

ORIGINAL REPORT

Risk of preeclampsia after gestational exposure to selective serotonin reuptake inhibitors and other antidepressants: A study from The Norwegian Mother and Child Cohort Study

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Abstract

Purpose: To describe the risk of early- and late-onset preeclampsia across pregnancies exposed to antidepressants and to evaluate the impact of timing and length of gestational exposure to antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), on preeclampsia.

Methods: The Norwegian Mother and Child Cohort, a prospective population-based study, and the Medical Birth Registry of Norway provided information on antidepressant exposure, depression, and anxiety symptoms in pregnancy, preeclampsia diagnoses, and important covariates. Within a pregnancy cohort of depressed women, we compared the risk of late-onset preeclampsia between SSRI-exposed and nonmedicated pregnancies using marginal structural models (weighted) and modified Poisson regression models.

Results: Of the 5887 pregnancies included, 11.1% were exposed at any time before week 34 to SSRIs, 1.3% to serotonin-norepinephrine reuptake inhibitors, 0.4% to tricyclic antidepressants, and 0.5% to other antidepressants. The risks of early- and late-onset preeclampsia by exposure status in pregnancy were 0.3% and 3.6% (nonmedicated), 0.4% and 3.7% (SSRIs), 1.5% and 4.1% (serotonin-norepinephrine reuptake inhibitors), and 7.1% and 10.0% (tricyclic antidepressants). Compared with nonmedicated pregnancies, SSRI-exposed in mid and late gestation had adjusted relative risks for late-onset mild preeclampsia of 0.76 (95% confidence interval, 0.38-1.53) and 1.56 (0.71-3.44) (weighted models), respectively. There was no association between SSRI exposure in pregnancy and severe late-onset preeclampsia.

Conclusions: We have provided evidence that SSRI use in early and midpregnancy does not substantially increase the risk of late-onset preeclampsia.

KEYWORDS

antidepressant, MoBa, pharmacoepidemiology, preeclampsia, pregnancy, SSRI, The Norwegian Mother and Child Cohort Study

PRIOR POSTINGS AND PRESENTATIONS; Preliminary results of this work have been presented as an abstract (oral presentation) at the ICPE 2016.

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1 | INTRODUCTION

During pregnancy, up to 20% of women have depressive symptoms,¹ and 1% to 8% are treated with antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs).^{2,3} It has been suggested that SSRIs may increase the risk of preeclampsia.⁴⁻⁷ Preeclampsia is a major complication affecting 3% to 5% of all pregnancies and is cause of maternal-infant morbidity and mortality.⁸

Toh et al⁴ were the first to show an association between use of SSRI beyond the first trimester and increased risk of preeclampsia compared to no use (4.9-fold magnitude). While some studies replicated this association, albeit with smaller effect sizes (16-60% increased risk),^{5,6,9,10} other studies did not.^{7,11} Three of these^{7,9,11} found that women prenatally exposed to serotonin-norepinephrine reuptake inhibitors (SNRIs) or tricyclic antidepressants (TCAs) had an elevated risk of preeclampsia.

Antidepressants and maternal mood disorders may via different pathways trigger pathogenic vascular processes leading to preeclampsia,^{12,13} and this poses challenges in disentangling the effect of pharmacotherapy from that of the underlying depression. Although some prior studies have compared the risk of preeclampsia in depressed women treated versus untreated with antidepressants and adjusted for proxy measures of depression severity (eg, number of outpatient and inpatient depression diagnoses or other antidepressant [OAD] indications),^{5,9-11} none of them could directly measure depression severity and account for its possible fluctuation at 2 time points in pregnancy.

In a pregnancy cohort of depressed women, we aimed to (1) describe the risk of early- and late-onset preeclampsia across women prenatally exposed to various antidepressants and (2) closely examine the association between timing and length of gestational exposure to SSRIs and late-onset preeclampsia, accounting for time-varying exposure and severity of depressive and anxiety symptoms during pregnancy.

2 | METHODS

This study is based on The Norwegian Mother and Child Cohort Study (MoBa) linked to the Medical Birth Registry of Norway (MBRN) via women's personal identification number. The MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.¹⁴ Participants were recruited from all over Norway in 1999 to 2008 through a postal invitation in connection with a routine ultrasound at gestational weeks (GWs) 17 and 18. Data were gathered prospectively from 2 self-completed questionnaires at GWs 17 (Q1) and 30 (Q3). Women consented to participation in 41% of the pregnancies, and among these, the response rate was 95% for Q1 and 92% for Q3.¹⁵ The cohort now includes 114 500 children, 95 200 mothers, and 75 200 fathers. The current study is based on version 8 of the quality-assured data files released for research including women who delivered between 1999 and 2009. The establishment and data collection in MoBa has obtained a license from the Norwegian Data Inspectorate and approval from The Regional Committee for Medical Research Ethics. All participants gave their written informed consent prior to participation.

KEY POINTS

- This study extends the literature by considering 2 measures of depressive and anxiety symptom severity in pregnancy.
- SSRI exposure in early and midpregnancy did not substantially increase the risk of late-onset preeclampsia.
- Our study could rule out a 2-fold increased risk of late-onset preeclampsia following SSRI exposure in late pregnancy, although we were unable to confirm or refute whether a smaller increased risk exists.
- The crude risk of early- and late-onset preeclampsia was higher among SNRI- and TCA-exposed pregnancies than among depressed nonexposed.

The MBRN is based on compulsory notification of all live births, stillbirths, and induced abortions after GW 12 (after week 16 up to 2002) since 1967.¹⁶ This study included pregnancies within women with a medicated depression in the 6 months prior to pregnancy and/or with depression during pregnancy, as self-reported in Q1 and/or Q3. Both questionnaires included a list of previous and/or concurrent illnesses, including depression, and were completed at a mean GW of 17.5 (SD, 2.8) and 30.7 (SD, 1.7). The exclusion criteria and flowchart to achieve the final analysis cohort are outlined in Figure 1.

2.1 | Depression and anxiety symptoms in pregnancy

The short versions of The Hopkins Symptom Checklist-25 (SCL-25), ie, the 5- (SCL-5) and 8-item (SCL-8) scales, were used to measure severity of depressive and anxiety symptoms at GWs 17 and 30, respectively.^{15,16} Both scales measure symptoms in the last 2 weeks prior to completion and are highly correlated to the SCL-25,¹⁷ a reliable screening instrument for depression as defined by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems.¹⁷ For each SCL item, a score from 1 to 4 can be assigned. The sum score was calculated and divided by the number of items in each instrument.

To reflect the temporality of data collection in MoBa, as well as the time points in gestation when on average Q1 and Q3 were completed, and the SCL measurement validity time span, we considered 3 time points: T0 (GWs 0-16), T1 (GWs 17-28), and T2 (GWs 29-34) (Figure 2).

2.2 | Exposure

The Q1 and Q3 provided information about antidepressant exposure. Women reported the name of the medication taken along with timing of use (6 months before pregnancy and during pregnancy by 4-week intervals). Drug classification was based on the Anatomical Therapeutic Chemical (ATC) Classification System.¹⁸ Exposure to antidepressants was defined as exposure to a drug belonging to the ATC group

FIGURE 1 Flowchart to achieve the final analysis cohort*. MBRN, Medical Birth Registry of Norway; MoBa, The Norwegian Mother and Child Cohort Study; Q1, MoBa questionnaire 1; Q3, MoBa questionnaire 3. *Conditions may overlap. ^aWomen with multifetal gestation have one pregnancy record per fetus; a single pregnancy record was retained in the final eligible cohort. ^bIncludes both induced and spontaneous abortions. ^cWomen who did not report any medication for treatment of depression but checked the boxes related to timing of use of medication either before or during pregnancy. ^dWomen on therapy with antidepressants belonging to different antidepressant groups (eg, selective serotonin reuptake inhibitor and tricyclic antidepressant). ^ePreeclampsia with onset after gestational week 34, also including eclampsia and hemolysis, elevated liver enzymes, and low platelet count syndrome postdelivery. ^fPreeclampsia with onset between gestational weeks 20 and 34

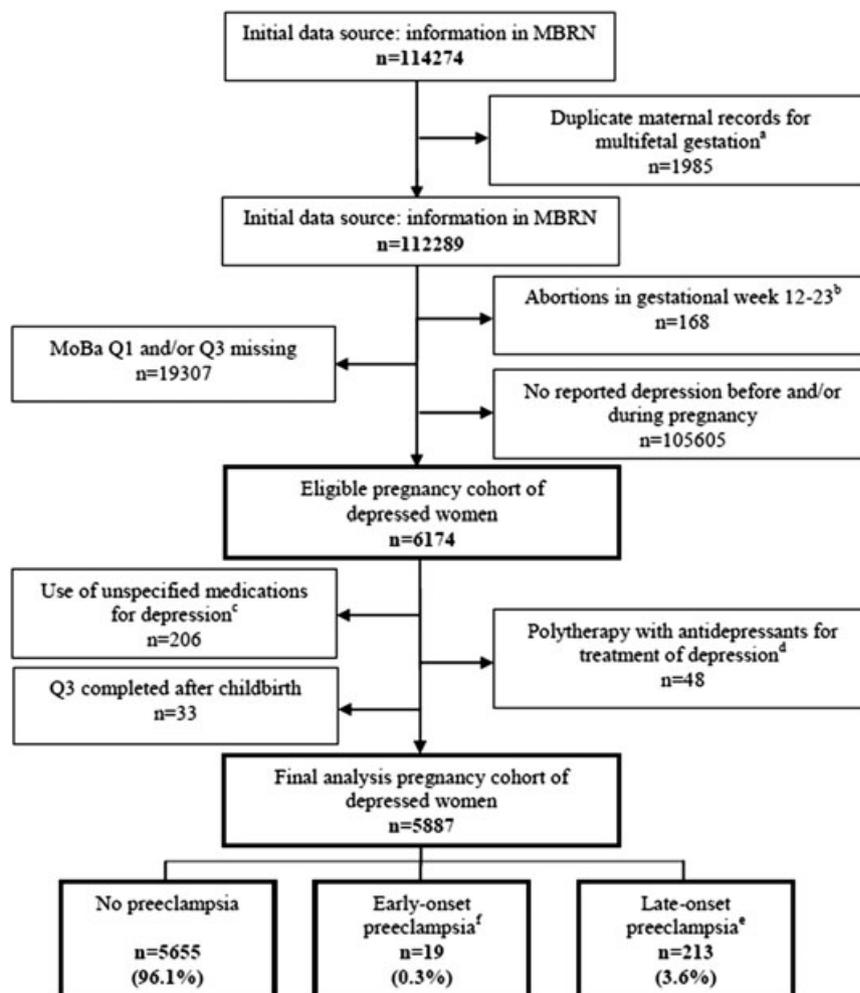
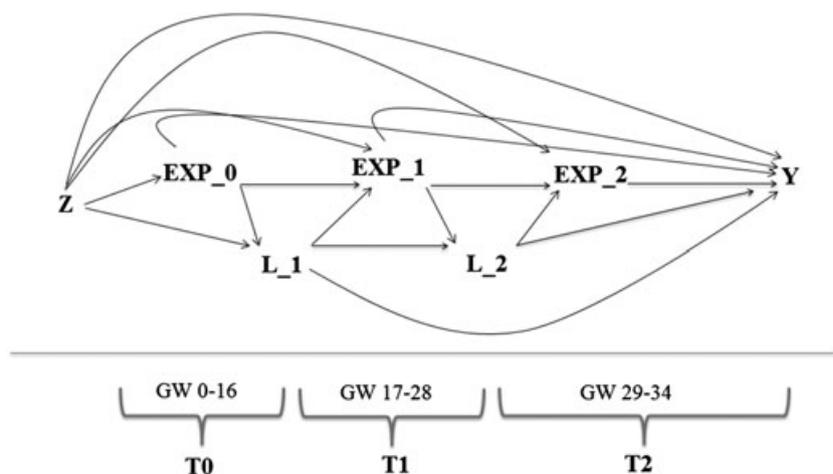


FIGURE 2 Directed acyclic graph for the outcome late-onset preeclampsia. GW, gestational week. Z is a vector of baseline covariates; EXP_0, EXP_1, and EXP_2 represent antidepressant exposure, specifically selective serotonin reuptake inhibitors in GW 0-16, 17-28, and 29-34; L_1 is a vector of time-varying confounders, including comedication with analgesics during weeks 0-16 and depressive/anxiety symptoms measured at GW 17; L_2 is a vector of time-varying confounders, including comedication with analgesics during weeks 17-28 and depressive/anxiety symptoms measured at GW 30. Y is the outcome measure, late-onset preeclampsia



N06A, subdivided into SSRIs (ATC: N06AB), SNRIs (venlafaxine and duloxetine), TCAs (ATC: N06AA), and OADs (mianserin, nefazodone, mirtazapine, bupropion, and reboxetine). Women on antidepressant polytherapy, ie, exposed to multiple antidepressant groups in pregnancy, were excluded (Figure 1).

The primary exposure windows were early (T0), mid (T1), and late (T2) pregnancy, with the addition of any time in pregnancy (T0-T2). The rationale behind this exposure definition is described in Appendix 1.

Length of antidepressant exposure was defined according to how many 4-week intervals were checked in the questionnaires: 0, 1, 2 to 4, and 5 to 8 intervals. Women were classified as exposed if they reported use of SSRIs, SNRIs, TCAs, or OADs during these periods. When more than one medication was reported for the same indication, we assumed that all medications were taken at the intervals checked. Based on previous studies,^{4,7,9} we also defined, among the pre-pregnancy SSRI exposed, continuers beyond the first trimester and discontinuers within the same period. We expanded this approach to

later gestation, ie, continuers in first half of third trimester versus discontinuers among midpregnancy SSRI users.

2.3 | Outcome

The main outcome variable was late-onset preeclampsia (any severity, mild, and severe), ie, preeclampsia developing after GW 34 as registered in the MBRN. Information provided in the registry is based on forms completed by midwives/obstetricians at delivery and during prenatal checkups. The main outcome variable included any diagnosis of late-onset preeclampsia (mild, severe, or unspecified); hemolysis, elevated liver enzymes, and low platelet count; and eclampsia. Severe preeclampsia included the following diagnoses: severe preeclampsia; hemolysis, elevated liver enzymes, and low platelet count syndrome; or eclampsia. Mild preeclampsia diagnosis was used when given alone. Early-onset preeclampsia was included as secondary outcome, ie, developing between GWs 20 and 34. Late- and early-onset preeclampsia were treated as mutually exclusive outcomes since they are generally regarded as subtypes of preeclampsia.^{19,20} Details about the diagnostic criteria for preeclampsia in Norway²¹ are outlined in Appendix 1. The validity of preeclampsia registration in the MBRN for MoBa participants has been assessed against antenatal records/hospital discharge codes, yielding a positive predictive value of 84%; upon generalization to the whole eligible MoBa population, the sensitivity was 43% and the specificity 99%.²²

2.4 | Covariates

Relevant confounding factors were identified with the aid of directed acyclic graphs.²³ Maternal age, parity, education, income, body mass index at conception, smoking status during pregnancy until week 30, depressive and anxiety symptoms in pregnancy, and comedication with analgesics (ie, opioids and nonsteroidal anti-inflammatory drugs) or other psychotropics (ie, antipsychotics, anxiolytics, hypnotics, and sedatives) in pregnancy were all ascertained from Q1 and Q3. The MoBa Q1 also captured information about lifetime event of major depression via utilization of the "The Life Time History of Major Depression" instrument,²⁴ comprising 6 items, which closely correspond to the DSM-III criteria for lifetime major depression. Obstetric risk factors for preeclampsia were ascertained from the MBRN (ie, multiple gestation, history of preeclampsia, chronic hypertension, gestational diabetes, and infertility treatment) and Q1 (ie, maternal blood pressure at the first antenatal visit).

2.5 | Statistical analysis

All statistical analyses were performed by using STATA version 14. Details about the study power in relation to SSRIs/late-onset preeclampsia are given in Appendix 1. Our study was underpowered for the SNRI-, TCA-, and OAD-exposed group, as well as for the outcome early-onset preeclampsia, for which only descriptive statistics are presented.

To estimate the relative risks (RRs) of late-onset preeclampsia (overall and by severity) along with their corresponding 95% confidence interval (CI) in relation to SSRI exposure, 2 sets of analyses were performed. First, we used modified Poisson regression models within

the generalized linear model framework (unweighted models). A robust variance estimator was applied to account for women's participation with more than one pregnancy in MoBa. We computed crude and adjusted RRs (aRRs) with 95% CI for the exposure windows; adjustment was done for a sufficient set of confounders (ie, maternal age, parity, body mass index, education, income, smoking status and weight gain, comedication with analgesics and other psychotropics, depressive symptoms as average of the standardized z-scores at each time point, and lifetime event of major depression).

In the second set (weighted models), we fit marginal structural models to account for time-varying SSRI exposure and time-varying confounders (depressive and anxiety symptoms in pregnancy and comedication with analgesics) (Figure 2).²⁵ We estimated the probability of SSRI treatment using a pooled logistic regression in which the outcome was current SSRI treatment. The covariates were maternal baseline factors, time-varying confounders at T1 and T2, time-fixed confounders, and SSRI history treatment (T0 exposure) (Appendix 2). We derived stabilized inverse probability of treatment weights (IPTW) for each pregnancy at each time point. We then fit a modified Poisson regression model with robust standard errors applying the IPTW. To avoid violation of the positivity assumption, we only included pregnancies of depressed women in the analysis. Data are presented as crude and aRR with 95% CI in both weighted and unweighted models.

Missing values on confounders ranged from 1% to 15%. Under the assumption that data were missing at random, we imputed missing values via multiple imputation (20 replications). Imputed data were used in both analysis sets. Details about missing data are provided in Appendix 1.

2.6 | Sensitivity and subanalyses

A number of sensitivity and subanalyses were undertaken. We considered in the main analyses major obstetric risk factors for preeclampsia and baseline maternal blood pressure by adjustment and restriction. Since parity is a major risk factor for preeclampsia, we run subanalyses among nulliparous women and explored any effect modification by parity. We also repeated the analysis restricted to the first pregnancy recorded in case of multiple participations in MoBa to limit selection bias by healthier maternal status. For comparison purposes with prior research,^{4,5,9-11} we explored in the unweighted models the effect of early SSRI exposure on preeclampsia as an aggregated outcome measure and compared SSRI-exposed pregnancies in the specific time windows to the depressed, never medicated counterpart. We examined the sensitivity of the findings in the weighted models by applying different model specifications including obstetric risk factors for preeclampsia and baseline maternal blood pressure or excluding covariates thought to lead to more extreme stabilized weights (cf Appendix 2). To explore the bias-precision trade-off, we progressively truncated the IPTW at 1st/99th and 5th/95th percentile.²⁵ We conducted complete-case analyses and considered in the analysis only SCL imputed values whenever more than a half of the items were completed with exclusion of pregnancies with missing information on the other important covariates. We conducted probabilistic sensitivity analyses to correct for exposure and outcome misclassification, unmeasured confounding and random error simultaneously using bias

parameters (10 000 simulations) stemming from existing studies.^{22,26,27} The latter validation study²⁷ showed a specificity of 99.9% and a sensitivity of 81.7% for SSRI use in mid/late pregnancy as reported in MoBa. To address unmeasured confounding by nutrition (ie, adherence to the Nordic diet, consisting of healthy foods native to a Nordic climate), we used prevalence estimates for high diet adherence ranging from 0.30 to 0.50²⁸ and assumed that high adherence to the Nordic diet was half as prevalent in SSRI users than in nonusers. We allowed the association between high diet adherence and late-onset preeclampsia to vary between 0.50 and 0.80.²⁸

3 | RESULTS

The final analysis cohort included 5887 pregnancies ending with a live-born (99.8%) or stillborn (0.2%, >GW 34) infant (Figure 1). Lost to follow-up (ie, Q3 not completed) occurred more often within younger, more disadvantaged women with more severe early gestation depressive symptoms compared to women remaining in the study (ie, both Q1 and Q3 completed). Lost to follow-up pregnancies presented higher rates of early- but not of late-onset preeclampsia.

Baseline sociodemographic, lifestyle, and health characteristics of the 5887 pregnancies in women with depression by antidepressant treatment status are shown in Table 1. The SSRI monotherapy (hereafter, SSRI) was the most common antidepressant exposure at any time in pregnancy before GW 34 (654/5887; 11.1%), with rates of use ranging from 10.1% in early to 4.1% and 3.4% in mid and late pregnancy, respectively. Few pregnancies were exposed to monotherapy with SNRIs (1.3%), TCAs (0.4%), or OADs (0.5%) at any time before GW 34 (Table 1).

Early- and late-onset preeclampsia complicated 19 (0.3%) and 213 (3.6%) of the pregnancies. The incidence of late-onset mild, severe, and unspecified preeclampsia was 2.4%, 1.0%, and 0.2%, respectively. The risk of late-onset preeclampsia by exposure status at any time before GW 34 is outlined in Figure 3A, whereas Figure 3B depicts the risk of early-preeclampsia according to antidepressant exposure in early pregnancy.

Five thousand seven hundred forty-five pregnancies from 5550 women were analyzed in relation to the effect of SSRIs on late-onset preeclampsia (hereafter, preeclampsia). There was no association between SSRI exposure in early, mid, late, or at any time in pregnancy and preeclampsia of any severity in the unweighted models (Table 2). Adjustment for the necessary set of confounders did not substantially affect the crude estimates, with depressive and anxiety symptoms being the covariates having the largest impact. There was no effect modification by parity. In the weighted model, the effect estimate for SSRI exposure in midpregnancy (aRR, 0.66; CI, 0.33-1.28) was lower than the one observed in the unweighted model, while larger for the late pregnancy window (aRR, 1.34; CI, 0.61-2.93); however, the CIs were wide and included the null. Table 2 also outlines the effect estimates for mild preeclampsia according to timing of SSRI exposure.

Table 3 summarizes unweighted RR for preeclampsia (any severity) according to length of SSRI exposure and continuation/discontinuation beyond first trimester. No severity-specific analyses were

conducted because of low statistical power. Of the 240 pregnancies exposed to SSRIs in midpregnancy, 194 continued the treatment in late pregnancy and 8 of these (4.1%) developed preeclampsia, compared to none among discontinuers.

3.1 | Sensitivity and subanalyses

The results of the unweighted (not shown) and weighted (Appendix 2) main models accounting for major obstetric risk factors for preeclampsia and maternal baseline blood pressure did not materially change our main findings. Restriction to nulliparous women, aggregation of early/late-onset preeclampsia in a unique outcome (Appendices 3 and 4), comparison of SSRI-exposed pregnancies in the specific time windows to the depressed, never medicated counterpart in the unweighted analysis, and alternative model specifications in the weighted (Appendix 2) did not produce substantially different results. The progressive IPTW truncation yielded an SSRI late exposure estimate with larger standard error, and the stabilized weight did not achieve better precision.

Appendices 1, 5, and 6 outline the distribution of key variables in relation to missingness and results of the complete case analyses. The complete case analysis estimates were higher than those found in the imputed data, particularly for SSRI early exposure. The unweighted and weighted results of the complete case analyses expanded to pregnancies with only SCL imputed values did not substantially deviate from the main findings (Appendix 7). Results of probabilistic bias analyses are summarized in Appendices 8 and 9 and supported our main findings.

4 | DISCUSSION

This study adds to the conflicting literature on the effect of SSRIs in pregnancy on preeclampsia and has the unique advantage of being able to account for severity of anxiety and depressive symptoms throughout gestation. We found no evidence that exposure to SSRIs in early or midpregnancy increases the risk of late-onset preeclampsia. Our findings on SSRI midpregnancy exposure are partly in line with one prior study¹¹ but also in contrast with 5 other studies.^{4-6,9,10} These discrepancies may be caused by several factors: different definitions of timing of exposure and outcome, lack of information on depression severity during gestation in all prior research, and cohort inclusion conditions (ie, live birth only versus live birth and stillbirth pregnancies), which may have introduced collider stratification bias. Missing data handling may have also produced divergent results. Our unweighted complete case analysis produced larger point estimates, which were partly in line with some prior studies.^{5,9,10} The missing data mechanism in our study seemed to be linked to maternal age and to the extent of completion of the SCL items, and as supported by our sensitivity analyses, a complete case analysis approach could have yielded biased estimates.²⁹

When accounting for time-varying severity of maternal depression and anxiety symptoms, we found that compared to nonexposed, the risk of late-onset mild preeclampsia was lower among midpregnancy SSRI-exposed (24% decreased risk) but higher (56% increased risk)

TABLE 1 Sociodemographic, lifestyle, and health characteristics of the sample by antidepressant use status during pregnancy before gestational week 34 (n = 5887)

	Depression, Nonmedicated n = 5106	Depression, SSRI Monotherapy n = 654	Depression, SNRI Monotherapy n = 75	Depression, TCA Monotherapy n = 21	Depression, OAD Monotherapy n = 31
Maternal age, y; mean ± SD	29.6 ± 5.1	30.0 ± 5.0	29.2 ± 5.6	31.0 ± 5.5	30.9 ± 4.3
Multiple gestation; no., %					
No	5030 (98.5)	637 (97.4)	73 (97.3)	21 (100.0)	30 (96.8)
Yes	76 (1.5)	17 (2.6)	2 (2.7)	—	1 (3.2)
Gestational age at delivery, wk; mean ± SD	39.4 ± 1.70	39.1 ± 1.81	39.2 ± 1.98	38.6 ± 1.53	39.1 ± 1.88
Parity; no., %					
0	2410 (47.2)	357 (54.6)	38 (50.7)	10 (47.6)	12 (38.7)
≥1	2696 (52.8)	297 (45.4)	37 (49.3)	11 (52.4)	19 (61.3)
Marital status; no., %					
Married/cohabiting	4663 (91.3)	566 (86.5)	62 (82.7)	20 (95.2)	28 (90.3)
Other	399 (7.8)	84 (12.8)	11 (14.7)	1 (4.8)	3 (9.7)
Educational level; no., %					
University/college	2428 (47.6)	311 (47.6)	29 (38.7)	7 (33.3)	15 (48.4)
Lower than university/college	2326 (45.6)	301 (46.0)	43 (57.3)	14 (66.7)	16 (51.6)
Woman's gross yearly income, NOK; no., %					
No income	204 (4.0)	29 (4.4)	1 (1.3)	1 (4.8)	1 (3.2)
<199 999	1858 (36.4)	277 (42.4)	31 (41.3)	9 (42.9)	16 (51.6)
200-399 999	2470 (48.4)	286 (43.7)	33 (44.0)	10 (47.6)	11 (35.5)
>400 000	402 (7.9)	43 (6.6)	7 (9.3)	1 (4.8)	1 (3.2)
BMI at conception; mean ± SD	24.3 ± 4.6	24.5 ± 4.9	24.5 ± 5.0	25.6 ± 4.5	22.6 ± 3.7
Weight gain, kg, until GW 30; mean ± SD	9.8 ± 5.4	9.5 ± 5.4	10.9 ± 6.0	10.0 ± 4.8	9.7 ± 6.6
Smoking status at GW 30; no., %					
No	3643 (71.4)	439 (67.1)	42 (56.0)	15 (71.4)	13 (41.9)
Yes	728 (14.3)	111 (17.0)	22 (29.3)	3 (14.3)	10 (32.3)
Stopped in pregnancy	683 (13.4)	100 (15.3)	9 (12.0)	3 (14.3)	8 (25.8)
Infertility treatment; no., %					
No	4831 (94.6)	623 (95.3)	72 (96.0)	20 (95.2)	28 (90.3)
Yes	275 (5.4)	31 (4.7)	3 (4.0)	1 (4.8)	3 (9.7)
Chronic hypertension and use of antihypertensive before conception; no., %					
No	5098 (99.8)	653 (99.9)	75 (100.0)	21 (100.0)	31 (100.0)
Yes	8 (0.2)	1 (0.1)	—	—	—
Systolic blood pressure, mm Hg ^a ; mean ± SD	113.1 ± 12.5	111.7 ± 13.1	107.7 ± 9.8	114.8 ± 14.4	110.0 ± 15.0
Diastolic blood pressure, mm Hg ^a ; mean ± SD	68.1 ± 9.6	67.3 ± 9.7	66.0 ± 8.2	69.4 ± 9.0	66.8 ± 9.7
Preexisting diabetes; no., %					
No	5181 (99.4)	650 (99.4)	75 (100.0)	21 (100.0)	31 (100.0)
Yes	34 (0.7)	4 (0.6)	—	—	—
Preeclampsia history; no., %					
No	4910 (96.2)	627 (95.9)	71 (94.7)	21 (100.0)	29 (93.6)
Yes	196 (3.8)	27 (4.1)	4 (5.3)	—	2 (6.5)
History of spontaneous abortion(s) ^b ; no., %					
No	3480 (68.2)	466 (71.3)	53 (70.7)	13 (61.9)	18 (58.1)
Yes	1000 (19.6)	121 (18.5)	12 (16.0)	6 (28.6)	12 (38.7)
Lifetime major depression ^c ; no., %					
No	1328 (26.0)	46 (7.0)	7 (9.3)	2 (9.5)	2 (6.4)
Yes	3491 (68.4)	582 (89.0)	66 (88.0)	19 (90.5)	29 (93.6)
Depressive symptoms at GW 17; z-score ± SD	-0.03 ± 0.98	0.18 ± 1.11	0.37 ± 1.15	0.14 ± 0.87	0.39 ± 1.08
Depressive symptoms at GW 30; z-score ± SD	-0.02 ± 0.97	0.10 ± 1.13	0.43 ± 1.39	0.31 ± 1.08	0.44 ± 1.31

(Continues)

TABLE 1 (Continued)

	Depression, Nonmedicated n = 5106	Depression, SSRI Monotherapy n = 654	Depression, SNRI Monotherapy n = 75	Depression, TCA Monotherapy n = 21	Depression, OAD Monotherapy n = 31
Comedication use in pregnancy; no., %					
Other psychotropic drugs ^d	142 (2.8)	81 (12.4)	10 (13.3)	5 (23.8)	8 (25.8)
NSAIDs and/or opioid analgesics	450 (8.8)	85 (13.0)	11 (14.7)	3 (14.3)	6 (19.4)

Abbreviations: BMI, body mass index; GW, gestational week; NOK, Norwegian Krone (1 NOK=0.13 USD); NSAID, nonsteroidal anti-inflammatory drugs; OADs, other antidepressants; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

Numbers may not add up to total due to missing values, ranging from 1% to 3% for smoking, BMI, and socioeconomic status, to 5% to 7% for educational level, lifetime history of major depression and depressive, and anxiety symptoms in GW 17, 8% to 10% for depressive and anxiety symptoms in GW 30 and weight gain, and 14% for baseline blood pressure values.

^aSelf-reported systolic and diastolic blood pressure as measured at first antenatal visit.

^bDefined as history of spontaneous abortion(s) before GW 12.

^cDefined as Kendlers lifetime major depression scale score of 3 or more of 6 depressive symptoms of duration of more than 2 weeks.

^dOther psychotropic drugs include all medications under the Anatomical Therapeutic Chemical code N05, ie, antipsychotics, anxiolytics, hypnotics, and sedatives.

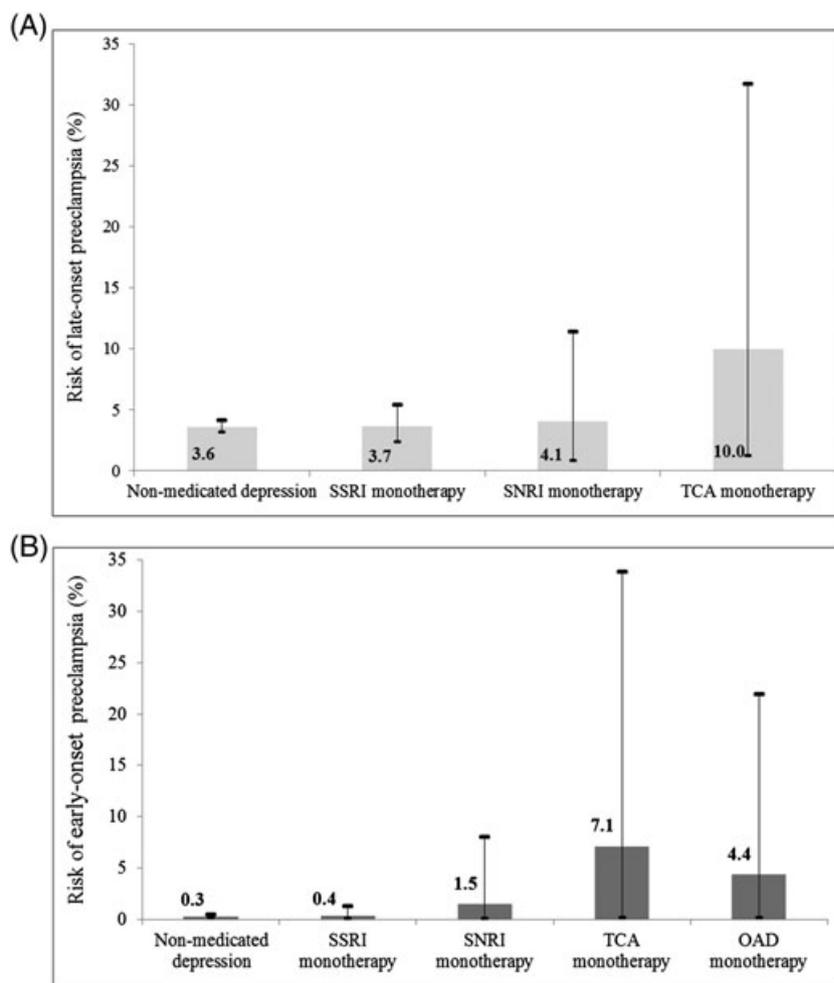


FIGURE 3 Risk of A, late-onset (ie, later than week 34) and B, early-onset (ie, weeks 20-34) preeclampsia by antidepressant exposure status. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; OAD, other antidepressant. Antidepressant exposure in gestational weeks 0-34 (within A) and antidepressant exposure in gestational weeks 0-16 (within B). The Other antidepressant (OAD) exposure group not presented in A, since there were no cases of late-onset preeclampsia

among SSRI-exposed in late pregnancy. Although the estimate CIs were wide and crossed the null effect, these divergent estimates may suggest the importance of timing of SSRI exposure and/or of time-specific interplay of biological mechanisms in relation to preeclampsia. Depression and anxiety may plausibly increase the risk of preeclampsia

via an altered excretion of vasoactive hormones or other neuroendocrine transmitters.^{30,31} Treatment with SSRIs seems to normalize the dysfunction of the hypothalamic-pituitary-adrenal axis and could thereby reduce the risk of preeclampsia posed by depression through this mechanism.³² It is possible that our findings on late pregnancy

TABLE 2 Risk of late-onset preeclampsia—overall and by severity—according to timing of SSRI exposure in pregnancy (n = 5745)

Depressed Cohort	Total	N (%) with Outcome	Crude RR (95% CI)	Unweighted Adjusted RR ^a (95% CI)	Weighted Adjusted RR ^b (95% CI)
Preeclampsia, any severity					
Nonmedicated, GWs 0-16	5154	186 (3.6)	Reference	Reference	
SSRI, GWs 0-16	591	22 (3.7)	1.03 (0.67-1.59)	0.96 (0.63-1.46)	—
Nonmedicated, GWs 17-28	5505	200 (3.6)	Reference	Reference	Reference
SSRI, GWs 17-28	240	8 (3.3)	0.92 (0.46-1.84)	0.92 (0.48-1.79)	0.66 (0.33-1.28)
Nonmedicated, GWs 29-34	5547	200 (3.6)	Reference	Reference	Reference
SSRIs, GWs 29-34	198	8 (4.0)	1.12 (0.56-2.24)	1.08 (0.57-2.07)	1.34 (0.61-2.93)
Nonmedicated, GWs 0-34	5093	184 (3.6)	Reference	Reference	
SSRIs, GWs 0-34	652	24 (3.7)	1.02 (0.67-1.55)	0.96 (0.64-1.45)	—
Preeclampsia, mild					
Nonmedicated, GWs 0-16	5092	124 (2.4)	Reference	Reference	
SSRI, GWs 0-16	585	16 (2.7)	1.12 (0.67-1.88)	1.05 (0.63-1.75)	—
Nonmedicated, GWs 17-28	5438	133 (2.5)	Reference	Reference	Reference
SSRI, GWs 17-28	239	7 (2.9)	1.20 (0.57-2.53)	1.22 (0.59-2.54)	0.76 (0.38-1.53)
Nonmedicated, GWs 29-34	5480	133 (2.4)	Reference	Reference	Reference
SSRI, GWs 29-34	197	7 (3.6)	1.46 (0.69-3.09)	1.49 (0.73-3.04)	1.56 (0.71-3.44)
Nonmedicated, GWs 0-34	5031	122 (2.4)	Reference	Reference	
SSRI, GWs 0-34	646	18 (2.8)	1.15 (0.71-1.87)	1.10 (0.67-1.80)	—
Preeclampsia, severe					
Nonmedicated, GWs 0-34	4959	50 (1.0)	Reference	Reference	
SSRI, GWs 0-34	633	5 (0.8)	0.78 (0.31-1.96)	0.72 (0.31-1.68)	—

Abbreviations: CI, confidence interval; GW, gestational week; RR, relative risk; SSRI, selective serotonin reuptake inhibitors.

Numbers of severe and mild late-onset preeclampsia may not add up to total due to cases of unspecified late-onset preeclampsia. Data are not shown because of low number of cases. Severe late-onset preeclampsia could only be explored in relation to the exposure window GWs 0-34 because of low statistical power.

^aAdjusted for maternal age, body mass index at conception, woman's socioeconomic status, educational level, parity, smoking status in pregnancy, weight gain, comedication with analgesics or other psychotropics, lifetime history of major depression, and average z-score of depressive and anxiety symptoms at 2 time points in pregnancy.

^bMarginal structural model weighted with stabilized inverse probability of treatment weighting constructed at each time point using baseline covariates, time-varying and time-fixed confounding factors, and SSRI history treatment.

TABLE 3 Risk of late-onset preeclampsia (any severity) according to length of SSRI exposure in pregnancy and continuation/discontinuation in early pregnancy (n = 5745)

Depressed Cohort	Total	N (%) with Outcome	Crude RR (95% CI)	Unweighted Adjusted RR ^a (95% CI)
Preeclampsia, any severity				
Nonmedicated, ever	5127	186 (3.6)	Reference	Reference
SSRI in 1 interval	220	6 (2.7)	0.75 (0.34-1.68)	0.70 (0.32-1.55)
SSRI in 2-4 intervals	203	8 (3.9)	1.09 (0.54-2.17)	0.96 (0.48-1.91)
SSRI in 5-8 intervals	195	8 (4.1)	1.13 (0.57-2.26)	1.16 (0.60-2.24)
SSRI in 1 interval	220	6 (2.7)	Reference	Reference
SSRI in 2-4 intervals	203	8 (3.9)	1.44 (0.51-4.10)	1.27 (0.42-3.82)
SSRI in 5-8 intervals	195	8 (4.1)	1.50 (0.53-4.26)	1.47 (0.56-3.90)
SSRI discontinuers ^b	246	7 (2.9)	Reference	Reference
SSRI continuers ^c	208	11 (5.3)	1.86 (0.73-4.71)	1.63 (0.66-4.03)

Abbreviations: CI, confidence interval; RR, relative risk; SSRI, selective serotonin reuptake inhibitor.

^aAdjusted for maternal age, body mass index at conception, woman's socioeconomic status, educational level, parity, smoking status in pregnancy, weight gain, comedication with analgesics or other psychotropics, lifetime history of major depression, and average z-score of depressive and anxiety symptoms at 2 time points in pregnancy.

^bDefined as SSRI exposed pregnancies before pregnancy, but SSRI treatment discontinued within the first trimester (ie, before gestational week 13).

^cDefined as SSRI exposed pregnancies before pregnancy and SSRI treatment continued in and beyond the first trimester.

SSRI exposure may be ascribed to residual confounding by depression severity or stress at the very end of gestation.

There are however biological mechanisms supporting a role of SSRIs in preeclampsia, which may be relevant during the maternal systemic response to preeclampsia. The SSRIs elicit increased levels of serotonin,¹² which in turn enhance vasoconstriction on the umbilical-placental vessels, and they also inhibit synthesis of nitric oxide, an important vasodilator.^{33,34} In late gestation pregnant sheep, for instance, there was a transient reduction of uterine artery blood flow following fluoxetine administration.³⁵ Our point estimate by length of SSRI exposure (5-8 vs one 4-week interval) was of similar magnitude to that observed in a prior study,¹¹ although the CIs were wide and crossed the null effect. Palmsten et al¹¹ also found no association between cumulative SSRI dose and preeclampsia, which raises the question of whether timing of exposure may be linked to preeclampsia rather than cumulative dose; this could also be supported by our findings on the extent of preeclampsia in relation to SSRI continuation/discontinuation in the first half of the third trimester. Since maternal susceptibility to vascular damage and factors other than poor placentation are etiologically relevant for late-onset preeclampsia,³⁶ our findings may provide, together with prior research,³⁷ some hints about the underlying mechanisms of this elusive syndrome.

The elevated risk for preeclampsia observed among TCA-exposed pregnancies at any time before week 34 aligns with findings of 2 previous studies (10-11%),^{9,11} while the one for SNRI exposure was not as large (6-9%). Because of their vasoconstrictive effects,¹² SNRIs and TCAs may plausibly be linked to preeclampsia, but the elevated risk seen in relation to early preeclampsia would also indicate a potential role of these medications on placentation. The small sample size however impeded us to conduct adjusted analyses and further explore these potential associations.

4.1 | Strengths and limitations of the study

There are several strengths and limitations inherent this investigation and the MoBa study. Data collection was conducted prospectively, avoiding the risk of recall bias. Distinction of early- from late-onset preeclampsia reduced the risk of reverse causality. We could account for several health-related and maternal factors, including severity of depressive and anxiety symptoms in pregnancy via a validated instrument. Although this latter measurement cannot replace a clinical interview and is not designed to measure perinatal mood specifically, it provides a reliable measure of the severity of these psychiatric conditions.^{17,38} We accounted for unmeasured confounding by diet quality,²⁸ conducted several sensitivity and subanalyses to explore the robustness of our findings, and also explored the impact of missing information on important covariates on our estimates. However, residual confounding by depression severity or number of cigarette smoked during gestation cannot be ruled out.

One limitation is that antenatal depression was self-reported in MoBa. However, our analysis cohort was about 5% of the initial data source, which equals estimates of major depression in pregnancy based on structural clinical interviews.¹ Depressive and anxiety symptoms were not measured at baseline, but only at 2 time points in

pregnancy; however, information about lifetime history of major depression was used in the generation of the stabilized weights. Exposure and outcome misclassification could be an additional concern. Use of antidepressants was self-reported; however, the impact of SSRI misclassification has been explored and assessed as minimal for mid/late pregnancy exposure.²⁷ Yet the impact of misclassification of SSRI exposure in terms of length and by the individual 4-week intervals has not been addressed. Information on dosage is not available in the MoBa, and data about duration of exposure are not complete. The positive predictive value for a diagnosis registration of preeclampsia in the MBRN was found to be 84%, and false negative cases seemed to have mild forms of preeclampsia.²² The results of probabilistic bias analyses did not materially change our main conclusions.

The MoBa study has a low response rate (41%), with a possible self-selection of the healthiest women.¹⁵ Its potential for bias has been thoroughly explored by comparing the MoBa with the total Norwegian birthing population,³⁹ and although the prevalence estimates could not necessarily be generalized, the measures of associations tested were valid in the MoBa. We cannot, however, rule out that selection bias and/or lost to follow-up of more disadvantaged women may have impacted the study results. Our sample size limited the statistical power of the analysis on mid and late pregnancy SSRI exposure, and impeded us to explore antidepressants other than SSRIs, as well as early-onset preeclampsia.

To conclude, SSRI use in early and midpregnancy does not substantially increase the risk of late-onset preeclampsia. This information may assist clinicians when evaluating the risk of treatment with SSRIs versus that of nonmedicated depression. The elevated risk of late-onset preeclampsia (mainly mild) among SSRI-exposed in late pregnancy needs to be refuted or confirmed by additional studies with greater numbers of exposed cases. Whether SNRIs and TCAs have an etiological role in relation to early- and late-onset preeclampsia needs to be further elucidated in both epidemiological and biological research.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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