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ORIGINAL ARTICLE

Association between antidepressant use in pregnancy and gestational diabetes mellitus: Results from the Norwegian Mother, Father and Child Cohort Study

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Abstract

Purpose: This study sought to determine the association between gestational diabetes mellitus (GDM) and antidepressant exposure during early-mid pregnancy, overall and according to antidepressant affinity to the histamine-1 (H_1) receptor.

Methods: Data originate from the nation-wide, Norwegian Mother, Father and Child Cohort Study conducted in 1999–2008, linked to the national Medical Birth Registry. The study included 6647 pregnancies within women with depressive/anxiety disorders during and/or 6 months prior to pregnancy. Pregnancies exposed in early-mid gestation to antidepressants having low (group 1, $n = 814$) or high (group 2, $n = 77$) affinity to the H_1 receptor were compared to non-medicated ($n = 5756$). We fit crude and weighted modified Poisson regression models using inverse probability of treatment weighting (IPTW).

Results: Overall, 84 (1.3%) of the pregnancies developed GDM. Relative to non-medicated pregnancies, the risk of GDM was slightly lower in antidepressant group 1 exposed (1.3% vs 1.1%), but more elevated in those exposed to group 2 antidepressants (3.9%). In the weighted analysis, there was no evidence for an association between antidepressant group 1 exposure in early-mid pregnancy and risk of GDM [relative risk (RR): 0.69, 95% confidence interval: 0.31–1.51].

Conclusions: Gestational use of antidepressants with low H_1 receptor affinity, mainly SSRIs and SNRIs, does not pose a substantial risk of GDM in women with depressive/anxiety disorders in pregnancy, compared to no use.

KEYWORDS
antidepressants, gestational diabetes mellitus, MoBa, pregnancy, Norwegian Mother, Father, and Child Cohort Study

Key Points

- This study extends the literature by considering whether the risk of gestational diabetes mellitus (GDM) may vary according to antidepressant's affinity to the histamine-1 receptor.

(i) Poster presentation at the 36th ICPE annual conference; (ii) abstract selected for presentation at the ENTIS annual meeting (canceled meeting) but published in *Reprod. Toxicol.* 2020;97:5. doi: 10.1016/j.reprotox.2020.04.010.

- Early-mid pregnancy use of antidepressants with low affinity to the histamine-1 receptor, including the most common antidepressant group of selective serotonin reuptake inhibitors (SSRIs), does not increase the risk of GDM.
- Our study could rule out a two-fold increased risk of GDM following antidepressant exposure, although we were unable to confirm or refute whether a smaller increased risk exists.
- The risk for GDM was greater in pregnancies within women who took antidepressant with high affinity to histamine-1 receptor compared to unexposed women with depression and/or anxiety, but no adjusted association measured could be estimated due to low statistical power.

Language Summary

This study among pregnant women in Norway examined whether antidepressant use in early-mid pregnancy can increase the risk of gestational diabetes. The results suggest that women who used antidepressant medication in pregnancy do not have a greater risk for gestational diabetes than women who had depression or anxiety but did not take these medications.

1 | INTRODUCTION

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition in pregnancy,[1] affect as many as 5% of pregnant women in Europe.[2,3] Its global prevalence varies markedly (from 1% to <30%), owing among other factors, to lack of consensus on diagnostic criteria and varying distribution of maternal life-style and genetic factors.[4] Beyond carrying risks for an array of adverse perinatal outcomes for both offspring and mother (e.g., early fetal loss, prematurity, macrosomia, and preeclampsia),[5] GDM is a strong predictor of diabetes mellitus type II in the woman later in life.[6]

Studies in non-pregnant subjects have shown a link between antidepressant medication and risk for type II diabetes (T2DM) (21%–31% increased risk).[7] Multiple biological mechanisms have been proposed for this association, including serotonin dysregulation which controls food intake and weight regulation,[8,9] altered brain-gut relationship via the microbiome,[10] impairment of pancreatic beta cells,[11] or antagonism to the histamine-1 (H_1) receptor.[7,12] Because pregnancy per se predisposes to insulin resistance, understanding the metabolic safety of antidepressants in the pregnant women is a clinically relevant question.

Two studies[13,14] identified a moderate risk of GDM (31%–37% increased risk) with antidepressant exposure in early-mid pregnancy, compared to unexposed women who may or may not have a perinatal mental disorder. This comparison raises however concerns of confounding by indication.[15,16] Two additional studies[17,18] could not replicate these findings for the whole antidepressant group when using as comparator women with depression, albeit the GDM risk was elevated after use of venlafaxine, amitriptyline, or sertraline.[17,18] Although studies in non-pregnant subjects have shown that the risk of T2DM increases following the use of antidepressants with greater affinity to the H_1 receptor,[7,12] this research question has not been systematically studied in the context of GDM.

In this study we sought (i) to describe the risk of GDM according to maternal use of antidepressants with different affinity to the H_1 receptor in early-mid pregnancy; and (ii) to quantify the association between GDM and maternal use of antidepressants in early-mid pregnancy, overall and by drug affinity to the H_1 receptor, relative to non-medicated depressive/anxiety disorders.

2 | METHODS

2.1 | Study population and data collection

This study was based on data from the Norwegian Mother, Father and Child Cohort Study (MoBa), linked to records in the Medical Birth Registry of Norway (MBRN). Linkage of data was done using the unique personal identifier number of each citizen of Norway. MoBa is a nationwide, prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health.[19] Pregnant women were recruited from all over Norway in 1999–2008 through a postal invitation in connection with a publicly offered routine ultrasound at 17–18 weeks of gestation. In MoBa, data were gathered prospectively via two prenatal questionnaires at week 17 (Q1) and week 30 (Q3) and multiple postnatal self-administered questionnaires at 6 months postpartum, and then at different child ages up to adolescence.[20] All MoBa questionnaires are available online.[20] The current study is based on version 9 of the quality-assured MoBa data files released for research. The cohort now includes 114 500 children, 95 200 mothers, and 77 300 fathers.[19] The participation rate for all invited pregnancies is 41%. Of those agreeing to participate, the response rate was 92%–95% for Q3 and Q1.[21]

The MBRN is based on compulsory notification of all live births, stillbirths, and induced abortions after week 12.[3] The registry comprises maternal medical records during prenatal care, as well as mother and child health at the delivery ward. These include information on maternal chronic diseases (e.g., pre-existing diabetes), child health at birth, pregnancy health and outcomes, and gestational length.

This study included women who had returned both questionnaire Q1 and Q3, since these provide data on medication exposure in pregnancy, before the birth outcome was known (Figure 1).

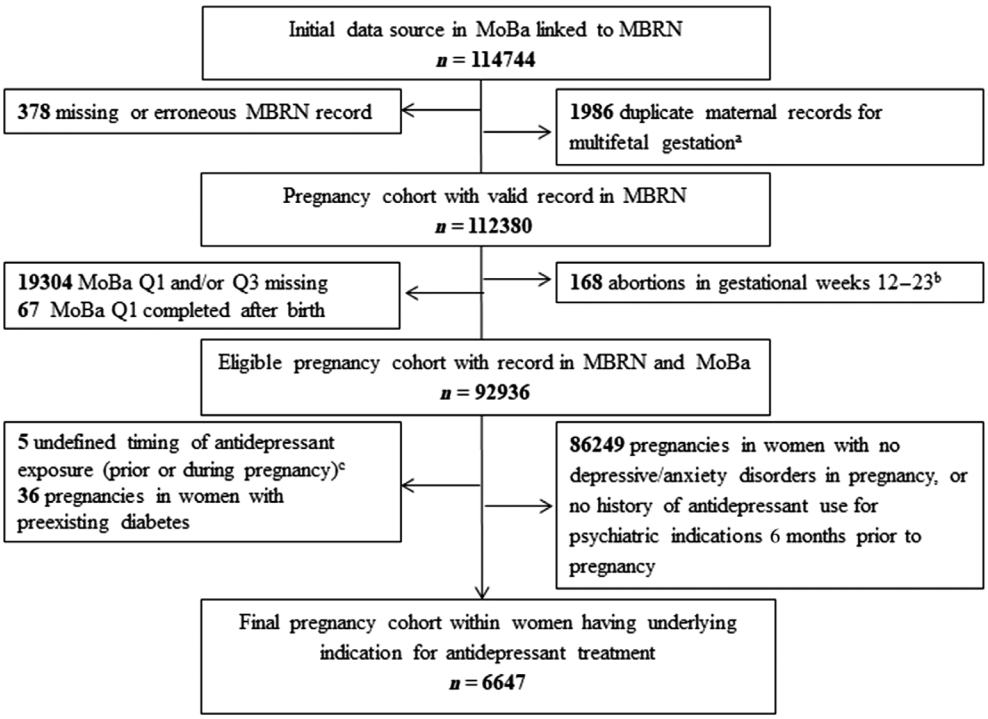

FIGURE 1 Flow-chart to achieve the final study cohort (conditions for exclusion of observations may overlap). GDM, gestational diabetes mellitus; MBRN, Medical Birth Registry of Norway; MoBa, The Norwegian Mother, Father and Child Cohort Study; Q1, MoBa questionnaire 1 filled at gestation week 17; Q3, MoBa questionnaire 3 filled at gestation week 30. [a]Women with multifetal gestation have one pregnancy record per fetus; a single pregnancy record was retained in the final study population. [b]Includes both induced and spontaneous abortions. [c]Women with unclear timing of antidepressant use

2.2 | Maternal depression and anxiety as inclusion criteria

In MoBa, Q1 and Q3 women were presented with a list of previous/concurrent illnesses, including depression (both Q1 and Q3), anxiety (only Q1), and other mental disorders (both Q1 and Q3) (hereafter, clinical depression/anxiety).[20] Women were asked to check off if and when (i.e., before or during early or mid-late pregnancy) these disorders were present. To emulate the design of a target trial using observational data and to reduce risk of indication bias,[15,22–24] this study included pregnancies with an underlying indication for treatment with antidepressants in pregnancy; that is, women who self-reported depression/anxiety specifically during pregnancy, and/or had depression/anxiety in the 6 months prior to pregnancy medicated with a psychotropic (cf. Figure 1).

2.3 | Outcome

The main outcome was GDM (yes/no), based on MBRN obstetric records throughout the course of pregnancy. In Norway, GDM screening is recommended for high-risk women at gestational weeks 24–28,[25] via administration of the "Glucose Challenge Test". Maternal use of any medication and psychiatric disorders are not criteria for the targeted screening. The diagnostic criteria for GDM are (i) fasting plasma glucose level ≥7.0 mmoL/L; or (ii) 2 h after glucose challenge test glucose level ≥11.1 mmoL/L.[25] The validity of any diabetes registration in the MBRN has been assessed against filled prescription records for antidiabetic medications, yielding a sensitivity and specificity of 72% and 99%.[26]

2.4 | Exposure

Information on antidepressant exposure and indication for use was collected from MoBa Q1 (from week 0 to 12) and Q3 (from week 13 to >29).[20] Women reported the name of the medication taken and timing of use in 4-week intervals throughout pregnancy (e.g., week 0–4, 5–8, etc.). Drug classification was based on the Anatomical Therapeutic Chemical (ATC) Classification System.[27] Gestational exposure to each individual antidepressant (fifth level of the ATC system) was defined as exposure to a drug belonging to the ATC group N06A. Individual antidepressants were then assembled into two groups based on their affinity to the H_1 receptor, in alignment with prior research.[7,12,28] Group 1 included antidepressants with lower H_1 receptor affinity (but high serotonin receptor affinity), specifically: selective serotonin reuptake inhibitors (SSRIs, including sertraline, fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine); serotonin noradrenaline reuptake inhibitors (SNRIs, including venlafaxine and duloxetine); and clomipramine. Group 2 included antidepressants with higher H_1 receptor affinity: amitriptyline, trimipramine, maprotiline, nortriptyline, mianserin, mirtazapine, doxepin, and nefazodone. There was no exposure to bupropion, reboxetine, maprotiline in the sample. Whenever women were taking antidepressants belonging to different groups, we assigned exposure to the group with higher H_1 receptor affinity. For comparison with prior research, we additionally examined exposure to any antidepressant.

Because screening for GDM in pregnant women Norway is done at gestational week 24–28,[25] we defined as primary antidepressant exposure window the period between start of pregnancy and gestation week 24 (hereafter, early-mid pregnancy).

2.5 | Measured confounders

A sufficient set of confounding factors was examined and selected with the aid of directed acyclic graphs (DAGs) via Dagitty,[29,30] which included: parity and marital status (all ascertained in MBRN); maternal education, gross yearly income, smoking, alcohol use, and physical activity in the 3-month period before pregnancy, BMI at the time of pregnancy start (all ascertained in MoBa); self-reported use in the 6-month period before pregnancy of non-steroidal anti-inflammatory medication (NSAIDs) (ATC code M01A), opioid analgesics (ATC code N02A), acetaminophen (ATC code N02BE01), benzodiazepines/z-hypnotics (ATC codes N05B and N05C), antipsychotics and mood stabilizers (ATC code N05A) or antiepileptics (ATC code N03A); and an adapted obstetric comorbidity index,[31] based on MBRN records. To address history of depression severity, we included as confounder "Life Time History of Major Depression" (LTH of MD), as measured in MoBa Q1 via five key depressive symptoms closely corresponding to the DSM-III criteria for lifetime major depression.[32] In a separate model, we also included symptoms severity of depression and anxiety in early pregnancy, as measured in MoBa Q1 via the short five-item version of The Hopkins Symptom Checklist-25 (SCL-5). The SCL-5 scales were modeled as numeric variables, and could range from 1 to 4 (higher score indicates greater depressive symptoms).[33,34] More details on covariates are given in the Supporting Information.

2.6 | Data analysis

All statistical analyses were performed by using STATA MP version 15/16. Details about the study power are given in the Supplement. Our study was underpowered for the antidepressant group 2, for which only descriptive statistics are presented.

To estimate the relative risk (RR) of GDM along with their corresponding 95% CI by antidepressant exposure in early-mid pregnancy, overall and by H_1 receptor affinity (group 1), crude and weighted analyses were conducted. Adjustment for a sufficient set of confounders was done via use of inverse probability of treatment weighting (IPTW), using the propensity score.[35,36] Logistic regression models were first fit to estimate the probability of "antidepressant exposure" in early-mid pregnancy as any and by H_1 receptor affinity (group 1), relative to no exposure in the time window, given the set of sufficient confounders. Modified Poisson regression within the generalized linear model framework with robust standard errors were then fit applying the IPTW.[37] A robust variance estimator was applied to account for women's participation with more than one pregnancy in the MoBa study. Balance of covariates (standardized difference) between the exposure group and comparator was assessed before and after the application of the IPTW, and was considered adequate whenever differences were ≤0.1.[35] Data are presented as crude and weighted RR with 95% CI.

Missing data on individual confounding variables ranged from less than 1% to 10%, leading to 19.3% missing data information in at least one of the sufficient confounders. Under the assumption that data were missing at random, we imputed incomplete data via multiple imputation with chained equation (10 replications).[38–40] More detail is provided in the Supporting Information. The distribution of key variables in relation to missingness is given in Table S1.

2.7 | Sensitivity analyses

We conducted a number of sensitivity analyses to assess the robustness of the study findings. In the main analysis, the weighted models included additional confounders beyond those considered in the sufficient set (i.e., multiple pregnancy, history of GDM, thyroid disorders, periconceptional use of folate). Because multiple imputation was adopted, a complete case analysis approach was also undertaken. Because some women had more than one pregnancy included in the cohort, a sensitivity analysis restricted to the first pregnancy recorded was also conducted. To allow a longer lag time between antidepressant exposure and outcome onset, we additionally defined a stricter exposure window, from pregnancy start to week 20. We also examined the influence of some confounders measured in early pregnancy rather than before on our results (see the Supporting Information).

3 | RESULTS

We included 6647 pregnancies within 6421 women with clinical depression/anxiety in the 6 months prior to and/or during pregnancy. Figure 1 shows the data flow to achieve this final study population. Most pregnancies (99.5%) had a live-born offspring. Overall, 891 pregnancies were exposed to any antidepresssant in early-mid gestation, that is within the first 24 gestation weeks. Antidepressants with lower H_1 receptor affinity (group 1) were the most commonly used ($n = 814$, 12.3%), mainly citalopram, sertraline, escitalopram (SSRIs). Use of antidepressants with higher H_1 receptor affinity (group 2) was less common ($n = 76$, 1.2%), and the mainly used substances were mianserin, mirtazapine, and amitriptyline. Table 1 shows baseline sociodemographic, life-style and health characteristics of the final cohort according to antidepressant exposure group in early-mid gestation.

Overall, 84 pregnancies (1.3%) had GDM and this proportion increased over the study years (from 0.5% to 1.0% in 2001–2003, to 1.3% to 1.6% in 2004–2008, and 2.3% in 2009). Figure 2 shows the proportion of GDM with 95% CI by antidepressant exposure in early-mid pregnancy, which ranged from 1.1% in group 1 antidepressant exposed to 3.9% in group 2 antidepressant exposed. As shown in Table 2, exposure to any antidepressant was not associated with greater risk of GDM relative to non-medicated. Similarly, there was no evidence for an association between the use of antidepressants with low H_1 receptor affinity and risk of GDM in both crude and weighted models (weighted RR: 0.69, 95% CI: 0.31–1.56). Further inclusion of depressive and anxiety symptoms at week 17 in the IPTW did not materially change the effect estimates (Table 2).

TABLE 1 Sociodemographic, lifestyle and health characteristics of the final pregnancy cohort by antidepressant group exposure during early-mid pregnancy ($n = 6647$)

	Non-medicated $n = 5756$	Medicated, antidepressant group 1 $n = 814$	Medicated, antidepressant group 2 $n = 77$
Sociodemographics and life-style factors			
Maternal age (years); mean ± SD	29.7 ± 5.1	30.1 ± 5.1	31.7 ± 5.5
Multiple gestation (yes)	73 (1.3)	18 (2.2)	–
Live-birth (yes)	5731 (99.6)	809 (99.4)	76 (98.7)
Primiparous (yes)	2618 (45.5)	434 (53.3)	38 (49.4)
Marital status			
Married/Cohabiting	5258 (91.3)	720 (88.5)	66 (85.7)
Other	498 (8.7)	94 (11.5)	11 (14.3)
Educational level[a]			
University/College	2912 (50.6)	417 (51.2)	39 (50.7)
Lower than University/College	2806 (48.8)	396 (48.7)	38 (49.4)
Missing	38 (0.7)	<5	–
Gross yearly income[b]			
Average	3498 (61.6)	502 (61.7)	43 (55.8)
Low	1540 (26.7)	236 (29.0)	26 (33.8)
High	451 (7.8)	55 (6.8)	5 (6.5)
Missing	217 (3.8)	21 (2.6)	4 (4.2)
BMI at time of pregnancy start; mean ± SD	24.2 ± 4.6	24.6 ± 4.9	23.7 ± 4.4
Alcohol use 3 months before pregnancy			
No/very limited	228 (38.7)	326 (40.1)	30 (39.0)
Medium/weekly use	3318 (57.6)	465 (57.1)	44 (57.1)
Missing	210 (6.7)	23 (2.8)	<5
Alcohol use at week 17			
No/very limited	4802 (83.4)	691 (84.9)	69 (89.6)
Medium/weekly use	169 (2.9)	23 (2.8)	–
Missing	785 (13.6)	100 (12.3)	8 (10.4)
Smoking status 3 months before pregnancy			
No	3504 (60.9)	430 (52.8)	43 (55.8)
Yes	2252 (38.1)	384 (47.2)	34 (44.2)
Smoking status at week 17			
No	4149 (72.1)	533 (65.5)	48 (62.3)
Yes	787 (13.7)	156 (19.2)	17 (22.1)
Stopped in pregnancy	750 (13.1)	120 (14.7)	12 (15.6)
Missing	66 (1.2)	5 (0.6)	–
Physical activity 3 months before pregnancy			
Never	560 (9.7)	86 (10.6)	7 (9.1)
<once per week	1002 (17.4)	141 (17.3)	16 (20.8)
1–2 times per week	2064 (35.9)	293 (36.0)	24 (31.2)
3–5 times or more per week	1759 (30.6)	261 (32.1)	6 (7.8)
Missing	371 (6.5)	33 (4.1)	6 (7.8)
Physical activity during early pregnancy			
Never	1008 (17.5)	151 (18.6)	17 (22.1)
<once per week	1368 (23.8)	194 (23.8)	19 (24.7)
1–2 times per week	1912 (33.2)	289 (35.5)	20 (26.0)
3–5 times or more per week	1054 (18.3)	135 (16.6)	15 (19.5)
Missing	414 (7.2)	45 (5.5)	6 (7.8)

(Continues)

TABLE 1 (Continued)

	Non-medicated $n = 5756$	Medicated, antidepressant group 1 $n = 814$	Medicated, antidepressant group 2 $n = 77$
Periconceptional folate use (yes)	4478 (77.8)	651 (80.0)	65 (84.4)
Maternal health-related factors			
Thyroid disorders (yes)	104 (1.8)	39 (4.8)	4 (5.2)
History of GDM (yes)	48 (0.8)	6 (0.7)	<5
Migraine before pregnancy (yes)	820 (14.3)	138 (17.0)	15 (19.5)
Chronic pain condition before pregnancy (yes)[c]	272 (4.7)	42 (5.2)	5 (6.5)
Adapted obstetric index[d]; mean ± SD	0.5 ± 0.8	0.5 ± 0.9	0.8 ± 1.1
Chronic hypertension	41 (0.7)	6 (0.7)	—
Pre-existing asthma	312 (5.4)	38 (4.7)	7 (9.1)
Pre-existing heart disease	32 (0.6)	7 (0.9)	—
Congenital heart disease	44 (0.8)	9 (1.1)	<5
Illicit substance use before pregnancy	130 (2.3)	28 (3.4)	5 (6.5)
Previous cesarean section	490 (8.5)	59 (7.3)	7 (9.1)
LTH of MD (yes)[e]	1142 (19.8)	370 (45.5)	24 (31.2)
Missing	183 (3.2)	17 (2.1)	
Depressive/anxiety symptoms at GW 17; mean score ± SD	1.8 ± 0.6	1.8 ± 0.7	2.0 ± 0.7
Number of psychiatric disorders in pregnancy			
None	298 (5.2)	15 (1.8)	10 (13.0)
One	4688 (81.5)	550 (67.6)	44 (57.1)
Two	663 (11.5)	181 (22.2)	19 (24.7)
Three	107 (1.9)	68 (8.4)	5 (5.3)
Use of other medication 6 months before pregnancy (yes)			
Benzodiazepines/z-hypnotics	199 (3.5)	74 (9.1)	8 (10.4)
Antipsychotics/mood stabilizers	47 (0.8)	21 (2.6)	7 (9.1)
Antiepileptics	33 (0.6)	23 (2.8)	<5
Opioid analgesics	155 (2.7)	26 (3.2)	<5
NSAIDs	671 (11.7)	104 (12.8)	11 (14.3)
Paracetamol	1727 (30.0)	216 (26.5)	31 (40.3)
Use of other medication in early pregnancy (yes)			
Benzodiazepines/z-hypnotics	112 (2.1)	71 (8.7)	18 (23.4)
Antipsychotics/mood stabilizers	98 (1.7)	30 (3.7)	9 (11.7)
Antiepileptics	35 (0.6)	20 (2.5)	<3
Opioid analgesics	157 (2.7)	35 (4.3)	5 (6.5)
NSAIDs	415 (7.2)	83 (10.2)	8 (10.4)
Paracetamol	2694 (46.8)	391 (48.0)	45 (58.4)

Note: Data are number (%) unless stated otherwise. Missing values for numeric variables were 5.9% for depressive and anxiety symptoms in gestational week 17, and 3.1% for BMI. Whenever missing data are not indicated, it means that there were none. Group 1 includes antidepressants with lower H1 receptor affinity: all selective serotonin reuptake inhibitors, venlafaxine and duloxetine, and clomipramine. Group 2 included antidepressants with higher H1 receptor affinity: amitriptyline, trimipramine, maprotiline, nortriptyline, mianserin, mirtazapine, doxepin, and nefazodone.

Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; GW, gestational week; LTH of MD, Life time history of major depression; NSAID, non-steroidal anti-inflammatory drugs; SCL-5, short version (5-item) of The Hopkins Symptom Checklist.

[a]Includes ongoing or completed education.

[b]Average indicates income approximately between 17 501 and 46 800 USD; Low indicates income ≤17 500 USD; High indicates income ≥46 801 USD.

[c]Includes pre-existing sciatica, fibromyalgia, multiple sclerosis, and arthritis.

[d]Includes also lupus and chronic renal disease, but these are not reported due to small cell number across exposure groups (<5).

[e]Defined as Kendlers Life time major depression scale score of 3 or more simultaneous depressive symptoms of duration of more than 2 weeks.

After weighting, there was balance (standardized mean difference ≤0.1)[35] in the distribution of confounding factors between non-medicated and antidepressant group 1 or any antidepressant exposed (Figures S1–S2).

3.1 | Sensitivity analyses

Adding multiple pregnancy, history of GDM, thyroid disorders, and periconceptional use of folate in the IPTW estimation did not materially change the main results for group 1 antidepressant. Results of the complete case analyses were generally in line with the main findings on GDM, although the 95% CI were wider due to lower study power. Results of the sensitivity analyses restricted to the first registered pregnancy were in line with the main findings, and likewise when narrowing the exposure definition within the first 20 weeks of gestation (data not shown). When we included in the IPTW confounding variables measured in early pregnancy, the effect estimates were closer or greater than 1 (see Table S2) and the 95% CI still included the null.

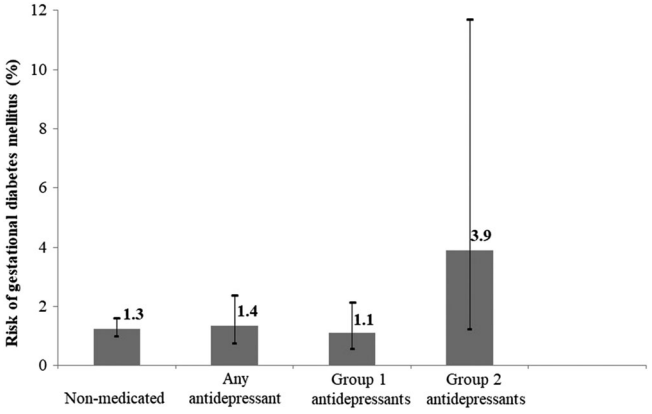

FIGURE 2 Risk of GDM according to antidepressant group exposure in early-mid pregnancy. Group 1 includes antidepressants with lower H_1 receptor affinity: all selective serotonin reuptake inhibitors, venlafaxine and duloxetine, and clomipramine. Group 2 included antidepressants with higher H_1 receptor affinity: amitriptyline, trimipramine, maprotiline, nortriptyline, mianserin, mirtazapine, doxepin, and nefazodone

4 | DISCUSSION

This study adds to the conflicting literature on the effect of antidepressants in pregnancy on risk of GDM and has the unique advantage of being able to account for severity of anxiety and depressive symptoms in early pregnancy. We found no evidence for a substantial association between GDM and maternal use in early-mid pregnancy of antidepressants with low H_1 receptor affinity, which mainly include SSRI and SNRI antidepressants. Our measure of association was 0.69, with an upper bound of the 95% CI equal to 1.51. This finding is clinically relevant, as SSRIs constitute the preferred therapeutic choice in the pregnant population.[41] Although the risk of GDM was elevated following the use of antidepressants with high affinity to the H_1 receptor, this finding is merely descriptive as the low statistical power impeded us to conduct adjusted association analyses.

Prior studies among non-pregnant subjects have linked antidepressant treatment to a modest elevated risk for T2DM,[7] and this association seemed to rise in magnitude as the antidepressant H_1 receptor affinity increased.[7,12,28] Our findings however do not support the notion that antidepressants with low H_1 receptor affinity, that is mainly SSRIs and SNRIs, pose any increased risk for GDM in pregnant women. This contrasts two prior studies in pregnant women showing a modest association with GDM (31%–37% increased odds)[13,14] although these included unexposed healthy pregnant women as comparators, raising concerns about the choice of a fair comparison group.

Our findings are generally in line with those by Wartko et al.,[17] where antidepressant-exposed women were compared to unexposed having an underlying indication for treatment with antidepressants in pregnancy, limiting the risk of indication bias.[15] Maternal depression in pregnancy has also been found to be associated with gestational diabetes,[16] for instance by triggering oxidative stress, chronic inflammation, and insulin resistance,[42] and thus disentangling the effect of medication exposure from that of the underlying maternal disease is crucial.

The unadjusted risk for GDM in pregnancies exposed to antidepressant with high H_1 receptor affinity was more elevated than in non-medicated or among pregnancies exposed to antidepressants with lower H1 receptor affinity. In the study by Dandjinou et al.,[18] venlafaxine and amitriptyline were the sole antidepressants found to be associated with GDM, with amitriptyline posing the largest risk (52% increased risk). This antidepressant has indeed high H_1 receptor affinity and can possibly pose a greater metabolic risk than other antidepressants.[12] Nevertheless, our results are merely descriptive, and

TABLE 2 Association of GDM and antidepressant exposure in early-mid pregnancy ($n = 6647$)

Antidepressant use in early-mid pregnancy	Total	With GDM	Crude RR (95% CI)	Weighted RR[a] (95% CI)	Weighted RR[b] (95% CI)
Non-medicated	5756	72 (1.3)	1	1	1
Medicated, any antidepressant	891	12 (1.4)	1.08 (0.59–1.98)	0.88 (0.43–1.82)	0.87 (0.42–1.79)
Medicated, group 1 antidepressant	814	9 (1.1)	0.88 (0.44–1.76)	0.69 (0.31–1.56)	0.67 (0.30–1.51)

Note: Group 1 includes antidepressants with lower H_1 receptor affinity: all selective serotonin reuptake inhibitors, venlafaxine and duloxetine, and clomipramine. Group 2 is not shown due to low statistical power.

[a]Model weighted via IPTW, including all baseline covariates.

[b]As in the main IPTW but adding depressive and anxiety symptoms at gestational week 17.

these antidepressants are often taken to treat conditions other than depression or anxiety (e.g., pains, migraine), which raises concerns about uncontrolled confounding by indication.

The study has several strengths and limitations that need mentioning. In the MoBa study, data collection was carried out prospectively, avoiding the risk of recall bias after the outcome was known to women. The registration of GDM in the MBRN stemmed from medical records during prenatal care check-ups, and it is thus medically confirmed. The study included data on a vast array of health and sociodemographic factors, including maternal mental health indicators prior to gestation, depression and anxiety symptom severity in early pregnancy, pre-conception BMI and physical activity. In line with recent methodological advances,[15,22–24] the study was restricted to women with depressive/anxiety disorders during pregnancy and/or in the 6-month period prior to gestation, limiting the risk of confounding by indication and by other factors correlated with maternal disease. The utilization of DAGs permitted a priori selection of confounding factors, thus diminishing the risk for adjustment of mediators or colliders. Information on depression and anxiety severity in early pregnancy is a unique strength of the study, and although such measurement cannot replace a clinical interview, it provides a reliable measure of the severity of these psychiatric conditions.[33,34] In addition, several sensitivity analyses were conducted to explore the robustness of the findings, and likewise to explore the impact of missing information on important covariates on the effect estimates.

One limitation is that depressive/anxiety disorders before and/or during pregnancy were self-reported in MoBa and thus based on maternal perception of illness and accuracy in reporting. In addition, anxiety was solely measured in MoBa Q1. However, the final study population of women with depression/anxiety was about 6% of the eligible population, which is equal to estimates of major depression with/without anxiety in pregnancy based on structural clinical interviews.[43] The use of antidepressants was also self-reported, and thus based on woman's accuracy in reporting and willingness to disclose information on her treatment. However, the impact of misclassification for SSRI, the most commonly used antidepressant group in this study has been explored and assessed as minimal in prior research examining SSRI self-report in MoBa versus filled prescriptions in the Norwegian Prescription Database.[44,45] Information on medication dosage is not available in the MoBa study and data about duration of exposure is not always adequate. Due to low statistical power, we did not examine the association between GDM and longer-term maternal exposure to antidepressants, and likewise between GDM and antidepressant with high H_1 receptor affinity. Outcome misclassification could be an additional concern. The validity of any diabetes registration in the MBRN has been assessed against filled prescription records for antidiabetic medications, yielding a sensitivity and specificity of 72% and 99%[26]; however, this does not relate specifically to GDM. In Norway, there is targeted screening for GDM in women with risk factors such as being overweight or obese, history of GDM or preeclampsia, ethnicity. Even though antidepressant use or having a mental health disorders are not criteria for the targeted GDM screening, we cannot exclude the possibility of bias due to outcome misclassification. However, if present, such misclassification bias is most likely non-differential.

The MoBa study has a low response rate (41% of all women invited), with a possible self-selection of the healthiest women to the study. On the other hand, among those who accepted the invitation, the response rate was high.[21] One prior study by Nilsen et al.[46] has thoroughly examined self-selection and its potential for bias by comparing the MoBa study population with the total Norwegian birthing population, by comparing effect estimates for known associations (e.g., smoking and low birth weight). This study showed that although the prevalence estimates could not necessarily be generalized to all Norwegian women, the measures of association tested were valid in the MoBa study. Moreover, the available sample size limited our ability to detect small effect sizes and to examine individual antidepressants.

To conclude, antidepressants with low H_1 receptor affinity do not substantially increase the risk of GDM. This information may assist clinicians when evaluating the risk of treatment with this group of antidepressants, that is, SSRIs and SNRIs, versus that of non-medicated depressive/anxiety disorders, in particular among women with risk factors for metabolic disorders in pregnancy. The elevated risk of GDM among women exposed to antidepressants with high H_1 receptor affinity needs to be refuted or confirmed by additional studies with greater numbers of exposed cases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

ETHICS STATEMENT

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data protection agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is based on regulations based on the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics (reference number: 2016/871/REK Sør-Øst).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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