pregnancy was even higher (aRR 1.84; 1.39 to 2.44), with no increased risk observed for women with a psychiatric illness but no antidepressant use (aRR 1.10; 0.85 to 1.42) (**Table 3**). This associated risk for antidepressant use remained significant irrespective of method of delivery. In absolute terms, women with late gestation antidepressant exposure had an adjusted excess risk of 5.8% (2.5% to 9.1%) for any PPH, with a number needed to harm of 17; the figure for

adjusted excess risk of severe PPH was 3.9% (1.5% to 6.1%), with a number needed to harm of 26.

The prevalence of measured risk factors for PPH were compared according to maternal exposure status associated with an increased risk of PPH according to exposure status, with none observed to be substantial mediators of the current associations between antidepressant use and PPH (**Table S1 S2**).

In order to further explore the relationship between antidepressant use and PPH, we also investigated the association with the identification of postpartum anaemia. In accordance with the observed increased risk of PPH, use of antidepressants in late pregnancy was associated with a significantly increased risk of postpartum anaemia (aRR 1.80; 1,46 to 2.22) (**Table 4**). No increased risk was observed among women with a psychiatric illness but no antidepressant use (aRR 1.01; 0.83, 1.22).

Discussion

Main findings

Antidepressant use in late gestation was associated with about a 1.5-fold increase in risk of PPH and 6% excess risk. This increased risk was observed to be independent of the mode of delivery and could not be explained by an increased risk of known measured risk factors for PPH among antidepressant users.

Strengths and Limitations

Strengths of this study included the inclusion of a control group of women with non-medicated psychiatric illness and in contrast to previous studies, we were able to adjust for a range of behavioural factors including the use of tobacco, alcohol and illicit drugs, which are often inadequately collected in data on healthcare use.

This study is subject to a number of limitations. While we adjusted for a number of measured potential confounders with standard multivariable regression which did not affect the results, the potential for unmeasured confounding remains. We did not have sufficient data on some known risk factors for PPH, such as use of oxytocin in delivery. The inclusion of a control group of women with an identified psychiatric illness, but who were not taking antidepressants in late pregnancy, failed to demonstrate any increased risk of PPH associated with underlying maternal illness, a finding consistent across previous studies.[15, 17] No information, however, was available on the severity of the psychiatric illness and it remains possible that women continuing to take antidepressants into late pregnancy have more severe underlying illness and that unmeasured factors that are associated with the severity of the illness could have confounded the results. While the hospital pharmacy dispensing records utilised in this study are an efficient alternative to paper-based medical records in determining late gestation exposure to SSRIs, they underestimate exposure by approximately 25%.[18] As a result of this underestimation it is possible that some women in the control groups were actually exposed to an antidepressant in late gestation. Based on previous research, we are aware that this form of misclassification bias due to incomplete ascertainment of antidepressant use in late gestation is unlikely to have substantially biased the risk estimates, with slight attenuation towards the null.[22, 23] We did not have adequate power to examine the associations according to the individual type of antidepressant, their dose, or between antidepressants and severe PPH leading to a blood transfusion or mortality. Outcome misclassification is another source of bias, which would likely result in an underestimation of a true association. While estimating blood loss is notoriously difficult and prone to inaccuracy, given the recording of blood loss is likely to be independent of antidepressant exposure, this is unlikely to explain the observed associations. Moreover, the

risk of PPH amongst the control group was in line with state wide statistics (12% prevalence),

[24]

Interpretation

Our findings our very similar to those reported by Palmsten et al., who, through a large data-linkage study of more than 10,000 women exposed to antidepressants in the US, observed that use of serotonin reuptake inhibitors near delivery was associated with a 1.47-fold increased risk (95% CI 1.33 to 1.62) of PPH[17] Similarly, a large Swedish data-linkage study undertaken by Reis et al. identified a very similar 1.45-fold increased risk for PPH (95% CI 1.27–1.65). In this study, antidepressant use was combined into a single group and examined during late pregnancy.[13] Overall, these findings are slightly higher than those observed in a case-control study undertaken by Salkeld et al., who investigated outcomes separately for SSRI (aOR 1.33; 0.94, 1.89) and non-SSRI antidepressants (aOR 1.29; 0.58, 2.84).[16] This study, however, suffered from a small number of exposed cases, limiting the precision of the identified risk estimates. All three of these studies utilised standardised ICD-9 codes for the identification of PPH.[13, 16, 17] In contrast to these and our study, Lupattelli *et al.* investigated outcomes among women taking antidepressants within the Norwegian Birth Cohort Study.[15] They observed an increased risk among women exposed to TCAs and other antidepressants in late pregnancy (aOR 3.75; 1.09, 12.94), but not following exposure to SSRIs or SNRIs combined (aOR 0.97; 0.57, 1.65). A notable difference did exist in their definition of PPH, however, defined as a blood loss greater than 500mL irrespective of the method of delivery, deviating from existing guidelines[25]

While Lupattelli et al. is the only study to have directly measured and adjusted for maternal depressive symptoms, the presence of depressive symptoms themselves in the absence of antidepressant exposure did not appear to be associated with any appreciable risk

of PPH (aOR 1.14; 0.97, 1.34).[15] Despite the absence of direct measures of depressive symptoms, Palmsten *et al.* restricted their analyses to women with diagnoses for mood or anxiety disorders in the 1-5 months prior to delivery, whilst also adjusting for a number of confounders likely associated with severity of underlying maternal illness.[17] Similarly, we attempted to control for underlying maternal illness by including a control group of women with a non-medicated psychiatric illness, with no increased risk of PPH observed in this group.

While the exact mechanism linking the use of antidepressants with postpartum haemorrhage and other bleeding related events remains uncertain, it is thought that this may occur, at least in part, though alterations in platelet function.[26, 27] Serotonin has been demonstrated to play an important role in potentiating platelet aggregation,[26] with platelets reliant on serotonin transporters for the uptake of serotonin from the circulation as they are not capable of synthesising serotonin themselves.[27] Administration of antidepressants that block the activity of the serotonin transporter lead to a depletion of platelet serotonin and interfere with the serotonin-dependant intracellular signalling pathway that facilitates platelet activation in conjunction with other cofactors. Risk of bleeding is unlikely to be restricted to the use of serotonin reuptake inhibitors, as the administration of 5-HT$_{2A}$ receptor antagonists, which represents a key mechanism of action of some antidepressants, is also associated with a decrease in platelet response and aggregation.[28] Of additional interest is the role of the vesicular monoamine transporter (VMAT) within the platelet, which is involved in transporting serotonin across the dense granule membrane and vesicular storage. This raises the possibility that other antidepressants such as bupropion, which are thought to have indirect serotonergic activity through alterations in the regulation of the vesicular monoamine transporter,[29] may also have an effect on intracellular serotonin concentrations and therefore platelet function.

Conclusion

This study is the first to report an association between late gestation exposure to antidepressants and risk of PPH in an Australian population. This increased risk was observed regardless of mode of delivery, was independent of underlying maternal illness, and could not be explained by an increased risk of identified risk factors for PPH among antidepressant users. Such increases in risk were similar in magnitude of those previously reported from Canadian, Swedish and US populations.[13, 16, 17] As it is not possible to rule out residual confounding, further studies that account for clinical measures of severity of depression and behavioural factors associated with antidepressant use in late gestation are still required. If assumed causal, this represents just one component of the overall factors that should be considered in evaluating the benefits and risks associated with antidepressant use. While women and their physicians should be aware of the potential risks of PPH when making treatment decisions near the end of pregnancy, caution is advised against the routine cessation of antidepressants in late gestation until further research regarding optimal management strategies are available.

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None

Conflict of Interest

All authors have completed the Unified Competing Interest form at

http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial

relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contributors Statement

LEG conceptualised and designed the study, carried out the initial analyses, and drafted the initial manuscript.RM, GAD, and VLC helped design the study, assisted in interpretation of results, and reviewed and revised the initial manuscript. All authors approved the final manuscript as submitted.

Ethics Approval

This project was approved by the Human Research Ethics Committees of the Children, Youth, Women's Health Service and the University of Adelaide, in South Australia, Australia (REC2219-10-14; 29th October 2009).

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Table/Figure Captions

Table 1. Characteristics of Pregnant Women According to Exposure Status in Late Gestation

Characteristic	Antidepressant Use (n=558)	Psychiatric Illness (n=1,292)	Unexposed (n=28,348)
	No. (%)†		
Year of Delivery			
2002-2004	236 (42.3)	457 (35.4)	10834 (38.2)
2005-2006	144 (25.8)	436 (33.8)	8298 (29.3)
2007-2008	178 (31.9)	399 (31.0)	9216 (32.5)
Age,			
< 20	27 (4.8)	100 (7.7)	1,432 (5.1)
≥ 20-25	88 (15.8)	281 (21.8)	4,811 (17.0)
≥ 25-30	141 (25.3)	352 (27.2)	8,160 (28.8)
≥ 30-35	180 (32.3)	328 (25.4)	8,540 (30.1)
≥ 35	122 (21.9)	231 (17.9)	5,405 (19.1)
Socioeconomic Status			
1 (Lowest)	149 (26.8)	342 (26.5)	6,322 (22.4)
2	104 (18.7)	225 (17.4)	5,699 (20.2)
3	91 (16.3)	261 (20.2)	5,236 (18.5)
4	104 (18.7)	233 (18.1)	5,601 (19.8)
5 (Highest)	109 (19.6)	229 (17.8)	5,403 (19.1)
Smoking Status			
Non-Smoker	352 (64.2)	698 (54.8)	21,667 (78.9)
Quit	18 (3.3)	79 (6.2)	1,121 (4.1)
Smoker	178 (32.5)	497 (39.0)	4,681 (17.0)
Race			
Caucasian	509 (91.2)	1,139 (88.2)	21,990 (77.6)
Asian	37 (6.6)	113 (8.8)	2,916 (10.3)
Other	12 (2.2)	40 (3.1)	3,431 (12.1)
Parity ≥ 1	360 (64.8)	721 (55.9)	15,706 (55.4)
Plurality > 1	18 (3.2)	29 (2.2)	777 (2.7)
Psychotropic Medication Use	91 (16.3)	98 (7.6)	356 (1.3)
Pre-Existing Medical Conditions			
Coagulopathies	6 (1.1)	6 (0.5)	102 (0.4)
Diabetes	16 (2.9)	15 (1.2)	244 (0.9)
Hypertension	20 (2.6)	21 (1.6)	363 (1.3)
Asthma	94 (16.9)	217 (16.8)	2,029 (7.2)
Previous Obstetric History			
Caesarean Section	115 (20.6)	188 (14.6)	4,088 (14.4)
Antepartum haemorrhage	7 (1.3)	30 (2.3)	324 (1.1)
Postpartum haemorrhage	25 (4.5)	44 (3.4)	895 (3.2)

† percentages calculated from non-missing values

Table 2. Relative risks (RR) and 95% confidence intervals (CI) comparing risk for primary postpartum haemorrhage (≥ 500 mL following vaginal delivery or ≥ 1000 mL following caesarean section) according to exposure to antidepressants, psychiatric illness, or neither during pregnancy

	Total	No (%) of women with PPH	Unadjusted	Adjusted for delivery year*		Fully Adjusted†	
			RR	RR	95% CI	RR	95% CI
Any Type of Delivery							
Antidepressants	558	91 (16.3)	1.48	**1.47**	**1.22, 1.78**	**1.53**	**1.25, 1.86**
Psychiatric Illness	1292	139 (10.8)	0.98	0.99	0.84, 1.16	1.04	0.89, 1.23
Unexposed	28348	3128 (11.0)	Reference	Reference		Reference	
Caesarean Section							
Antidepressants	210	29 (13.8)	1.68	**1.68**	**1.19, 2.37**	**1.70**	**1.20, 2.40**
Psychiatric Illness	391	34 (8.7)	1.06	1.08	0.78, 1.51	1.20	0.86, 1.67
Unexposed	7 997	657 (8.2)	Reference	Reference		Reference	
Vaginal Delivery							
Antidepressants	348	62 (17.8)	1.47	**1.45**	**1.16, 1.82**	**1.47**	**1.16, 1.86**
Psychiatric Illness	901	105 (11.7)	0.96	0.97	0.81, 1.17	1.01	0.84, 1.22
Unexposed	20351	2471 (12.1)	Reference	Reference		Reference	

*2002, 2003, 2004, 2005, 2006, 2007, 2008

† Delivery year, age, socioeconomic status, race, multiple pregnancy, parity, smoking status, alcohol or substance abuse during pregnancy, coagulation defects, asthma, diabetes, hypertension, previous caesarean section, and use of other psychotropic medications

Table 3. Relative risks (RR) and 95% confidence intervals (CI) comparing risk for severe primary postpartum haemorrhage (≥1000mL) according to exposure to antidepressants, psychiatric illness, or neither during pregnancy

	Total	No (%) of women with severe PPH	Unadjusted	Adjusted for delivery year*		Fully Adjusted†	
			RR	RR	95% CI	RR	95% CI
Any Type of Delivery							
Antidepressants	558	49 (8.8)	1.94	**1.92**	**1.46, 2.52**	**1.84**	**1.39, 2.44**
Psychiatric Illness	1292	62 (4.8)	1.06	1.09	0.84, 1.40	1.10	0.85, 1.42
Unexposed	28 348	1 283 (4.5)	Reference	Reference		Reference	
Caesarean Section							
Antidepressants	210	29 (13.8)	1.68	**1.68**	**1.19, 2.37**	**1.70**	**1.20, 2.40**
Psychiatric Illness	391	34 (8.7)	1.06	1.08	0.78, 1.51	1.20	0.86, 1.67
Unexposed	7 997	657 (8.2)	Reference	Reference		Reference	
Vaginal Delivery							
Antidepressants	348	20 (5.8)	1.87	**1.83**	**1.19, 2.81**	**1.73**	**1.10, 2.73**
Psychiatric Illness	901	28 (3.1)	1.01	1.04	0.71, 1.53	0.98	0.66, 1.46
Unexposed	20 351	626 (3.1)	Reference	Reference		Reference	

*2002, 2003, 2004, 2005, 2006, 2007, 2008

† Delivery year, age, socioeconomic status, race, multiple pregnancy, parity, smoking status, alcohol or substance abuse during pregnancy, coagulation defects, asthma, diabetes, hypertension, previous caesarean section, and use of other psychotropic medications

Table 4. Relative risks (RR) and 95% confidence intervals (CI) comparing risk for postpartum anaemia according to exposure to antidepressants, psychiatric illness, or neither during pregnancy

	Total	No (%) of women with postpartum anaemia	Unadjusted	Adjusted for delivery year*		Fully Adjusted†	
			RR	RR	95% CI	RR	95% CI
Any Type of Delivery							
Antidepressants	558	83 (14.9)	1.82	**1.81**	**1.48, 2.21**	**1.80**	**1.46, 2.22**
Psychiatric Illness	1292	105 (8.1)	0.99	1.01	0.83, 1.21	1.01	0.83, 1.22
Unexposed	28 348	2322 (8.2)	Reference	Reference		Reference	
Caesarean Section							
Antidepressants	210	42 (20.0)	1.43	**1.41**	**1.07, 1.87**	**1.44**	**1.07, 1.93**
Psychiatric Illness	391	55 (14.7)	1.01	1.04	0.80, 1.33	1.07	0.83, 1.39
Unexposed	7997	1119 (14.0)	Reference	Reference		Reference	
Vaginal Delivery							
Antidepressants	348	41 (11.8)	1.99	**1.99**	**1.49, 2.66**	**2.02**	**1.50, 2.73**
Psychiatric Illness	901	50 (5.6)	0.94	0.95	0.72, 1.25	0.91	0.68, 1.22
Unexposed	20351	1203 (5.9)	Reference	Reference		Reference	

*2002, 2003, 2004, 2005, 2006, 2007, 2008

† Delivery year, age, socioeconomic status, race, multiple pregnancy, parity, smoking status, alcohol or substance abuse during pregnancy, coagulation defects, asthma, diabetes, hypertension, previous caesarean section, and use of other psychotropic medications

Table S1. Prevalence of risk factors for postpartum haemorrhage according to exposure status among all women included in the study (N=30,198)

	Antidepressant	Psychiatric Illness	Unexposed	p-value
N	558	1,292	28,348	
Primary PPH	91 (16)	139 (11)	3,128 (11)	<0.001
Severe PPH	49 (9)	62 (5)	1,283 (5)	<0.001
Tone				
Previous PPH	25 (4)	44 (3)	895 (3)	0.186
Obesity	101 (27.3)	214 (23.8)	3,616 (18.6)	<0.001
Antenatal Anaemia	98 (18)	134 (10)	2,787 (10)	<0.001
Placenta Praevia	13 (2)	12 (1)	313 (1)	0.032
Multiple Pregnancy	18 (3)	29 (2)	777 (3)	0.428
Prolonged Labour	9 (2)	33 (3)	811 (3)	0.180
Tissue				
Retained Placenta	15 (3)	17 (1)	457 (2)	0.105
Manual removal of placenta	15 (3)	20 (2)	473 (2)	0.172
Trauma				
Method of Delivery				
NVD	283 (51)	738 (57)	16,827 (59)	<0.001
Assisted Delivery	65 (12)	163 (13)	3,523 (12)	
Elective LSCS	85 (15)	142 (11)	2,792 (10)	
Emergency LSCS	125 (22)	249 (19)	5,206 (18)	
Macrosomia (>4,500g)	4 (<1)	16 (1)	458 (2)	0.160
Thrombin				
Pyrexia in labour	8 (1)	24 (2)	465 (1)	0.777
PIH	65 (12)	118 (9)	2,235 (8)	0.002
Pre-existing thrombotic disorders	6 (1)	6 (<1)	102 (<1)	0.035

Abbreviations: PPH, postpartum haemorrhage; NVD, normal vaginal delivery; PIH, pregnancy induced hypertensive disorders

Table S2. Prevalence of risk factors for postpartum haemorrhage according to exposure status only among women with severe postpartum haemorrhage (N=1,394)

	Antidepressant	Psychiatric Illness	Unexposed	p-value
Number	49	62	1,283	
Tone				
Previous PPH	3 (6.1)	6 (9.7)	83 (6.5)	0.582
Obesity	7 (21.2)	17 (39.5)	219 (24.9)	0.101
Antenatal Anaemia	13 (26.5)	6 (9.7)	161 (12.6)	0.020
Placenta Praevia	6 (12.2)	5 (8.1)	106 (8.3)	0.513
Multiple Pregnancy	3 (6.1)	3 (4.8)	71 (5.5)	0.943
Prolonged Labour	0	6 (9.7)	58 (4.5)	0.059
Tissue				
Retained Placenta	6 (12.2)	8 (12.9)	171 (13.3)	1.000
Trauma				
Method of Delivery				
NVD	16 (32.7)	22 (35.5)	497 (38.7)	0.895
Assisted Delivery	4 (8.2)	6 (9.7)	129 (10.0)	
Elective LSCS	7 (14.3)	9 (14.5)	199 (15.5)	
Emergency LSCS	22 (44.9)	25 (40.3)	458 (35.7)	
Macrosomia (>4,500g)	0	3 (4.8)	48 (3.7)	0.353
Thrombin				
Pyrexia in labour	0	5 (8.1)	45 (3.5)	0.080
PIH	7 (14.3)	11 (17.7)	131 (10.2)	0.117
Pre-existing thrombotic disorders	0	0	5 (0.4)	1.000

Abbreviations: PPH, postpartum haemorrhage; NVD, normal vaginal delivery; PIH, pregnancy induced hypertensive disorders