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Association Between Anti-Depressant Use And Spontaneous Abortions: A Systematic Review And Meta-Analysis Of Observational Studies

Vivek Valliappan[1*], Monica Karunakaran[2], Lokeshwar Vijayakumar[3], Rajan Rushender[4]

[1*]Assistant Professor, Department of Pharmacology, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Chengalpattu District- 603103, Tamilnadu, India.

Email id: vivekvalliappan@gmail.com

[2,3]Department of Anaesthesiology, Sri Lalithambigai Medical College and Hospital, Chennai, India, Email id: kmonicacpt@gmail.com, Email id: lokeshwarvijayakumaar@gmail.com

[4]Department of Community Medicine, St Peter's Medical College, Hospital & Research Institute, Hosur – 635130, India. Email ID: rushenderrajan@gmail.com

***Corresponding Author:** Vivek Valliappan

*Assistant Professor, Department of Pharmacology, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Chengalpattu District- 603103, Tamilnadu, India.

Email id: vivekvalliappan@gmail.com

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Abstract

Background: *Various studies have assessed the association between anti-depressant use and spontaneous abortion. However, no conclusive evidence could be generated across studies as they reported mixed results. Hence, this review was done to determine the association of antidepressant medications on spontaneous abortions.*

Methods: *Search was done in Medline, EMBASE, PubMed Central, ScienceDirect, Google Scholar and Cochrane library. The search was performed from inception until May 2024. We carried out meta-analysis with random-effects model and reported pooled odds ratio (OR) with 95% confidence interval (CI).*

Results*: We identified 32 studies with nearly 5.5 million participants. The pooled OR was 1.27 (95%CI 1.19-1.34; I^2=81.9%). Subgroup analysis based on type of antidepressants revealed that mothers taking selective serotonin reuptake inhibitors (SSRIs) had pooled OR of 1.35 (95%CI 1.20-1.52; I^2=94.5%), and those taking serotonin and norepinephrine reuptake inhibitors (SNRIs) had pooled OR of 1.75 (95%CI 1.04-2.96; I^2=96.2%). In contrast, the association with tricyclic antidepressants (TCAs) was non-significant (pooled OR=2.44; 95%CI 0.98-6.06; I^2=92%). For women with depression and antidepressant exposure compared to women with depression but without antidepressant exposure, pooled OR was 1.25 (95%CI 0.92-1.69; I^2=94.4%), indicating no significant difference in the spontaneous abortion rate between these groups. Subgroup analysis showed that SSRIs were associated with 9% lower risk of spontaneous abortion (pooled OR=0.91; 95%CI 0.86-0.95; I^2=0%).*

Conclusions*: Antidepressant intake during pregnancy is associated with moderately increased risk of*

spontaneous abortion, while there was no association compared to women with depression but without antidepressant exposure.

Keywords: *Anti-depressants, Meta-Analysis, Miscarriage, Spontaneous Abortion*

Synopsis

Study question

Is antidepressant exposure during the first trimester associated with spontaneous abortion?

What is Already Known

It has been reported that women taking antidepressants experience higher rates of spontaneous abortions compared to those not taking antidepressants. However, no conclusive evidence could be generated from all studies as they were mixed results (some studies showing association while some did not).

What this Paper Adds

Though the risk of spontaneous abortion was higher among patients that took antidepressants compared to non-users, there was no difference between women with depression and without antidepressant exposure. Treating a depressed mother with antidepressants should be considered.

BACKGROUND

Depression is a significant public health concern, particularly among women of childbearing age, with prevalence estimates ranging from 4% to 18% globally.[1,2] This condition poses considerable challenges during pregnancy, where the incidence of prenatal depression is especially pronounced during the first trimester.[3] This period, marked by critical foetal development, appears to be the most vulnerable, making the management of depression during early pregnancy a critical issue. Untreated maternal depression has been linked to a range of adverse outcomes for both the mother and the developing foetus, including low birth weight, lower Apgar scores, preterm birth, and significant foetal growth retardation.[4-7] These complications contribute to long-term health consequences, such as an increased risk of mental retardation, neurological morbidities, and even mortality in the offspring.[8-10] Despite the well-documented associations between maternal depression and poor neonatal outcomes, the exact mechanisms by which depression affects foetal development remain unclear.[11-14] Various factors, including marital dissatisfaction, poor socioeconomic status, lack of psychological or social support, and lower educational attainment, have been identified as contributing to the risk of maternal depression.[15,16]

In recent decades, the use of antidepressants during pregnancy has become more common, raising concerns about their safety, particularly their potential association with spontaneous abortion. The landmark study by Pastuszak et al. in 1993 was among the first to report a higher incidence of spontaneous abortion among women taking antidepressants, sparking ongoing debate and research into this issue.[17] Since then, numerous studies have attempted to clarify this association, with varying results. Some studies have suggested that antidepressant use during pregnancy, particularly in the first trimester, may increase the risk of spontaneous abortion, while others have found no such association.[18-20] This inconsistency in findings may be due to differences in study design, population characteristics, the specific types of antidepressants examined, and the timing of exposure during pregnancy.

Given the widespread use of antidepressants among pregnant women and the potential implications for fetal health, it is crucial to establish whether these medications indeed contribute to an increased risk of spontaneous abortion. The first trimester, a period of organogenesis, is particularly sensitive to external influences, making it essential to understand the risks associated with antidepressant exposure during this time. Despite the growing

body of research, a definitive conclusion has yet to be reached, highlighting the need for a comprehensive review of the evidence. By synthesizing data from existing studies, we seek to provide clearer guidance for clinicians and pregnant women on the safety of antidepressant medications during the early stages of pregnancy. Hence, this review aimed to address this gap by evaluating the association between antidepressant use during pregnancy and the risk of spontaneous abortion.

METHODS

Inclusion criteria

Study design

Observational analytical studies of any nature (cohort/case-control/cross-sectional) were included

Participants

Studies among pregnant women irrespective of the presence of depression were included.

Exposure

Studies comparing pregnant women who were taking anti-depressants and those who were not taking anti-depressants were eligible for inclusion in our analysis. Exposure window for anti-depressants use was before pregnancy until the end of the first trimester.

Outcome

Spontaneous abortion (loss of pregnancy naturally before twenty weeks of gestation in absence of elective medical/surgical measures to terminate pregnancy)

Data sources and selection

Search was done in PubMed/Medline, EMBASE, Scopus, Google Scholar, and Cochrane library. The terms used in our search strategy were as follows: “Anti-depressants”, “Pregnancy”, “Selective Serotonin Reuptake Inhibitors”, “SSRI”, “Tricyclic Anti-depressants”, “TCA”, “Serotonin and Norepinephrine Reuptake Inhibitors”, “SNRI”, “Spontaneous abortion” and “Miscarriage” (**Supplementary Appendix**). Search was done till May 2024 with restrictions to English language only.

PubMed Search Strategy:
((((((((((((agents, antidepressive[MeSH Terms]) OR (antidepressant[Title])) OR (agents, tricyclic antidepressive[MeSH Terms])) OR (antidepressant drugs, tricyclic[MeSH Terms])) OR (agents, second generation antidepressive[MeSH Terms])) OR (antidepressive drugs, second generation[MeSH Terms])) OR (selective serotonin reuptake inhibitors[MeSH Terms])) OR (fluoxetine[MeSH Terms])) OR (antidepressant drugs[MeSH Terms])) AND (abortion, spontaneous[MeSH Terms])) OR (miscarriage[MeSH Terms])) OR (abortions, spontaneous[MeSH Terms])) OR (miscarriages[MeSH Terms])) OR (miscarriage, recurrent[MeSH Terms]))
((((("agent"[All Fields] OR "agents"[All Fields]) AND "antidepressive agents"[MeSH Terms]) OR "antidepressant"[Title] OR "antidepressive agents, tricyclic"[MeSH Terms] OR "antidepressive agents, tricyclic"[MeSH Terms] OR "antidepressive agents, second generation"[MeSH Terms] OR "antidepressive agents, second generation"[MeSH Terms] OR "serotonin uptake inhibitors"[MeSH Terms] OR "fluoxetine"[MeSH Terms] OR "antidepressive agents"[MeSH Terms]) AND "abortion, spontaneous"[MeSH Terms]) OR "abortion, spontaneous"[MeSH Terms] OR "abortion, spontaneous"[MeSH Terms] OR

"abortion, spontaneous"[MeSH Terms] OR "abortion, habitual"[MeSH Terms]
Translations
agents: "agent"[All Fields] OR "agents"[All Fields]
, antidepressive[MeSH Terms]: "antidepressive agents"[MeSH Terms]
agents, tricyclic antidepressive[MeSH Terms]: "antidepressive agents, tricyclic"[MeSH Terms]
antidepressant drugs, tricyclic[MeSH Terms]: "antidepressive agents, tricyclic"[MeSH Terms]
agents, second generation antidepressive[MeSH Terms]: "antidepressive agents, secondgeneration"[MeSH Terms]
antidepressive drugs, second generation[MeSH Terms]: "antidepressive agents, secondgeneration"[MeSH Terms]
selective serotonin reuptake inhibitors[MeSH Terms]: "serotonin uptake inhibitors"[MeSH Terms]
fluoxetine[MeSH Terms]: "fluoxetine"[MeSH Terms]
antidepressant drugs[MeSH Terms]: "antidepressive agents"[MeSH Terms]
abortion, spontaneous[MeSH Terms]: "abortion, spontaneous"[MeSH Terms]
miscarriage[MeSH Terms]: "abortion, spontaneous"[MeSH Terms]
abortions, spontaneous[MeSH Terms]: "abortion, spontaneous"[MeSH Terms]
miscarriages[MeSH Terms]: "abortion, spontaneous"[MeSH Terms]
miscarriage, recurrent[MeSH Terms]: "abortion, habitual"[MeSH Terms]

Two investigators simultaneously performed screening of title and abstract without each other knowing the decision made in parallel. Both of them then screened full-text in similar manner and final set of studies were included after verifying against inclusion criteria.

Data extraction

Data extracted were as follows: author and journal details, design, setting, total sample, criteria for sample selection, baseline details, eligibility criteria, type of anti-depressant, the timing of administration of anti-depressants, bias-related information, and finally spontaneous abortion numbers and its definition. The corresponding author performed the data entry and the secondary investigator did the double-checking of the correct entry for the entire dataset.

Quality assessment

Two investigators simultaneously performed risk of bias assessment without each other knowing the decision made in parallel. The tool used was Newcastle Ottawa Quality Assessment Form for observational studies. It has following three domains: Selection, Comparability, and Outcome.[21] Based on the findings from these domains, risk of bias was graded as low, high, and unclear.

Meta-analysis

Given that the outcome of interest was dichotomous, we calculated pooled effect estimate as odds ratio (OR) by entering the number of events and the total number of participants in each group. To account for the methodological heterogeneity present among the included studies, we employed a random-effects model, utilizing inverse variance method to determine weight of each study.[22] This approach helps accommodate the variability across studies, providing a more generalized estimate of the association between antidepressant use and spontaneous abortion.

To evaluate the extent of heterogeneity between the studies, we employed the I^2 statistic.[22] Recognizing the potential for different antidepressant classes to have varied effects, we conducted subgroup analyses based on

the type of antidepressants used.

For visual representation and easy interpretation of the data, the overall estimates were displayed using forest plots. To ensure the reliability of our findings, a sensitivity analysis was conducted. This analysis allowed us to assess the stability of the results by identifying any significant variation that could influence the overall conclusions. Additionally, we examined the presence of publication bias through the use of funnel plots. To statistically assess this bias, we applied Egger's test, which helps determine if the asymmetry in the funnel plot could be due to publication bias or other factors.[22]

All statistical analyses, including the meta-analysis, were performed using STATA version 17 (StataCorp, College Station, TX, USA).

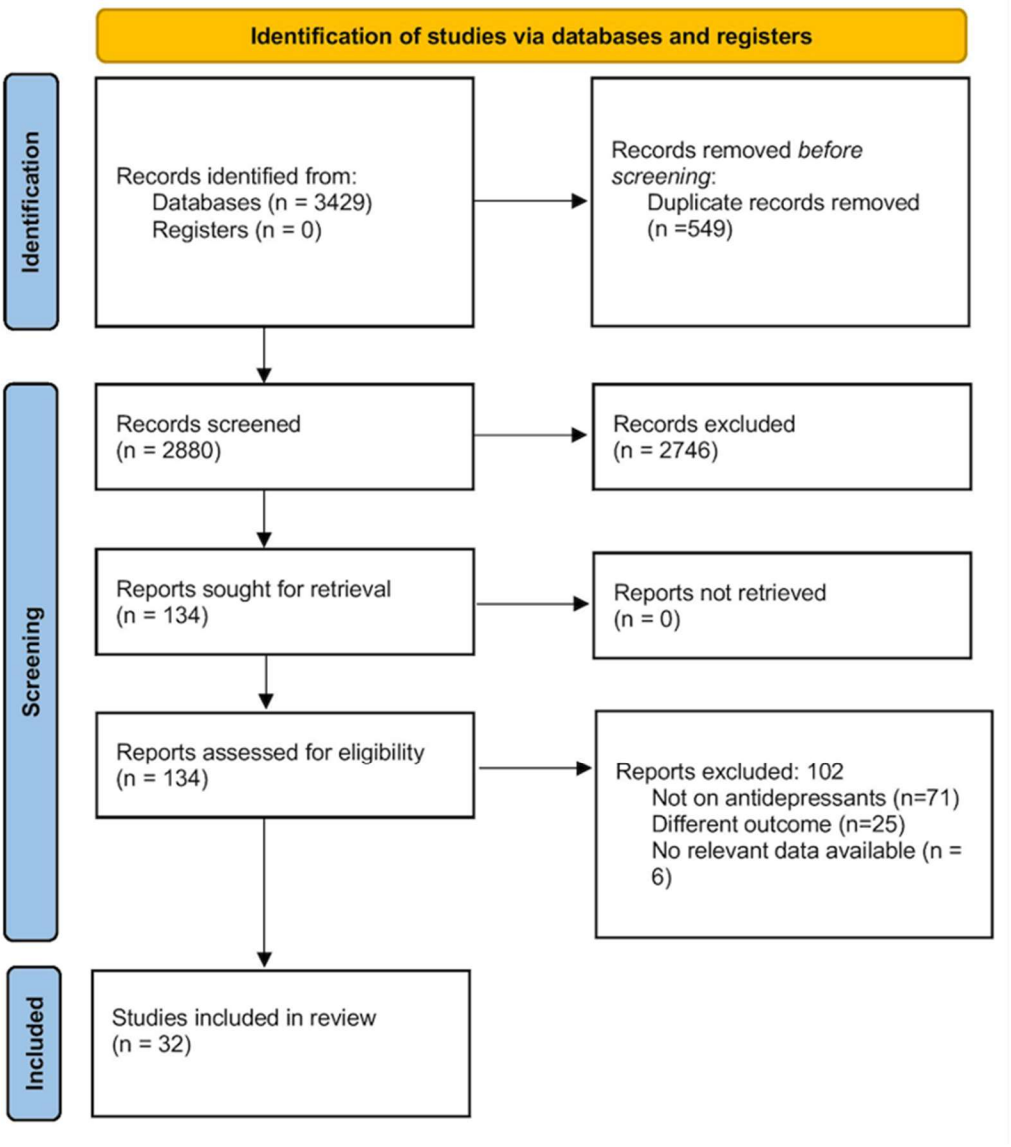
Ethics approval: Ethical approval was not required as this was a secondary analysis of data from publicly available resources.

RESULTS

Selection of studies

We identified 3429 studies, out of which 134 full-texts were retrieved for second stage. After screening them, 32 studies with nearly 5.5 million participants were included (**Figure 1**).[17-20,23-50]

Figure 1 PRISMA Search Strategy



Characteristics of studies included

Most studies were prospective. Most studies were multicentric studies with the majority involving Canada and the USA. Half of the studies have studied the antidepressant exposure during the first trimester while the rest of the studies reported the effect starting from pre-conception exposure until the first trimester. Majority of the included studies were high-quality studies (**Table 1**).

Table 1: Characteristics of the included studies (N=19)

Study No	First author and year	Country	Study design	Sample size	Study participants	Type of Anti - depressants	Timing of administration	Quality of study
1	Abadie et al 2015	France	Nested Case control	5346	**Group 1:** First trimester drug exposure and called CPRV enquiring about drug exposure **Group 2:** Calling CPRV for assessing non- teratogen exposure	Any antidepressants	First trimester	High
2	Almeida et al 2016	Canada	Retrospective	34214	**Group 1**: Women prescribed antidepressants in the first trimester and with a recorded diagnosis of depression before pregnancy **Group 2:** Women with neither antidepressant use nor a depression diagnosis before or during pregnancy; women with depression diagnosis before pregnancy, but no antidepressants use; and women taking hypothyroid medication in the first trimester, but not antidepressants	SNRI, SSRI, TCA	First trimester	Low
3	Andersen et al 2014	Denmark	Retrospective	1279840	**Group 1:** Pregnancies exposed to an SSRI during the first trimester with a continuous exposure before pregnancy **Group 2:** Women not exposed to SSRI during the first trimester of pregnancy	SSRI	First 35 days of pregnancy	Low
4	Ankarfeldt et al 2021	Denmark	Prospective	1020288	**Group 1:** redemption of AD prescription in window from 30 days prior to LMP to 140 days post LMP or end of pregnancy, whichever came first **Group 2:** Duloxetine non-exposed (no redemption of prescription during the window) **Group 3:** SSRI exposed **Group 4:** Venlafaxine exposed	SSRI, SNRI	Anytime during pregnancy	High
5	Bahat et al 2020	Israel	Prospective	722	**Group 1:** Exposure to duloxetine during first trimester **Group 2:** women exposed to TCAs **Group 3:** Non-teratogenic exposure	SNRI, TCAs	Throughout follow-up after delivery	High
6	Ban et al 2012	United Kingdom	Prospective	331414	**Group 1:** depression and exposed to AD during first 90 days after conception **Group 2:** No history of depression and unexposed **Group 3:** history of depression	SSRIs, TCAs	First trimester	

					and unexposed **Group 4:** prescriptions for TCAs only **Group 5:** Prescriptions for SSRIs only **Group 6:** prescriptions for any other AD only			Low
7	Chambers et al 1996	USA	Prospective	423	**Group 1:** Women who were taking fluoxetine during the first trimester **Group 2:** Women who were not taking fluoxetine	SSRI	First trimester	High
8	Chan et al 2011	USA	Prospective	4536	**Group 1:** Women exposed to any antidepressants **Group 2:** Women not exposed to antidepressants	Any antidepressants	Anytime during pregnancy	Low
9	Chun-Fai-Chan et al 2005	Canada and USA	Prospective	263	**Group 1:** Women exposed to bupropion or any other anti-depressant during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	Any antidepressants	First trimester	High
10	Diav-Citrin et al 2008	Italy and Germany	Prospective	2276	**Group 1**: Women exposed to Paroxetine and fluoxetine during pregnancy **Group 2:** Women without exposure to any antidepressants during pregnancy	SSRI	First trimester	High
11	Djulus et al 2006	Canada, USA, Italy, Israel, Australia	Prospective	312	**Group 1**: Women exposed to mirtazapine during pregnancy **Group 2:** Women without exposure to any antidepressants during pregnancy	Any antidepressants	First trimester	High
12	Einarson et al 2001	Canada, USA, Italy, Brazil	Prospective	450	**Group 1:** Women exposed to venlafaxine or SSRI during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	SNRI, SSRI	First trimester	High
13	Einarson et al 2003	Canada, USA, Italy, Brazil	Prospective	441	**Group 1:** Women exposed to trazodone or nefazodone or any other anti-depressant during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	Any antidepressants	First trimester	High
14	Einarson et al 2009	Canada	Prospective	1874	**Group 1:** Women exposed to any anti-depressant during pregnancy **Group 2:** Women not exposed to anti-depressant during pregnancy	Any antidepressants	First trimester	High

15	Evans-Hoeker et al 2018	USA	Prospective	1650	**Group 1:** Absence of major depression(MD) and no anti-depressant use **Group 2:** Absence of MD and using anti-depressant **Group 3:** Presence of MD and no anti-depressant use **Group 4:** MD & using anti-depressant	Any antidepressants	Anytime during pregnancy	High
16	Giner-Soriano et al 2022	Spain	Retrospective	180692	**Group 1:** Women exposed to any anti-depressant during pregnancy **Group 2:** Women not exposed to anti-depressant during pregnancy	Any antidepressants	Exposure up to 120 days after pregnancy start date	High
17	Gomez-Lumbreras et al 2024	Spain	Retrospective	124435	**Group 1:** Women exposed to any antidepressants during pregnancy **Group 2:** Women not exposed to any anti-depressants during pregnancy	Any antidepressants	First trimester	High
18	Johansen et al 2014	Denmark	Retrospective	1185736	**Group 1:** Women exposed to SSRI before or during pregnancy **Group 2:** Women not exposed to any anti-depressants during pregnancy	Any antidepressants	First trimester	Low
19	Kitchin et al 2022	Spain	Nested case-control	72280	**Group 1:** when there were no prescriptions in any of these periods **Group 2:** women who had at least one prescription only during the prepregnancy period; **Group 3:** women who had at least one prescription during the prepregnancy period and also during the first trimester **Group 4:** women who had at least one pre- scription only during the first trimester.	Any antidepressants	Anytime during pregnancy	High
20	Kjaersgaard et al 2013	Denmark	Retrospective	1020962	**Group 1:** Women exposed to any anti-depressant before or during pregnancy **Group 2:** Women not exposed to anti-depressant during pregnancy	SSRI	30 days before conception up to 1 day before the end of pregnancy	Low

21	Klieger-Grossmann et al 2012	Canada, Italy, Switzerland	Prospective	637	**Group 1:** Women exposed to escitalopram or any anti-depressants during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	Any antidepressants	First trimester	Low
22	Kolding et al 2021	Denmark	Register based study	364012	**Group 1:** Women exposed to any anti-depressant before or during pregnancy **Group 2:** Women not exposed to anti-depressant during pregnancy	Any antidepressants	First trimester	High
23	Kulin et al 1998	Canada and USA	Prospective	534	**Group 1:** Women exposed to SSRI during pregnancy **Group 2:** Women not exposed to any anti-depressants during pregnancy	SSRI	First trimester	Low
24	Nakhai-Pour et al 2010	Canada	Retrospective	56364	**Group 1:** Women exposed to antidepressants during pregnancy **Group 2:** Women not exposed to any anti-depressants during pregnancy	Any antidepressants	First day of gestational age to abortion day	Low
25	Ostenfeld et al 2022	Denmark	Prospective	9500	**Group 1:** Women exposed to any anti-depressants during pregnancy **Group 2:** Women not exposed to anti-depressants during pregnancy	Any antidepressants	Exposure earlier than 22 weeks of completed gestation	High
26	Pastuszak et al 1993	Canada and USA	Prospective	478	**Group 1:** Women exposed to SSRI and TCA during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	SSRI, TCA	First trimester	High
27	Paulus et al 2010	Germany	Prospective	955	**Group 1:** Women exposed to paroxetine (SSRI) during pregnancy **Group 2:** Women not exposed to paroxetine (SSRI) during pregnancy	Paroxetine (SSRI)	First trimester	High
28	Richardson et al 2019	United Kingdom	Prospective	2529	**Group 1:** Women exposed to venlafaxine or SSRI during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	SNRI, SSRI	Prior to 24 weeks of gestation	High
29	Sivojelezova et al 2005	Canada	Prospective	396	**Group 1:** Women exposed to citalopram or any anti-depressants during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	Any antidepressants	First trimester	High

30	Te Winkel et al 2016	Multiple European countries	Prospective	1462	**Group 1:** Women exposed to venlafaxine during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	SSRI	Anytime during pregnancy	Low
31	Vial et al 2006	France	Prospective	1366	**Group 1:** Women exposed to paroxetine during pregnancy **Group 2:** Women exposed to non-teratogenic agents during pregnancy	SSRI	3-10 weeks of gestation	High
32	Wu et al 2019	USA	Prospective	5451	**Group 1:** Women exposed to any anti-depressants during pregnancy **Group 2:** Women not exposed to anti-depressants during pregnancy	Any antidepressants	First trimester	High

USA – United States of America, SSRI - selective serotonin reuptake inhibitor; TCA - tricyclic anti-depressants; SNRI - serotonin and norepinephrine reuptake inhibitors

Association of antidepressant use on spontaneous abortion rate

Women with depression and antidepressant exposure versus no depression and no antidepressant exposure

In total, 34 studies assessed the association of antidepressants on spontaneous abortion rate and reported it as OR with 95%CI. [17-20,23-50] The pooled OR was 1.27 (95% CI: 1.19 to 1.34; I^2=81.9%) (**Figure 2**). This indicates that pregnant women with depression and antidepressant exposure have 1.27 times higher risk of having a spontaneous abortion when compared to those women without depression and antidepressant exposure. Events and total participants in each group were reported in 28 studies. The pooled OR was 1.46 (95%CI: 1.30 to 1.64; I^2=95.2%) (**Figure 3**).

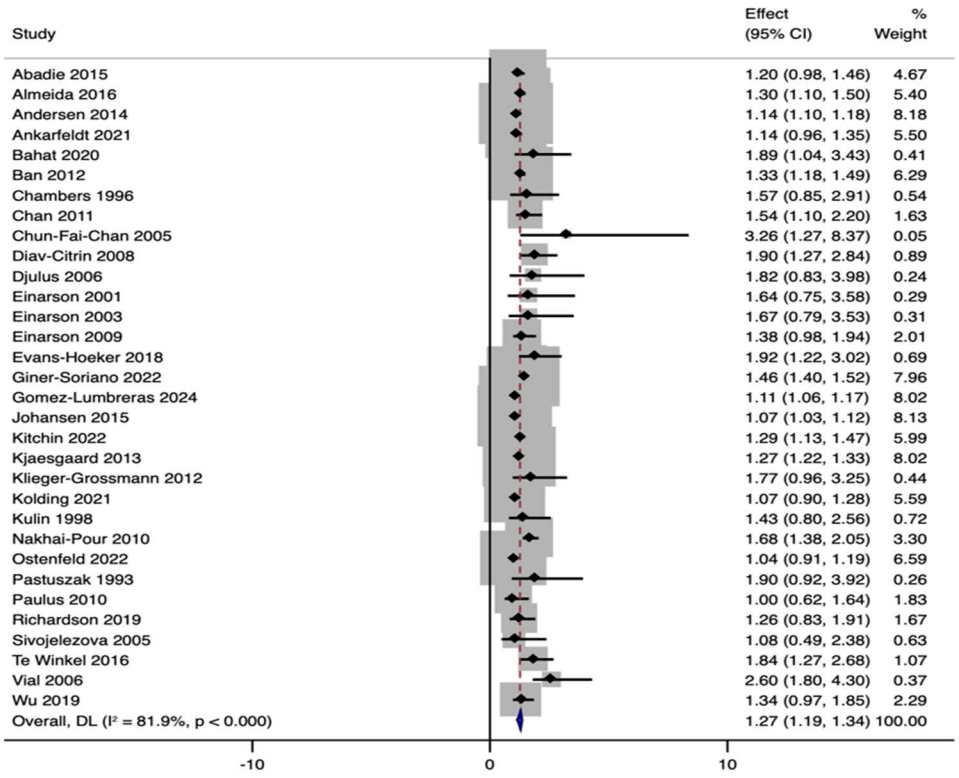


Figure 2 Forest plot showing the association of antidepressant exposure during pregnancy on spontaneous abortion compared to women without depression and without antidepressant exposure (reported as OR)

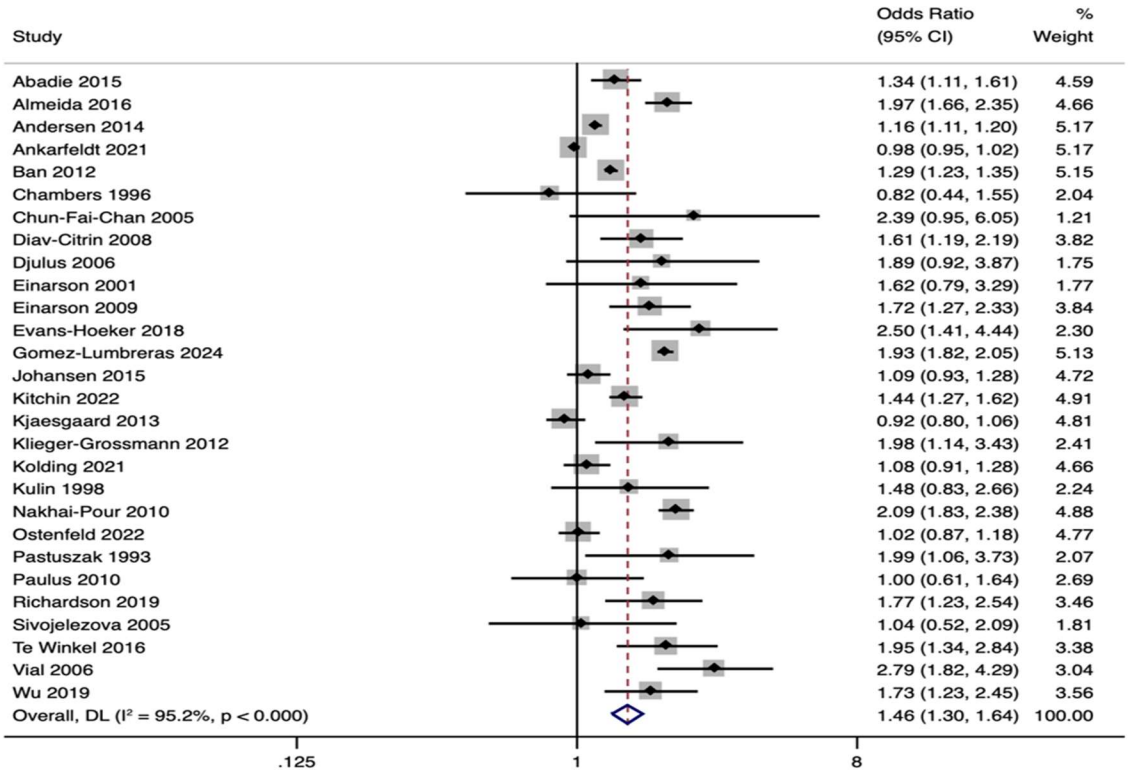


Figure 3 Forest plot showing the association of antidepressant exposure during pregnancy on spontaneous abortion compared to women without depression and without antidepressant exposure (reported as number of events)

Subgroup analysis based on type of antidepressants revealed that mother with depression taking selective serotonin reuptake inhibitors (SSRI) had 1.35 times higher odds of spontaneous abortion when compared to those mothers without depression and not taking any antidepressants (pooled OR 1.35, 95% CI 1.20, 1.52; I^2=94.5%) (**Figure 4**).

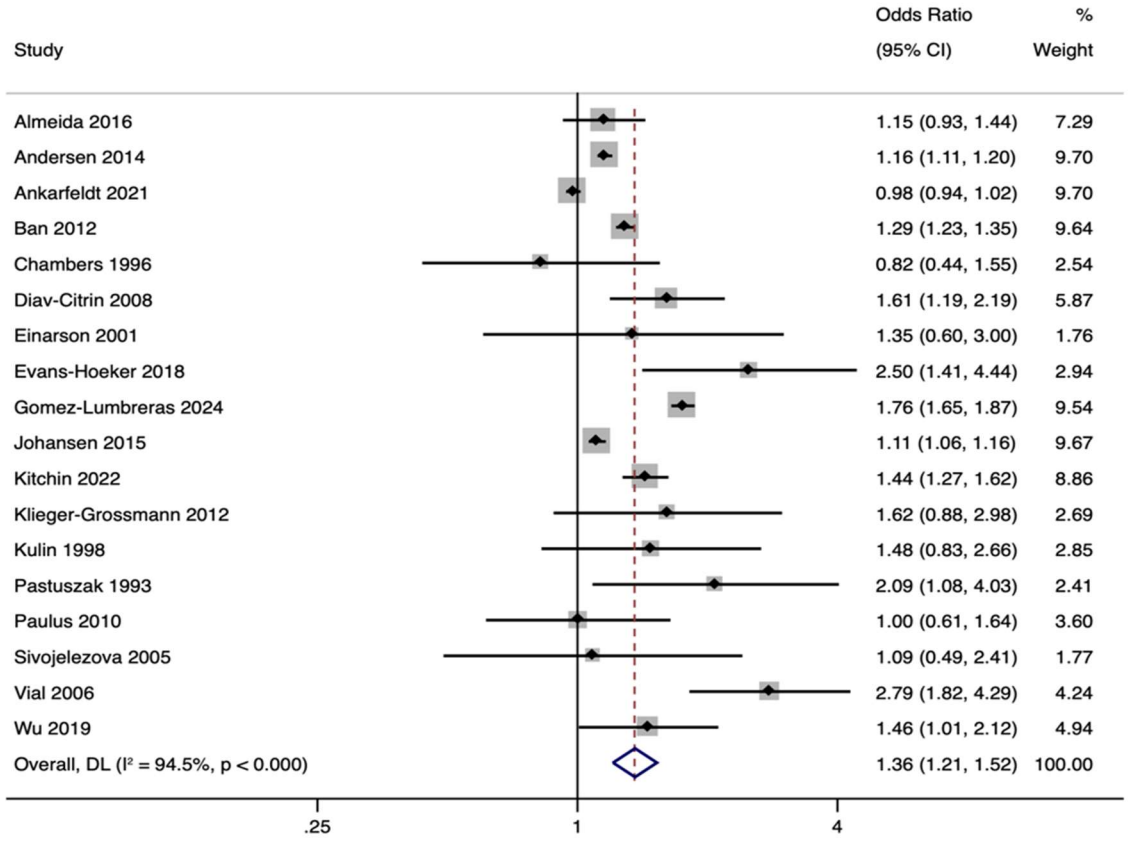


Figure 4 Forest plot showing the association of SSRIs during pregnancy on spontaneous abortion compared to women without depression and without antidepressant exposure

Patients taking Serotonin and norepinephrine reuptake inhibitors (SNRI) (pooled RR 1.75, 95% CI: 1.04, 2.96; I^2=96.2%) had higher odds of spontaneous abortion (**Figure 5**).

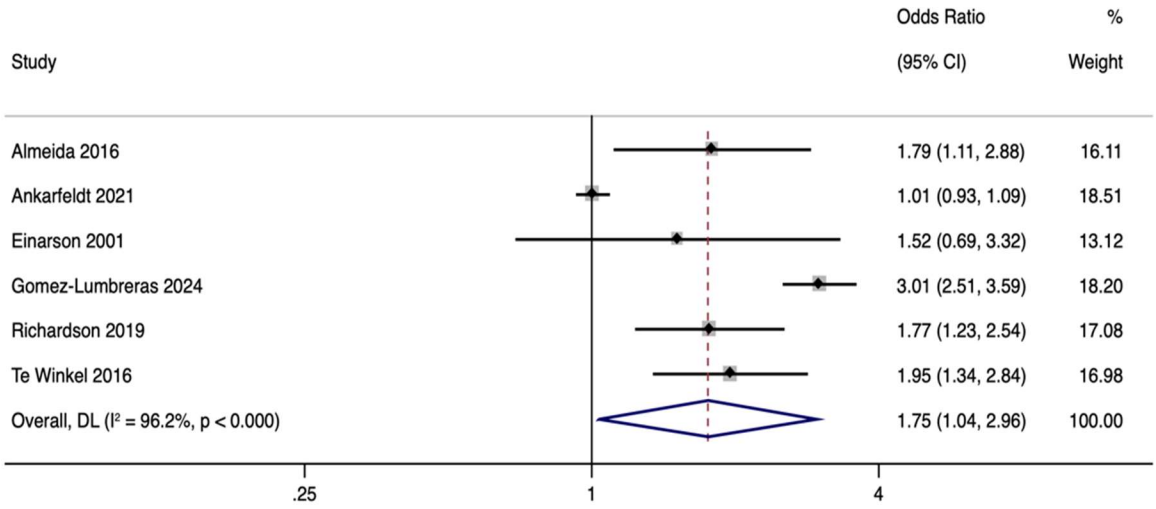


Figure 5 Forest plot showing the association of SNRIs during pregnancy on spontaneous abortion compared to women without depression and without antidepressant exposure

Patients on tricyclic antidepressants (TCA) (pooled RR 2.44; 95% CI: 0.98-6.06; I^2=92%) had non-significant association with spontaneous abortion (**Figure 6**).

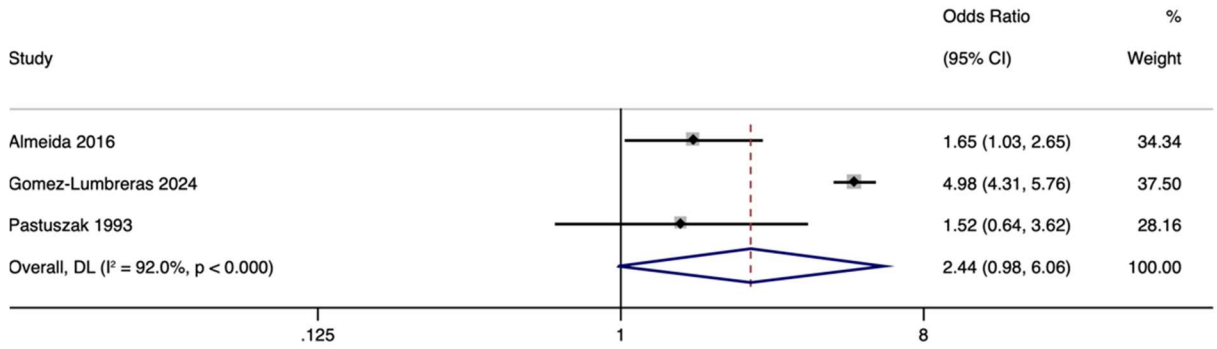


Figure 6 Forest plot showing the association of TCAs during pregnancy on spontaneous abortion compared to women without depression and without antidepressant exposure

Women with depression and antidepressant exposure versus women with depression but no antidepressant exposure

In total, 6 studies assessed the association of antidepressants on spontaneous abortion rate by comparing the women with depression and antidepressant exposure to women with depression and without antidepressant exposure.[18,23,24,30,31,33] The pooled RR was 1.25 (95% CI 0.92, 1.69; I^2=94.4%) (**Figure 7**).

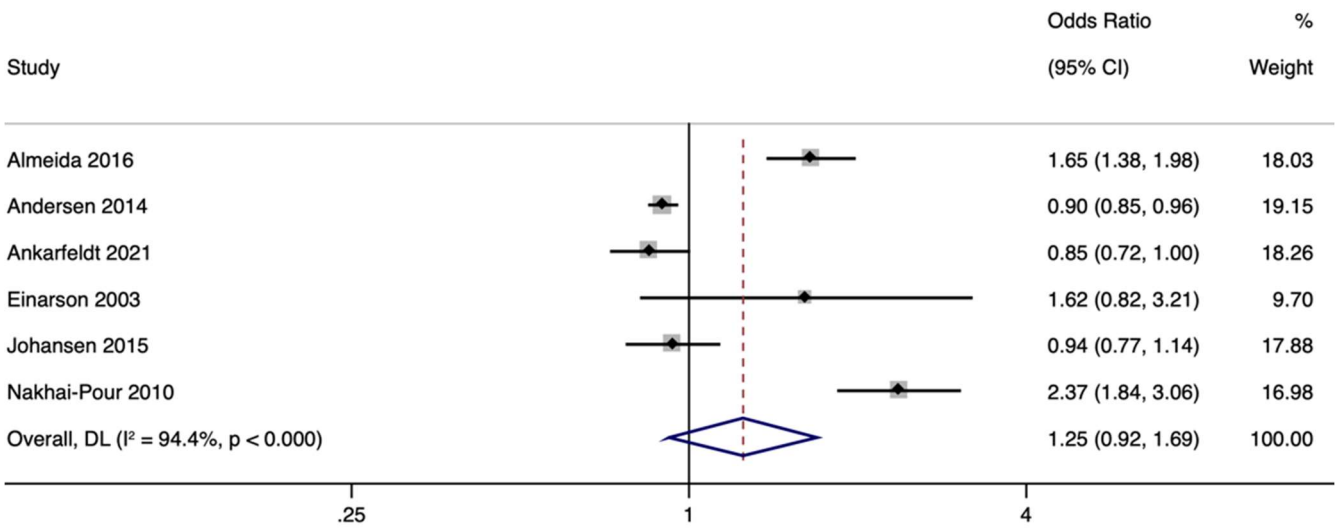


Figure 7 Forest plot showing the association of antidepressants during pregnancy on spontaneous abortion compared to women with depression and without antidepressant exposure

Subgroup analysis based on the type of antidepressants revealed that the mother with depression taking SSRIs had a 9% lesser risk of spontaneous abortion when compared to those mothers with depression and not taking any antidepressants (pooled RR 0.91; 95% CI 0.86, 0.95; I^2=0%) (**Figure 8**).

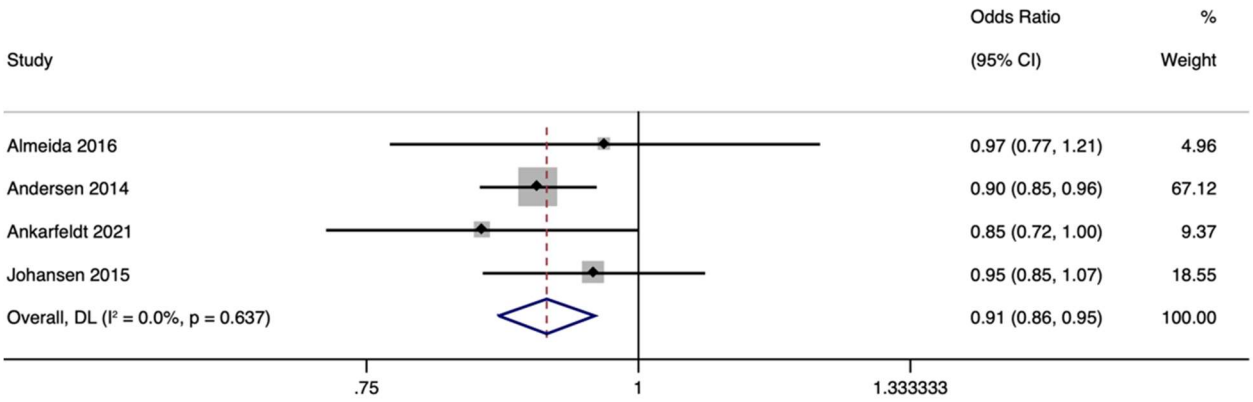


Figure 8 Forest plot showing the association of SSRIs during pregnancy on spontaneous abortion compared to women with depression and without antidepressant exposure

Analysis based on SNRIs showed no significant association (pooled OR=1.09; 95%CI: 0.65, 1.84; I^2=76.6%) (**Figure 9**).

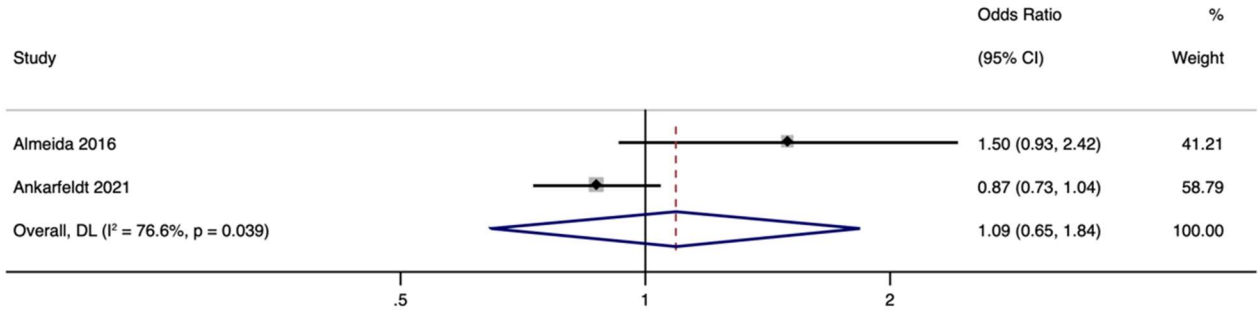
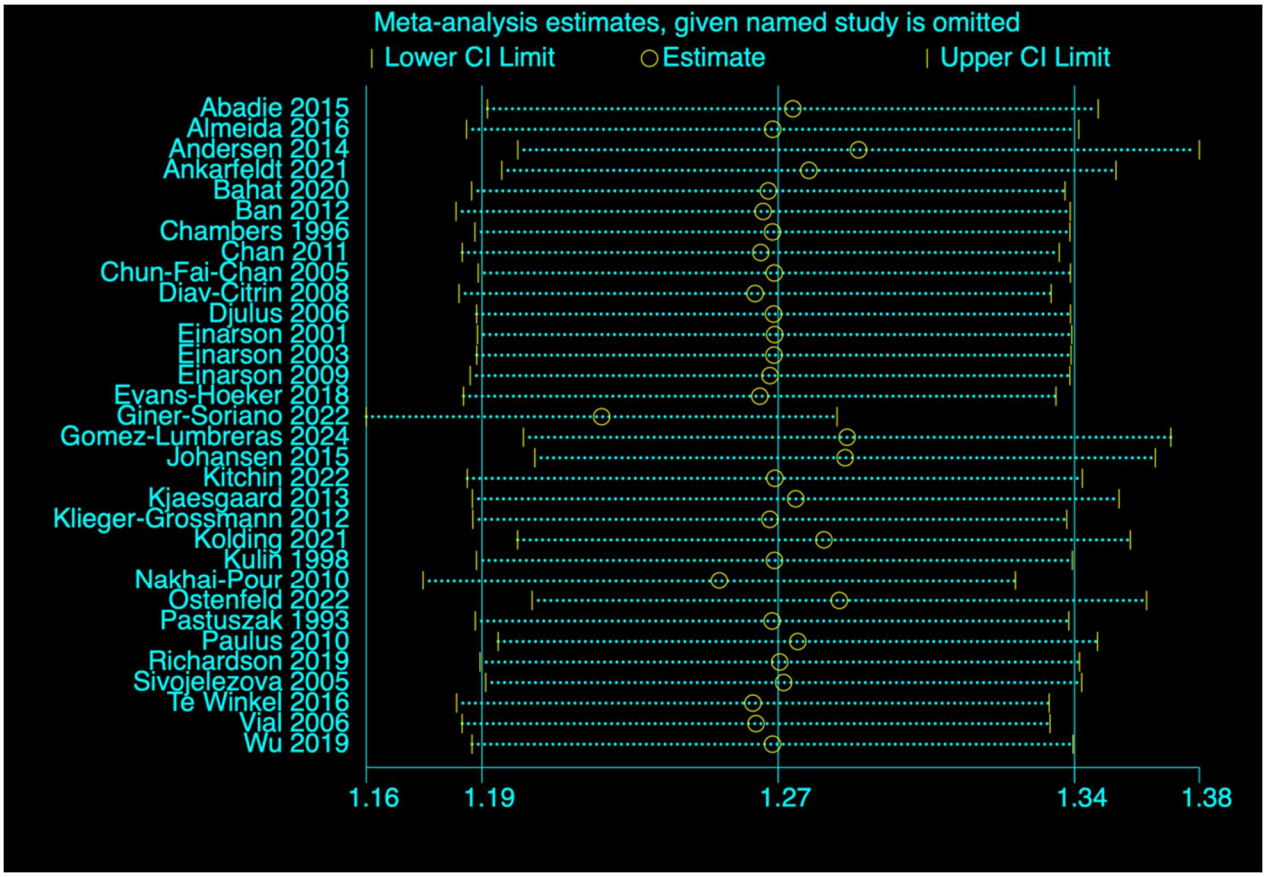


Figure 9 Forest plot showing the association of SNRIs during pregnancy on spontaneous abortion compared to women with depression and without antidepressant exposure

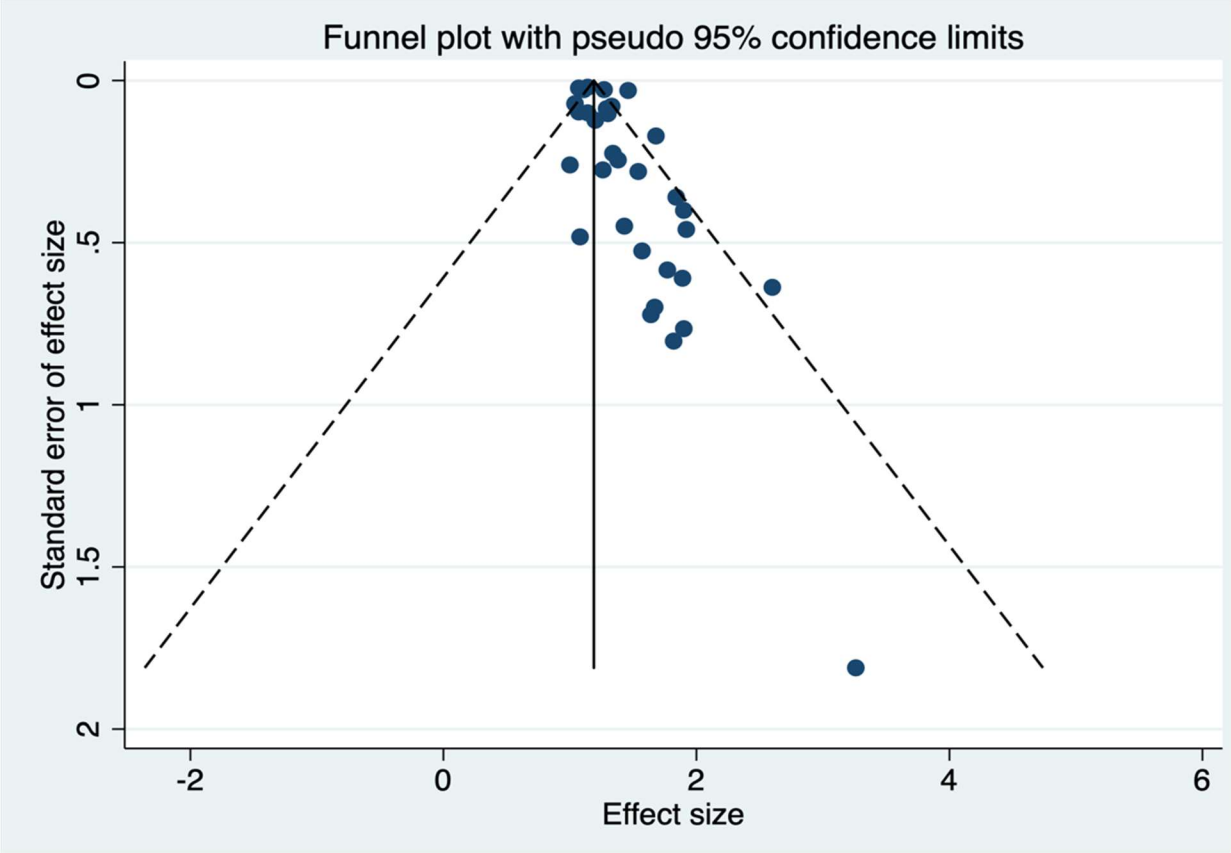
Analysis based on TCAs could not be performed due to limitations in the number of studies.

Additional analysis

Sensitivity analysis has shown that findings were robust to single study changes **(eFigure 1)**. Substantial publication bias was found in the Egger's test and demonstrated by asymmetrical funnel plot (p=0.04) **(eFigure 2).**



eFigure 1: Sensitivity analysis



eFigure 2: Funnel plot checking publication bias

Discussion

Antidepressants amongst women with depression was associated with a higher risk of spontaneous abortion when compared to pregnant women not having depression and exposed to antidepressant. We also found that the exposure to SNRIs had high risk of spontaneous abortion followed by exposure to SSRIs during pregnancy, while TCAs had no association.

The effect estimate in this study was almost similar to previous reviews conducted on this topic, reiterating the fact that antidepressant exposure during pregnancy can increase the risk of spontaneous abortion or miscarriages.[51-53] The risk was found especially during the first trimester, as this is the period of organogenesis for the foetus and exposure during such a critical period leads to such major adverse outcomes. We also performed subgroup analysis based on control of confounding for depression severity and timing of administration and found a similar association.

However, the second stage of the analysis showed no difference in the effect estimates between women with depression and antidepressant exposure and women with depression and without antidepressant exposure. Subgroup analysis in terms of the type of antidepressants showed a protective role of SSRIs in reducing the spontaneous abortion rate. This shows role of antidepressants, especially SSRIs, in management of depression during pregnancy. In addition, we performed subgroup analysis based on control of confounding due to depression severity. This provided a further interesting finding that the pooling of studies without adequate confounding control only reported spontaneous abortion risk, while the studies with adequate confounding control did not report any difference in risk of spontaneous abortion. This shows that depression severity is an important confounding factor that can influence the findings of this research question. Hence, future studies

should focus on adjusting for this important confounding factor and provide reliable estimates on the risk or protective role of antidepressants in mothers with depression against spontaneous abortion.

Findings from this systematic review have some important implications for clinical practice. The exact mechanism behind the association of anti-depressant use with the higher rate of spontaneous abortion is not well-understood. However, several theories like the rise in the 5-HT concentration in the foetal cerebral cortex have been proposed.[54,55] This 5-HT binding mechanism can antagonize the prolactin and progesterone section.[56,57] This is important because progesterone is necessary for implantation and maintaining the pregnancy.[58] Spontaneous abortion can be causally linked to the presence of depression among pregnant women.[59]

We found that the use of SSRIs can indeed be protective during the first trimester compared to untreated depressive mothers. This issue is particularly important, though the exposure to antidepressants has a higher risk of spontaneous abortion, while the non-use of anti-depressants among depressed mothers can lead to devastating effects on their mental health. Treating a depressed mother with anti-depressants is equally important to address spontaneous abortion as per the study finding. This can lead to a positive long-term impact on the physical and mental health of the mother and baby. Hence, clinicians need to work with depressed pregnant women and come up with the best possible solution to overcome this issue and find the right balance between the treatment of depression and avoiding a potentially elevated risk of spontaneous abortion or reducing it to the least possible rate.

This review has a greater number of studies when compared to previous reviews addressing similar research questions.[51-53] Hence, this study provides comprehensive evidence on the association of antidepressant exposure during pregnancy with the spontaneous abortion rate. However, there was higher between-study variance for the outcome.. In addition, there was publication bias, limiting credibility of evidence.

Implications

The findings of this review have significant implications for clinical practice, particularly in the management of depression during pregnancy. The association between antidepressant use, particularly SNRIs, and SSRIs, and an increased risk of spontaneous abortion underscores the need for careful consideration when prescribing these medications to pregnant women. While the review highlights an increased risk of spontaneous abortion, especially during the first trimester, it also indicates a potential protective role of SSRIs compared to untreated depression in pregnant women. This dual finding emphasizes the importance of balancing the risks and benefits of antidepressant therapy during pregnancy.

Clinicians should engage in thorough discussions with their pregnant patients who have depression, weighing the potential risks of antidepressant exposure against the severe consequences of untreated depression. Individualized treatment plans should be developed, taking into account the severity of the mother's depression, the specific antidepressant being considered, and the timing of administration. The protective effect observed with SSRIs suggests that, in some cases, these medications might offer a safer alternative during pregnancy, particularly in the first trimester, which is critical for foetal development. However, the decision to initiate or continue antidepressant therapy should be made collaboratively with the patient, considering her mental health needs and the potential risks to her pregnancy.

Furthermore, healthcare providers should be vigilant in monitoring pregnant women who are prescribed antidepressants, especially during the first trimester. Regular follow-ups and assessments are essential to ensure the mental well-being of the mother while minimizing the risk of adverse pregnancy outcomes. In cases where antidepressants are deemed necessary, SSRIs might be preferred, but the decision should always be based on a comprehensive evaluation of the patient's condition.

Recommendations for future research

This review identifies several important areas for future research to enhance the understanding of the relationship between antidepressant use during pregnancy and the risk of spontaneous abortion. First, there is a need for large-scale, high-quality studies that focus on controlling for confounding factors, particularly the severity of depression. The findings of this review suggest that the severity of depression is a critical confounder that can significantly influence the outcomes of studies examining the risk of spontaneous abortion. Future research should prioritize adjusting for this factor to provide more reliable and accurate estimates of the risks associated with antidepressant use during pregnancy.

Additionally, research should explore the underlying mechanisms that contribute to the increased risk of spontaneous abortion associated with antidepressant exposure. While several theories have been proposed, such as the role of 5-HT concentration in the foetal cerebral cortex and its impact on progesterone levels, more detailed investigations are needed to elucidate these pathways. Understanding the biological mechanisms involved could lead to the development of safer therapeutic options for managing depression during pregnancy.

Future studies should also consider the timing of antidepressant administration, as the first trimester appears to be particularly sensitive to the effects of these medications. Longitudinal studies that track the outcomes of pregnancies exposed to antidepressants at different stages could provide valuable insights into the safest periods for antidepressant use, if necessary.

CONCLUSIONS

This meta-analysis has helped in identifying the link between antidepressants and spontaneous abortion and urges clinicians to provide extra attention and care for patients with depression and/or taking antidepressants, as they are at increased risk for serious complications. Hence, these patients should be provided with a customized line of management before or early in pregnancy to minimize adverse clinical outcomes.

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References

1. Albert PR. Why is depression more prevalent in women? *Journal of Psychiatry & Neuroscience*. 2015; **40**:219-21
2. Ajinkya S, Jadhav PR, Srivastava NN. Depression during pregnancy: Prevalence and obstetric risk factors among pregnant women attending a tertiary care hospital in Navi Mumbai. *Industrial Psychiatry Journal*. 2013; **22**:37-40
3. Kishore MT, Satyanarayana V, Ananthanpillai ST, Desai G, Bhaskarapillai B, Thippeswamy H, et al. Life events and depressive symptoms among pregnant women in India: Moderating role of resilience and social support. *International Journal of Social Psychiatry.* 2018; **64**:570-577
4. Cárdenas EF, Kujawa A, Humphreys KL. Neurobiological changes during the peripartum period: implications for health and behavior. *Social Cognitive and Affective Neuroscience*. 2020; **15**:1097-1110
5. Sūdžiūtė, K., Murauskienė, G., Jarienė, K. Jaras, A., Minkauskienė, M., Adomaitienė, V., et al. Pre-existing mental health disorders affect pregnancy and neonatal outcomes: a retrospective cohort study. *BMC Pregnancy Childbirth*. 2020; **20**:419
6. Chang, F., Fan, X., Zhang, Y. Tang, B., & Jia, X. Prevalence of depressive symptoms and correlated factors among pregnant women during their second and third trimesters in northwest rural China: a cross-sectional study. *BMC Pregnancy Childbirth*. 2022; **22**:38
7. Bluett-Duncan M, Kishore MT, Patil DM, Satyanarayana VA, Sharp H. A systematic review of the association between perinatal depression and cognitive development in infancy in low and middle-income countries. *PLoS One*. 2021; **16**:e0253790
8. Fekadu Dadi A, Miller ER, Mwanri L. Antenatal depression and its association with adverse birth outcomes in low and middle-income countries: A systematic review and meta-analysis. *PLoS One*. 2020; **15**:e0227323.

9. Razaz N, Cnattingius S, Persson M, Tedroff K, Lisonkova S, Joseph KS. One-minute and five-minute Apgar scores and child developmental health at 5 years of age: a population-based cohort study in British Columbia, Canada. *BMJ Open*. 2019; **9**:e027655.
10. Zietlow AL, Nonnenmacher N, Reck C, Ditzen B, Müller M. Emotional Stress During Pregnancy - Associations With Maternal Anxiety Disorders, Infant Cortisol Reactivity, and Mother-Child Interaction at Pre-school Age. *Frontiers in Psychology*. 2019; **10**:2179
11. Allen MC. Preterm outcomes research: a critical component of neonatal intensive care. *Mental retardation and developmental disabilities research reviews*. 2003; **8**:221-33.
12. Omidvar S, Faramarzi M, Hajian-Tilak K, Nasiri Amiri F. Associations of psychosocial factors with pregnancy healthy life styles. *PLoS One*. 2018; **13**:e0191723
13. Zietlow AL, Nonnenmacher N, Reck C, Ditzen B, Müller M. Emotional stress during pregnancy–Associations with maternal anxiety disorders, infant cortisol reactivity, and mother–child interaction at pre-school age. *Frontiers in Psychology*. 2019; **21**:79.
14. Helbig A, Kaasen A, Malt UF, Haugen G. Does antenatal maternal psychological distress affect placental circulation in the third trimester?. *PloS One*. 2013; **8**:e57071.
15. Tsiarli, M., Rudine, A., Kendall, N. Pratt MO, Krall R, Thiels E, et al. Antenatal dexamethasone exposure differentially affects distinct cortical neural progenitor cells and triggers long-term changes in murine cerebral architecture and behavior. *Translational Psychiatry*. 2017; **7**:e1153
16. Gotlib IH, Whiffen VE, Mount JH. Prevalence rates and demographic characteristics associated with depression in pregnancy and the postpartum. *ournal of Consulting and Clinical Psychology*. 1989; **57**:269-74.
17. Klein MH, Essex MJ. Pregnant or depressed? The effect of overlap between symptoms of depression and somatic complaints of pregnancy on rates of major depression in the second trimester. *Depression*. 1994; **2**:1994-5.
18. Pastuszak A, Schick-Boschetto B, Zuber C, Feldkamp M, Pinelli M, Sihn S, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA*. 1993; **269**:2246-8.
19. Einarson A, Bonari L, Voyer-Lavigne S, Addis A, Matsui D, Johnson Y, et al. A multicentre prospective controlled study to determine the safety of trazodone/nefazodone use during pregnancy. *Canadian Journal of Psychiatry*. 2003; **48**:106-10.
20. Einarson A, Fatoye B, Sarkar M, Lavigne SV, Brochu J, Chambers C, et al. Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *American Journal of Psychiatry*. 2001; **158**:1728-30
21. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Newcastle-Ottawa quality assessment scale cohort studies. University of Ottawa. 2014.
22. Higgins JP and Green S: Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd, Chichester, UK, 2008.
23. Kulin NA, Pastuszak A, Sage SR, Schick-Boschetto B, Spivey G, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA*. 1998; **279**:609-10
24. Almeida ND, Basso O, Abrahamowicz M, Gagnon R, Tamblyn R. Risk of Miscarriage in Women Receiving Antidepressants in Early Pregnancy, Correcting for Induced Abortions. *Epidemiology*. 2016; **27**:538–46
25. Andersen JT, Andersen NL, Horwitz H, Poulsen HE, Jimenez-Solem E. Exposure to Selective Serotonin Reuptake Inhibitors in Early Pregnancy and the Risk of Miscarriage. *Obstetrics & Gynecology*. 2014; **124**:655–61
26. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. *New England Journal of Medicine*. 1996; **335**:1010-5.

27. Chun-Fai-Chan B, Koren G, Fayez I, Kalra S, Voyer-Lavigne S, Boshier A, et al. Pregnancy outcome of women exposed to bupropion during pregnancy: A prospective comparative study. *American Journal of Obstetrics and Gynecology*. 2005; 192:932–6
28. Diav-Citrin O, Shechtman S, Weinbaum D, Wajnberg R, Avgil M, Di Gianantonio E, et al. Paroxetine and fluoxetine in pregnancy: a prospective, multicentre, controlled, observational study. *British Journal of Clinical Pharmacology*. 2008; **66**:695-705
29. Djulus J, Koren G, Einarson TR, Wilton L, Shakir S, Diav-Citrin O, et al. Exposure to Mirtazapine During Pregnancy: A Prospective, Comparative Study of Birth Outcomes. *Journal of Clinical Psychiatry*. 2006; **67**:1280–4
30. Einarson A, Choi J, Einarson TR, Koren G. Rates of spontaneous and therapeutic abortions following use of antidepressants in pregnancy: results from a large prospective database. *Journal of Obstetrics and Gynaecology Canada*. 2009; **31**:452-6.
31. Johansen RLR, Mortensen LH, Andersen A-MN, Hansen AV, Strandberg-Larsen K. Maternal Use of Selective Serotonin Reuptake Inhibitors and Risk of Miscarriage - Assessing Potential Biases: Maternal use of SSRIs and risk of miscarriage - assessing potential biases. *Paediatric and Perinatal Epidemiology*. 2015; **29**:72–81
32. Ankarfeldt MZ, Petersen J, Andersen JT, Fernandes MFS, Li H, Motsko SP, et al. Duloxetine Exposure During Pregnancy and the Risk of Spontaneous and Elective Abortion: A Danish Nationwide Observational Study. *Drugs Real World Outcomes*. 2021; **8**:289-299
33. Klieger-Grossmann C, Weitzner B, Panchaud A, Pistelli A, Einarson T, Koren G, et al. Pregnancy Outcomes Following Use of Escitalopram: A Prospective Comparative Cohort Study. *The Journal of Clinical Pharmacology*. 2012; **52**:766–70
34. Nakhai-Pour HR, Broy P, Berard A. Use of antidepressants during pregnancy and the risk of spontaneous abortion. *Canadian Medical Association Journal*. 2010; **182**:1031–7
35. Sivojelezova A, Shuhaiber S, Sarkissian L, Einarson A, Koren G. Citalopram use in pregnancy: Prospective comparative evaluation of pregnancy and fetal outcome. *American Journal of Obstetrics and Gynecology*. 2005; **193**:2004–9
36. Vial T, Cournot MP, Bernard N, Carlier P, Jonville-Bera AP, Jean-Pastor M. J. et al. Paroxetine and congenital malformations: a prospective comparative study. *Drug Safety*. 2006; **29**:970.
37. Wu P, Velez Edwards DR, Gorrindo P, Sundermann AC, Torstenson ES, Jones SH, et al. Association between First Trimester Antidepressant Use and Risk of Spontaneous Abortion. *The Journal of Human Pharmacology and Drug Therapy*. 2019; **39**:889–98
38. Gomez-Lumbreras A, Lestón Vázquez M, Vilaplana-Carnerero C, Prat-Vallverdu O, Vedia C, Morros R, Giner-Soriano M. Drug Exposure During Pregnancy: A Case-Control Study from a Primary Care Database. Women's Health Reports. 2024 Jan 1;5(1):13-21.
39. Abadie D, Hurault-Delarue C, Damase-Michel C, *et al*. Medication exposure and spontaneous abortion: A case-control study using a French medical database. *Clin Exp Obstet Gynecol* 2015;42:431–6.
40. Te Winkel B, Beghin D, Pistelli A, *et al*. Venlafaxine exposure in pregnancy, a multicenter ENTIS study. *Pharmacoepidemiol Drug Saf* 2016;25:325–6.
41. Bahat M, Shechtman S, Diav-Citrin O. Pregnancy outcome after first trimester exposure to Duloxetine. *Reproductive Toxicology* 2020;97:3.
42. Kolding L, Ehrenstein V, Pedersen L, *et al*. Antidepressant use in pregnancy and severe cardiac malformations: danish register-based study. *BJOG* 2021;128:1949–57.
43. Ostenfeld A, Petersen TS, Pedersen LH, *et al*. Mirtazapine exposure in pregnancy and fetal safety: A nationwide cohort study. *Acta Psychiatr Scand* 2022;145:557–67.
44. Kitchin Á, Huerta C, Llorente-García A, *et al*. The role of prenatal exposure to antidepressants, anxiolytic, and hypnotics and its underlying illness on the risk of miscarriage using BIFAP database. *Pharmacoepidemiol Drug Saf* 2022;31:901–12.

45. Giner-Soriano MOP-VMLVCV-CCVAGG-LRM. Spontaneous abortion and drug exposure. case-control study with SIDIAP database. Pharmaceoepidemiology and drug safety; 2022. Conference: 38th international conference on Pharmacoepidemiology: advancing Pharmacoepidemiology and real-world evidence for the global community 238–9.
46. Evans-Hoeker EA, Eisenberg E, Diamond MP, *et al*. Major depression, antidepressant use, and male and female fertility. *Fertil Steril* 2018;109:879–87.
47. Chan RL, Jonsson Funk ML, Savitz DA, *et al*. Self-reported antidepressants use and spontaneous abortion. *Am J Epidemiol* 2011;173:S140.
48. Ban L, Tata LJ, West J, *et al*. Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. *PLoS One* 2012;7:e43462.
49. Paulus W, Schloemp S, Stoz F. Paroxetine exposure during pregnancy: increased risk of congenital malformations. *Arch Gynecol Obstet* 2010:282
50. Kjaersgaard MIS, Parner ET, Vestergaard M, *et al*. Prenatal antidepressant exposure and risk of spontaneous abortion - a population-based study. *PLoS ONE* 2013;8:e72095.
51. Hemels ME, Einarson A, Koren G, Lanctôt KL, Einarson TR. Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Annals of Pharmacotherapy*. 2005; **39**:803-9.
52. Nikfar S, Rahimi R, Hendoiee N, Abdollahi M. Increasing the risk of spontaneous abortion and major malformations in newborns following use of serotonin reuptake inhibitors during pregnancy: A systematic review and updated meta-analysis. *DARU Journal of Pharmaceutical Sciences*. 2012; **20**:1-0.
53. Ross LE, Grigoriadis S, Mamisashvili L, Vonderporten EH, Roerecke M, Rehm J, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA Psychiatry*. 2013; **70**:436-43.
54. Broy P, Berard A. Gestational exposure to antidepressants and the risk of spontaneous abortion: a review. *Current Drug Delivery*. 2010; **7**:76-92.
55. Yaris, F, Kadioglu, M, Kesim, M, Ulku C, Yaris E, Kalyoncu NI, et al. Newer antidepressants in pregnancy: prospective outcome of a case series. *Reproductive Toxicology.* 2004; **19**:235-238.
56. Bairy, K.L., Madhyastha, S, Ashok, K.P, Bairy, I, Malini, S. Developmental and behavioral consequences of prenatal fluoxetine. *Pharmacology*. 2007; **79**:1-11.
57. Moiseiwitsch, J.R. The role of serotonin and neurotransmitters during craniofacial development. *Critical Reviews in Oral Biology & Medicine*. 2000; **11**:230-239.
58. Mallmann, E.S, Ribeiro, M.F, Spritzer, P.M. Effect of serotonin depletion by p-chlorophenylalanine on serum prolactin levels in estrogen-treated ovariectomized rats: insights concerning the serotoninergic, dopaminergic and opioid systems. *Hormone Metabolic Research.* 2001; **33**:337-342.
59. Fact Sheets: Spontaneous Abortion (http://www.emcom.ca/health/abortion.shtml). McLaughlin Centre, Institute of Population Health, University of Ottawa, 2009.