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SYSTEMATIC REVIEW

Antidepressant Use During Pregnancy and the Potential Risks of Motor Outcomes and Intellectual Disabilities in Offspring: A Systematic Review

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Abstract

Background There is a risk of adverse neurodevelopmental outcomes in offspring from exposure to antidepressants during pregnancy.

Objective This study was performed to systematically review the available evidence regarding the impact of in utero exposure to antidepressants on motor and intellectual disability outcomes in children.

Patients and Methods A systematic literature search for published observational studies examining the effects of antidepressants on motor development or intellectual disabilities in children was conducted using the Cochrane Central Register of Controlled Trials, PubMed/Medline, and Google Scholar.

Results A total of 14 studies were included in this review. Studies have reported conflicting effects on motor development in infants with maternal exposure to antidepressants. Furthermore, not all of the studies included that assessed intellectual disabilities in infants found an association between maternal exposure to antidepressants and intellectual disabilities. However, methodological flaws existed in the studies, such as the use of scales with inadequate reliability or validity, a lack of statistical power, or confounding by indication or disease severity.

Conclusion The available literature provides inconclusive evidence on the relationship between in utero exposure to antidepressants and adverse effects on motor development outcomes or neurocognitive skills. Further observational studies with robust methodologies are needed to comprehensively evaluate the potential risks of prescribing antidepressants during pregnancy.

Key Points

The available evidence on the association between antidepressant use during pregnancy and poor motor development in offspring is inconclusive.

The results of the reviewed studies do not suggest an association between in utero exposure to antidepressants and delayed adverse effects on intellectual ability in children.

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1 Introduction

Maternal depression encompasses mild and severe non-psychotic depressive conditions affecting pregnant women and new mothers. It includes depressive episodes that occur during pregnancy and up to a year after childbirth [1, 2]. According to the World Health Organization, approximately 10% of pregnant women and 13% of new mothers (up to 12 months postpartum) experience depression [3]. The growing incidence of maternal depression imposes a substantial social and economic burden on many societies; hence, it is now recognized as a global public health issue [4].

Untreated maternal depression is associated with higher rates of pregnancy-related complications, such as premature death of the infant, and poor fetal outcomes, such as low fetal growth and increased fetal heart rate [5, 6]. Untreated depression during pregnancy is also associated with a higher risk of preterm birth (< 37 weeks) and lower birth weight (< 2500 g) than in women without depression [7]. Furthermore, having depression during pregnancy is associated with a broad range of neurodevelopmental problems in offspring, such as negative behavioral, emotional, or cognitive outcomes, intellectual disabilities, and language impairment [8–11]. Observational studies have shown that persistent depression during pregnancy is associated with increased risk of delayed cognitive and behavioral development in children and with antisocial and violent behavior in teenagers [8, 9], which emphasizes the importance of adequate maternal depression treatment during pregnancy to prevent severe adverse outcomes for mother and child.

Despite the need for appropriate treatment of maternal depression during pregnancy, there is limited information available to guide clinicians [12]. The prevalence of antidepressant use during pregnancy worldwide varies from 1.8 to 7.3% [13–15]. Currently, a combination of pharmacotherapy and psychotherapy is the most common treatment for moderate to severe maternal depression, while psychotherapy alone is recommended in mild cases [16–18]. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressants during pregnancy [16–18]. However, antidepressants have their own set of adverse effects on maternal and fetal outcomes. Since they can pass the placental barrier, their use during pregnancy may potentially affect the neurotransmitter systems in the brain of the offspring, and may eventually influence neurodevelopmental outcomes [19]. Consequently, clinicians often face the risk–benefit dilemma of whether to treat mothers with antidepressants during pregnancy. There is a need for a systematic examination of the published literature to provide evidence on the use of antidepressants during pregnancy and on the potential risk of neurodevelopmental outcomes in the offspring.

Studies assessing the safety of antidepressant use during pregnancy report conflicting results [12, 20–35]. For example, several studies have linked prenatal exposure to antidepressants to attention deficit hyperactivity disorder or autism spectrum disorder in children [20–27, 31–35]. However, after addressing confounding bias through sibling design, the risk was moved to the null finding [33–35]. On the other hand, only a few studies have examined the potential impact of antidepressant use on other neurodevelopment aspects, such as cognitive and motor development, intelligence quotient (IQ), or language competence [12, 29, 36–38], and there is no consensus on the effect of prenatal exposure to antidepressants on motor and intellectual development in offspring [12, 29, 39–51].

Therefore, this systematic review aims to evaluate the available literature concerning the prenatal use of antidepressants and its potential impact on motor and intellectual development in offspring.

2 Methodology

2.1 Data Sources

A systematic literature search for the papers published before December 2020 was performed in the Cochrane Central Register of Controlled Trials, PubMed/Medline, and Google Scholar. The reference lists of the selected articles and the systematic reviews/meta-analyses identified through the search were also screened for additional publications.

2.2 Search Terms

Medical subject headings combined with relevant keywords were used to search the databases. The search terms for motor outcomes were “antidepressant” OR “tricyclic antidepressants” OR “TCA(s)” OR “selective serotonin reuptake inhibitors” OR “SSRI(s)” OR “serotonin norepinephrine reuptake inhibitors” OR “SNRI(s)” AND “children” OR “offspring” OR “pregnancy” OR “pregnant” OR “maternal” OR “prenatal” OR “antenatal” OR “gestational” AND “motor performance” OR “neuromotor performance” OR “motor activity” OR “motor skills” OR “motor outcome.”

For intellectual disabilities, the search terms were “antidepressant” OR “tricyclic antidepressants” OR “TCA(s)” OR “selective serotonin reuptake inhibitors” OR “SSRI(s)” OR “serotonin norepinephrine reuptake inhibitors” OR “SNRI(s)” AND “children” OR “offspring” OR “pregnancy” OR “pregnant” OR “maternal” OR “prenatal” OR “antenatal” OR “gestational” AND cognitive” OR “cognitive development” OR “intelligence” OR “intelligence quotient (IQ)” OR “low IQ” OR “intellectual development disorder” OR

"intellectual disability" OR "mental retardation" OR "mental deficiency."

2.3 Inclusion Criteria

We included papers that met the following criteria. The study population was children, between 0 and 18 years old, of mothers exposed to antidepressants during pregnancy. The exposure window was from 30 days before conception to the time of delivery. The exposure of interest was the mother's use of antidepressants, including SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), and tricyclic antidepressants (TCAs). We studied the transient effects of prenatal exposure to antidepressants on motor or intellectual development events that had been assessed either by medical diagnoses or by standardized psychometric instruments.

2.4 Selection of Studies

The initial search was limited to human studies published in English. The titles and abstracts of all articles found in the initial search were screened for primary evaluation. Only observational studies (cohort, case–control design, or their variants) available in full text were included. Two reviewers independently conducted the systematic literature search, screening, and reviewing of articles. Upon completion of the literature search, both reviewers shared their findings and reached a consensus for the final study selection. The current review adheres to the guidelines and checklist of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

2.5 Quality Appraisal

Once the selection process was complete, the baseline characteristics of all studies included (i.e., first author's name, date of publication, study design, sample size, duration of antidepressant exposure, outcome measure, children's age, and adjusted variables) were carefully examined. The methodological quality and risk of bias for each study were assessed using the Risk of Bias in Non-Randomized Studies (ROBINS-I) tool (Table 4).

3 Results

The initial literature search resulted in 813 articles. After excluding duplicates, non-English studies, and animal studies, 670 records were screened. Of these, 626 records were excluded after title/abstract screening. In total, 44 articles remained for full-text screening. Thirty articles were subsequently excluded: 20 for addressing other outcomes and ten for being reviews. Finally, 14 studies remained for use in this systematic review. Figure 1 shows the flow diagram for article selection based on PRISMA. Tables 1 and 2 present the baseline characteristics and main findings of the studies included.

3.1 Motor Development

3.1.1 Characteristics of the Studies Included

Ten studies examined the association between antidepressant use during pregnancy and poor motor development outcomes in offspring [39–48]. The studies operationalized adverse motor development outcomes using an observer assessment scale or diagnostic codes (Table 1). Seven studies used psychometric evaluation instruments; six studies [40–42, 44, 47, 48] used either the 2nd or 3rd edition of the Bayley Scales of Infant Development (BSID-II and BSID-III), and one study used the Movement Assessment Battery for Children (Movement ABC) [45]. All psychometric evaluations were conducted by trained psychologists or occupational therapists who were blinded to the infants' exposure status. Two studies assessed motor activity in infants by observing the infants physically with activity monitoring devices and the Neonatal Behavioral Assessment Scale (NBAS) [39, 46]. Physical observations were done by trained assessors who were blinded to the infants' exposure status. One study based its outcome assessment on medical diagnosis by physicians in specialized care units [43].

3.1.2 Antidepressant Exposure

Antidepressant exposure was ascertained from self-reported questionnaires in five studies [39, 44, 45, 47, 48], while the remaining studies obtained exposure status from medical records. Most studies (six out of nine) specifically examined the association between maternal exposure to SSRIs and adverse effects on motor outcomes [39, 41, 43, 46, 48]. The timing of antidepressant exposure during pregnancy varied between studies, and only four studies classified antidepressant exposure by trimester [39, 44, 47, 48].

3.1.3 Bayley Scales of Infant Development

Using BSID-II or BSID-III, one study showed that the fine motor function performance in offspring of healthy mothers unexposed to antidepressants was 9.4% higher than that in exposed children [42]. However, these findings were not statistically significant (Table 1). In contrast, three studies showed a statistically insignificant higher score (ranging from 0.9 to 6.1%) in fine motor functions in offspring with in utero exposure to antidepressants in comparison to

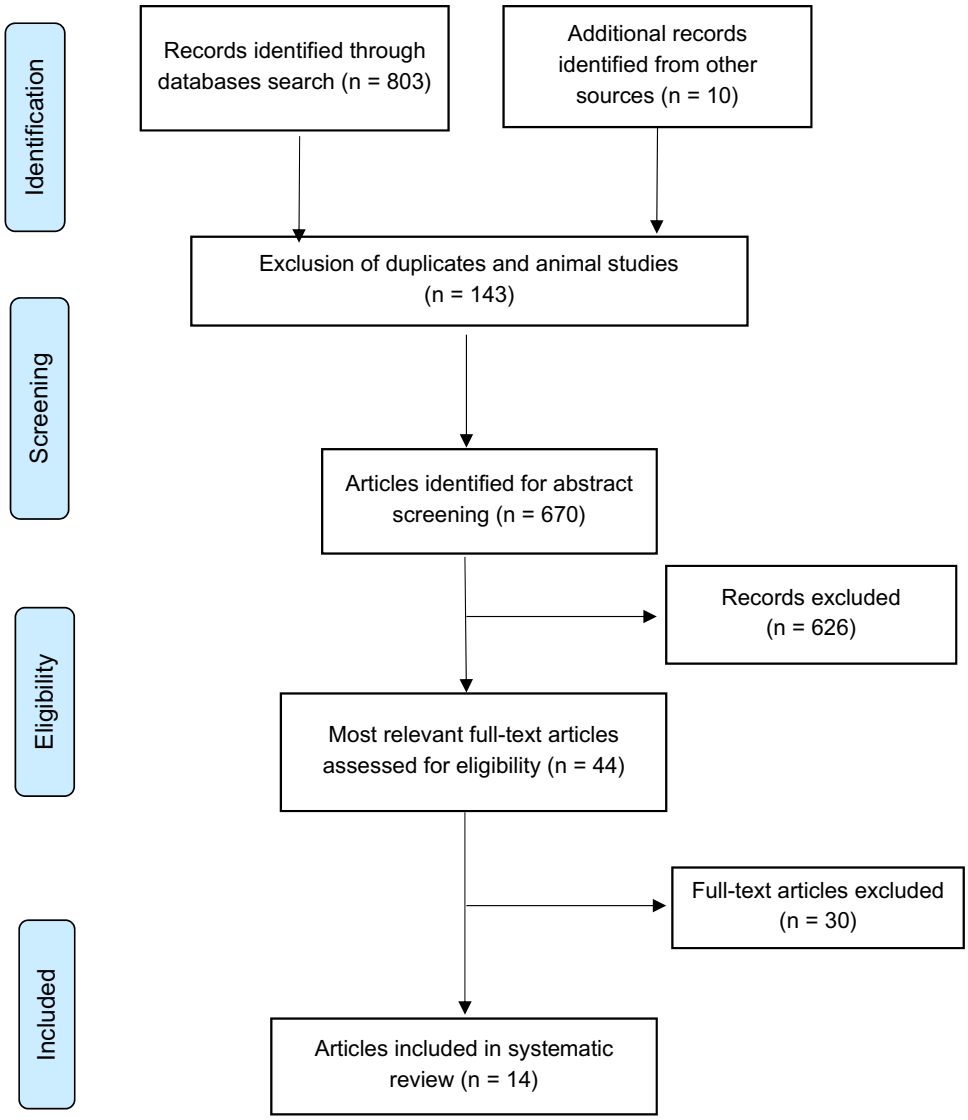

Fig. 1 PRISMA flow diagram for study selection. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses. From: Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6(7): e1000097. https://doi.org/10.1371/journal.pmed1000097

offspring of unexposed healthy mothers [40, 41, 44]. Notably, none of the studies considered the cumulative in utero exposure to antidepressants, nor the timing of the exposure by trimester (except one study). Casper et al. (2011) did link longer antidepressant use during pregnancy to adverse effects on motor development in offspring [47]. However, this study did not include a control group of unmedicated women with depression; therefore, confounding by indication cannot be ruled out.

Three studies showed that the score of gross motor function performance was 9.1–12.6% lower in children with in utero exposure to antidepressants in comparison to offspring of unexposed healthy mothers [40, 42, 48]. On the other hand, two studies demonstrated slightly higher scores (1.1–7.7%) in gross motor function in children with in utero exposure to antidepressants in comparison to unexposed children of healthy mothers [41, 44].

3.1.4 Neonatal Behavioral Assessment Scale

Two small studies examined the association of in utero antidepressant exposure with early motor development using NBAS and reported inconsistent findings. Zeskind and Stephens showed worse motor performance during sleep associated with in utero exposure to antidepressant (unspecified by trimester) in comparison to no exposure with healthy mothers [46]. Similarly, there was an association between maternal exposure to antidepressant during the third trimester and adverse motor outcomes in neonates in another study [39]. However, these differences in motor activity were no longer significant when adjusted for gestational age in both studies [39, 46].

Table 1 Characteristics of studies assessing the effect of antidepressants on motor development

Author [reference]	Study design	Data source	Sample size and exposure status	Control group	Outcome measure	Children's age	Results	Main findings
Casper et al. 2003 [41]	Partly prospective, partly retrospective, clinic-based	Women's Wellness Clinic or clinicians' offices in Stanford, California	Exposed = 31 (any time during pregnancy) Control = 13 Exposure ascertainment: medical records	Children of mothers who had a major depressive disorder in pregnancy but received no medication	BSID-II	6–40 months	(SSRI exposed vs. unexposed) Mean ± SD scores on gross motor movement (4.77 ± 0.44 vs. 4.43 ± 0.68, $p = 0.17$); fine motor movement (5 ± 0 vs. 4.71 ± 0.46, $p = 15$) and tremulousness (5 ± 0 vs. 4.87 ± 0.46, $p = 0.08$)	There were differences in motor quality factors, particularly fine motor development and tremulousness, between the SSRI-exposed and unexposed groups; however, these differences were not statistically significant

Table 1 (continued)

Author [reference]	Study design	Data source	Sample size and exposure status	Control group	Outcome measure	Children's age	Results	Main findings
Zeskind and Stephens 2004 [46]	Prospective cohort study	Carolinas Medical Center in Charlotte, North Carolina	Exposed = 17 (any time during pregnancy) Control = 17 Exposure ascertainment: medical records	Unexposed healthy mothers	NBAS	14–39 h	(SSRI exposed vs. unexposed) Mean ± SE scores on: Tremulousness (2.32 ± 0.2 vs. 1.8 ± 0.2, p = 0.038) Behavioral state (no. of differences: 2.5 ± 0.32 vs. 3.71 ± 0.32, p = 0.009; no. of changes: 7.15 ± 2.34 vs. 16.56 ± 2.34, p = 0.005) Active sleep (no. of epochs: 94.66 ± 6.64 vs. 83.46 ± 6.64, p = 0.13; no. of bouts: 3.36 ± 0.44 vs. 6.58 ± 0.44, p = 0.001; no. of startles: 14.59 ± 2.70 vs. 9.85 ± 2.59, p = 0.13) Motor activity (152.05 ± 21.25 vs. 106.5 ± 21.96, p = 0.08) No. of HRV rhythms (1.98 ± 0.19 vs. 2.39 ± 0.19, p = 0.07)	Infants exposed to SSRIs had insignificantly more active sleep and tremors than unexposed infants

Table 1 (continued)

Author [reference]	Study design	Data source	Sample size and exposure status	Control group	Outcome measure	Children's age	Results	Main findings
Casper et al. 2011 [47]	Prospective cohort study, clinic-based	Women's Clinic at Stanford University	Exposed = 55 1st trimester (N = 14); 2nd and 3rd trimester (N = 18); entire pregnancy (N = 23) Exposure ascertainment: medical records	None	BSID-II	12–40 months	PDI (p = 0.012, R2 = 0.11, r = −0.34)	Longer prenatal exposure to SSRI increased the risk of lower PDI on the BSID-II in infancy. However, there was an imbalance in the demographic characteristics between the groups and potential confounding by depression severity
Galbally et al. 2011 [42]	Prospective case–control study	Mercy Hospital for Women	Cases = 22 (any time during pregnancy) Control = 19 Exposure ascertainment: medical records	Unexposed healthy mothers	BSID-II	18–35 months	(Exposed vs. unexposed) Mean ± SD scores on motor outcomes (fine: 12.84 ± 2.99 vs. 14.18 ± 2.7, p = 0.07; gross: 12.89 ± 2.75 vs. 14.18 ± 3.13, p = 0.09)	Children of mothers exposed to antidepressants during pregnancy had lower score on motor subscales than non-exposed children; however, the differences were not statistically significant
Hanley et al. 2013 [40]	Prospective cohort study, clinic-based	Community midwife clinics, family physician clinics, and a reproductive mental health clinic in metropolitan Vancouver	Exposed = 31 (any time during pregnancy) Control = 52 Exposure ascertainment: medical records	Unexposed healthy mothers	BSID-III	10 months	(Exposed vs. unexposed) Mean ± SD scores on motor outcomes (fine: 11.3 ± 2.2 vs. 11.2 ± 1.7, p = 0.55; gross: 8.3 ± 3.3 vs. 9.5 ± 2.8, p = 0.03)	Infants prenatally exposed to SSRIs had significantly lower gross motor scores than non-exposed infants in subscales of the BSID-III

Table 1 (continued)

Author [reference]	Study design	Data source	Sample size and exposure status	Control group	Outcome measure	Children's age	Results	Main findings
Austin et al. 2013 [44]	Prospective, longitudinal case–control study	Perinatal mental health clinic at the Royal Hospital for Women	Exposed = 35 (any time during pregnancy) Controls = 23 Exposure ascertainment: self-reported	Unexposed healthy mothers	BSID-III	17–24 months	(Exposed vs. unexposed) Mean ± SD scores of motor outcomes (fine: 12.1 ± 2.4 vs. 11.8 ± 2.0, $p = 0.40$; gross: 9.2 ± 2.6 vs. 9.1 ± 2.0, $p = 0.71$)	Antidepressant exposure (mostly SSRIs) during pregnancy was not associated with worse motor development outcomes in infants
Smith et al. 2013 [39]	Prospective cohort study, clinic-based	Clinicians' offices or hospital-based clinics in Connecticut and western Massachusetts	Exposed = 6 (third trimester) Control = 61 Exposure ascertainment: self-reported	Unexposed healthy mothers	NBAS	24 h (± 8 h) post-delivery	(SSRI exposed vs. unexposed) Mean ± SE of motor scores (25.200 ± 3.962 vs. 28.9 ± 3.055, $p = 0.05$)	Differences in motor scores were statistically insignificant in infants exposed to SSRIs compared to those with no in utero exposure after controlling for gestational age
Galbally et al. 2015 [45]	Prospective case–control study	Victorian Psychotropic Registry	Exposed = 20 (entire pregnancy) Control = 21 Exposure ascertainment: self-reported	Unexposed healthy mothers	Movement ABC	4 years	(Exposed vs. unexposed) Motor development, total composite score (80.40 ± 13.11 vs. 83.43 ± 12.12, $p = 0.45$)	Exposure to antidepressants during pregnancy had no effect on motor development in offspring
Brown et al. 2016 [43]	Population-based, prospective cohort study	Finnish Medical Birth Register	Exposed = 15,596 (mothers received at least one prescriptions for antidepressants during pregnancy) Unmedicated = 9537 Control = 31,207 Exposure ascertainment: medical records	Children of depressed women who were untreated during pregnancy and children of non-depressed, healthy women	Diagnostic codes for speech/language, scholastic, or motor disorders	From birth to 14 years	(SSRI-exposed vs. unmedicated group; SSRI-exposed vs. unexposed group) Motor disorder (adjusted HR 1.18, 95% CI 0.81–1.72; 1.26, 95% CI 0.90–1.77)	There was no significant increase in risk of motor disorders in offspring in the SSRI-exposed group compared to the unexposed group and the unmedicated group

Table 1 (continued)

Author [reference]	Study design	Data source	Sample size and exposure status	Control group	Outcome measure	Children's age	Results	Main findings
van der Veere et al. 2020 [48]	Prospective cohort study SSRIs in pregnant mothers, outcome of the study on children (SMOK)	Pregnant women living near two level-2 hospitals in the north of the Netherlands were recruited through newspapers, midwives, general practitioners, gynecologists, and psychiatrists	SSRI-exposed = 61 (third trimester) Non-SSRI-exposed = 41 Exposure ascertainment: self-reported	Unexposed healthy mothers	BSID-III	2.5 years	(SSRI-exposed vs. unexposed) Mean ± SD of gross motor scores (7.9 ± 2.2 vs. 9.0 ± 2.5, p = 0.01)	Infants prenatally exposed to SSRIs had significantly lower gross motor scores than non-exposed infants in subscales of the BSID-III. However, these differences were not statistically significant when adjusted for maternal anxiety

BSID-II/III Bayley Scales of Infant Development, 2nd/3rd edition, *CI* confidence interval, *HR* hazard ratio, *HRV* heart rate variability, *Movement ABC* Movement Assessment Battery for Children, *NBAS* Neonatal Behavioral Assessment Scale, *PDI* Psychomotor Development Index, *SSRI* selective serotonin reuptake inhibitor

3.1.5 Movement Assessment Battery for Children

One study reported insignificant worse motor development effects (using the Movement ABC test) in offspring following antidepressant exposure during pregnancy in comparison to those born to healthy mothers with no antidepressant use [45]. The composite motor score was 3.6% lower in children with maternal exposure to antidepressants in comparison to those without exposure to antidepressant.

3.1.6 Diagnoses of Motor Disorders

Brown et al. (2016) [43] conducted a large population-based study using data on singleton live births from the Finnish Medical Birth Register using medical diagnoses as the measure of motor outcome. No significant differences were observed in motor outcomes between offspring in the antidepressant-exposed group and in the unmedicated group with mothers who had depression (hazard ratio [HR] 1.18; 95% confidence interval [CI] 0.81–1.72). The authors observed an insignificant increased risk of motor disorders in offspring of mothers with at least two antidepressant purchases compared to offspring of unexposed healthy mothers (HR 1.26; 95% CI 0.9–1.77). The risk increased with more refills of SSRI prescriptions (≥ 2) compared to only receiving one prescription; this might indicate confounding by depression severity, which the authors attempted to control for by adjusting for suicidal ideation and restricting the analysis to those with no other psychotropic agents [43].

3.1.7 Confounding Domains Assessed by the Included Studies

Table 3 shows the covariates evaluated by the studies included. Two potential confounders (maternal age and gestational age) were evaluated in all studies. Other variables controlled for in some studies including cigarette and alcohol use during pregnancy, the mother's education level, the mother's socioeconomic status, the mother's IQ, and the duration of antidepressant exposure (Table 3). Nine out of ten studies assessed either the severity of the maternal depression or the maternal psychiatric history. Zeskind and Stephens's study [46] was the only one that did not evaluate maternal depression or psychiatric comorbidity during pregnancy. The study mainly included postpartum mothers and was limited to measures of maternal treatment intensity in terms of number and duration of antidepressant use during pregnancy [46].

3.1.8 Risk of Bias

Of the ten studies assessing motor development as an outcome of maternal exposure to antidepressants, we considered

Table 2 Studies assessing the effect of antidepressants on intellectual disabilities

Author [reference]	Study design	Data source	Sample size	Control group	Outcome measure	Children's age	Results	Main findings
Nulman et al. 1997 [49]	Prospective cohort study, clinic-based	The Motherisk Program	TCA = 80 or fluoxetine = 55 through the first trimester or entire pregnancy Control = 84 Exposure ascertainment: self-reported	Unexposed healthy mothers	BSID-II and McCarthy Scales of Children's Abilities	16–86 months	(TCA-exposed vs. fluoxetine-exposed vs. control) Mean ± SD of global IQ scores on BSID (118 ± 17 vs. 117 ± 17 vs. 115 ± 14) Mean ± SD of global IQ scores on McCarthy General Cognitive Index (117 ± 10 vs. 114 ± 16 vs. 114 ± 13)	Antidepressant exposure during pregnancy did not significantly affect the global IQ in preschool children. Overall, the findings of this study should be interpreted with caution due to exposure misclassification, especially in the first trimester.
Nulman et al. 2002 [50]	Prospective cohort study, clinic-based	The Motherisk Program	TCA = 46 or fluoxetine = 40 through the entire pregnancy Control = 36 Exposure ascertainment: self-reported	Unexposed healthy mothers	BSID-II and McCarthy Scales of Children's Abilities	15–71 months	(TCA-exposed vs. fluoxetine-exposed vs. control) Mean ± SD scores on BSID-MDI (104.4 ± 15.5 vs. 110.9 ± 18.0 vs. 104 ±13.7) Mean ± SD scores on McCarthy Global Cognitive Index (108.7 ± 19.9 vs. 117.8 ± 10.4 vs. 118.4 ± 9.1)	Exposure to antidepressants throughout gestation did not affect the children's global IQ

Table 2 (continued)

Author [reference]	Study design	Data source	Sample size	Control group	Outcome measure	Children's age	Results	Main findings
Nulman et al. 2012 [51]	Prospective cohort study	The Motherisk Program	Venlafaxine = 62, SSRI = 62 (exposure through the entire pregnancy) Unmedicated = 54 Control = 62 Exposure ascertainment: self-reported	Children of depressed mothers who were untreated during pregnancy and children of non-depressed mothers	WPPSI-III	3 years to 6 years, 11 months	(Venlafaxine-exposed vs. SSRI-exposed vs. depression-exposed vs. unexposed) Mean ± SD scores of full-scale IQ (105 ± 14 vs. 105 ± 13 vs. 108 ± 14 vs. 112 ± 11] Verbal IQ (106 ± 14 vs. 107 ± 14 vs. 109 ± 13 vs. 113 ± 12) Performance IQ (103 ± 14 vs. 102 ± 14 vs. 105 ± 13 vs. 108 ± 10)	The children exposed to antidepressants and maternal depression during pregnancy had similar full-scale IQs. However, children born to non-depressed mothers had the highest IQ
Galbally et al. 2015 [45]	Prospective case–control study	Victorian Psychotropic Registry	Exposed = 20 (entire pregnancy) Control = 21 Exposure ascertainment: self-reported	Unexposed healthy mothers	WPPSI-III	4 years	(exposed vs. unexposed) Mean ± SD scores of WPPSI full score IQ (115.40 ± 13.96 vs. 115.76 ± 8.29, $p = 0.92$)	Exposure to antidepressants during pregnancy had no effect on the full IQ of children
Viktorin et al. 2017 [52]	Population-based cohort study	The Swedish National Patient Register	Exposed = 3982 (mothers received at least 2 prescriptions of antidepressants at any time during pregnancy) Unexposed = 172,646 Exposure ascertainment: medical records	Unexposed healthy mothers	Inpatient or outpatient specialist care and ICD-10 codes	7.9 (± 0.6) years on average	(Exposed vs. unexposed) Adjusted relative risk of intellectual disabilities is 1.33 (95% CI 0.90–1.98)	The study found no significant association between intellectual disabilities and antidepressant exposure during pregnancy

BSID-II Bayley Scales of Infant Development, 2nd edition, *CI* confidence interval, *ICD* International Statistical Classification of Diseases and Related Health Problems, *IQ* intelligence quotient, *MDI* Mental Development Index, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressants, *WPPSI-III* Wechsler Preschool and Primary Scale of Intelligence, 3rd edition

Table 3 Covariates controlled for/adjusted in the studies included

Authors	Potential confounders									Other adjusted variables
	Maternal age	Paternal age	Maternal depression severity	Socio-economic status	Maternal cigarette use	Maternal alcohol use	Gestational age	Maternal IQ	Duration of antidepressant exposure	
Nulman et al. [49]	Yes	No	Yes	Yes	No[b]	No[b]	Yes	Yes	No	Maternal IQ; child's head circumference
Nulman et al. [50]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Maternal IQ; depression duration; treatment duration; number of depressive episodes after delivery; medications used for depression treatment; child's head circumference
Casper et al. [41]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Frequency of miscarriages; illicit drug use; birth method; maternal education; marital status; frequency of preterm; child's head circumference; birth length
Zeskind and Stephens [46]	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Maternal ethnicity; maternal education; marijuana use; child's head circumference; birth length
Casper et al. [47]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Gravidity; prior miscarriages; frequency of caesarean delivery; birth complications; child's head circumference; birth length
Galbally et al. [42]	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Maternal education; marital status; occupational status; frequency of no miscarriage or termination; birth complications; child's head circumference; birth length
Hanley et al. [40]	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Previous live births; number of prior pregnancies; maternal education; preterm birth; infant's sex; birth length

Table 3 (continued)

Authors	Potential confounders									Other adjusted variables
	Maternal age	Paternal age	Maternal depression severity	Socio-economic status	Maternal cigarette use	Maternal alcohol use	Gestational age	Maternal IQ	Duration of antidepressant exposure	
Nulman et al. [51]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Antidepressant dose; duration of antidepressant treatment during pregnancy (weeks); severity of depression at the time of child's testing; maternal IQ; maternal weight gain; child's age and sex; child's head circumference
Austin et al. [44]	No	No	Yes	No	No	Yes	Yes	No	No	Infant's sex; head circumference; birth length; maternal and paternal education; marital status; type of birth; episodes of the full spectrum mental health disorders
Smith et al. [39]	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Maternal education; maternal ethnicity; illicit drug use; birth method; prior pregnancy; marital status; major medical complications; infant's head circumference; birth length
Galbally et al. [45]	Yes	No	Yes	Yes[a]	Yes	Yes	Yes	No	No	Maternal education; maternal depression
Brown et al. [43]	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Child's sex; previous births; marital status; exposure to antiepileptic drugs, mother's country of birth; parental death; maternal substance abuse; paternal age; place of residence; exposure to anxiolytics/sedatives; history of chronic diseases; maternal and paternal history of psychiatric diagnoses

Table 3 (continued)

Authors	Potential confounders								Other adjusted variables
	Maternal age	Paternal age	Maternal depression severity	Socio-economic status	Maternal cigarette use	Maternal alcohol use	Gestational age	Maternal IQ	Duration of antidepressant exposure	
Viktorin et al. [52]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Child's sex; birth date; paternal age; maternal and paternal education; maternal and paternal psychotropic medication that overlapped the pregnancy; mother's one-time dispensations of psychotropic medication that overlapped the pregnancy
van der Veere et al. [48]	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Maternal education; maternal anxiety; birth weight

IQ intelligence quotient

[a]The confounding domain appears to be controlled for, but data were not shown in the current study

[b]Data were obtained, but the confounding domains were not fully controlled in the analysis

nine studies [39–43, 45–48] at moderate risk of bias and one study [44] at serious risk of bias (Table 4).

3.2 Intellectual Disabilities

3.2.1 Characteristics of the Studies Included

Five studies [45, 49–52] examined the association between maternal antidepressant exposure during pregnancy and the risk of intellectual disabilities in offspring. The studies used a psychometric instrument (BSID-II) and the McCarthy Scales of Children's Abilities [49, 50], the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) [45, 51], or diagnostic codes [52]. The psychometric assessment was done by trained psychologists or occupational therapists blinded to the offspring's exposure status.

3.2.2 Antidepressant Exposure

In four studies, antidepressant exposure ascertainment was done through self-reported questionnaires [45, 49–51]. Maternal antidepressant exposure windows were specified in two studies, where the use of antidepressants went on throughout the pregnancy, starting from the first trimester, and this was a requirement for eligibility for the study [45, 50]. The other two studies did not restrict the timing or length of antidepressant use [49, 51, 52]. Most studies (three out of five) specifically examined the association between maternal exposure to SSRIs and adverse effects on intellectual performance outcomes [49, 50, 52].

3.2.3 Wechsler Preschool and Primary Scale of Intelligence

Two studies used the WPPSI to examine the association between exposure to antidepressants during the entire pregnancy and detrimental effects on intellectual ability [45, 51]. In one study, the full IQ test score was similar between children exposed to antidepressants and unexposed children of healthy mothers (mean IQ score ± SD = 115 ± 14 vs. 115 ± 8; $p = 0.92$) [45]. The other study reported slightly higher full IQ scores (IQ = 112 ± 11) in unexposed children of healthy mothers than in antidepressant-exposed children (IQ = 105 ± 13) [51]. However, neither study found a statistically significant association between in utero exposure to antidepressants and adverse mental outcomes.

3.2.4 Bayley Scales of Infant Development and McCarthy Scales of Children's Abilities

The McCarthy Scales of Children's Abilities and the BSID were used in two studies to assess the risk of adverse effects on a child's intellectual abilities following in utero exposure to antidepressants [49, 50]. Both studies included only

Table 4 Risk of bias among observational studies measuring prenatal antidepressant exposure and its potential impact on motor and intellectual development in children

Authors	Nulman et al. (1997)	Nulman et al. (2002)	Casper et al. (2003)	Zeskind and Stephens (2004)	Casper et al. (2011)	Galbally et al. (2011)	Hanley et al. (2013)	Nulman et al. (2012)	Austin et al. (2013)	Smith et al. (2013)	Galbally et al. (2015)	Brown et al. (2016)	Viktorin et al. (2017)	van der Veere et al. (2020)
Bias due to confounding	Serious	Moderate	Low	Low	Low	Low	Moderate	Low	Serious	Moderate	Low	Moderate	Low	Moderate
Bias in selection of participants for the study	Low	Low	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Bias in classification of interventions	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias due to deviations from intended interventions	Serious	Low	Moderate	Low	Low	Moderate	No information	Low	Moderate	Low	Low	Low	No information	Moderate
Bias due to missing data	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate	Low	Moderate	Moderate	Low	Low	Low
Bias in measurement of outcomes	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Bias in selection of the reported result	Moderate	Low	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	Low	Low	Low
Overall risk of bias	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Serious	Moderate	Moderate	Moderate	Low	Moderate

mothers who used antidepressants throughout the pregnancy, starting from the first trimester. The performance in global IQ assessments was similar or slightly higher in exposed children compared to unexposed children of healthy mothers (Table 2). The results of global cognitive function assessments were comparable between exposed children and unexposed children of healthy mothers (Table 2). In both studies, there was no association between in utero exposure to antidepressants and adverse effects on the offspring's cognitive development or intellectual ability compared to no exposure [49, 50].

3.2.5 Intellectual Disabilities Diagnosis

Viktorin et al. [52] used the Swedish national registers to conduct a retrospective cohort study comprising 179,007 infants. Infants exposed to antidepressants through their mother had a 33% higher risk of intellectual disability compared to unexposed infants of healthy mothers. However, the results were not statistically significant (relative risk 1.33; 95% CI 0.90–1.98) [52]. The specific timing of exposure to antidepressants and the length of exposure did not have an effect on the association between antidepressant exposure and intellectual disabilities in infants (Table 2).

3.2.6 Confounding Domains Assessed by the Studies Included

Table 3 highlights the covariates evaluated by the studies included that examined intellectual disabilities as an outcome. The maternal age and gestational age were evaluated by all studies. Covariates such as cigarette and alcohol use during pregnancy, the mother's education level, the mother's socioeconomic status, the mother's IQ, and the duration of antidepressant exposure were considered in the studies (Table 3). Adjustment for the use of psychotropic drugs other than antidepressants occurred in three studies [50–52].

3.2.7 Risk of Bias

Of the five studies [45, 49–52] that examined the association between maternal antidepressant exposure during pregnancy and the risk of intellectual disabilities in offspring, we assessed two studies [51, 52] at low risk of bias, two at moderate risk of bias [45, 50], and one at serious risk of bias [49].

4 Discussion

This systematic review was conducted to examine published studies investigating the relationship between in utero exposure to antidepressants and the risk of poor motor development and intellectual disability outcomes in offspring.

The available evidence concerning the association between antidepressant use during pregnancy and the risk of adverse motor development is inconsistent. A recently published meta-analysis [30] reported a small effect (effect size = 0.22; 95% CI 0.07–0.37) in the direction of an increased risk of worse motor development outcomes in children exposed to antidepressants. However, given the marked variations in outcome measurements among the studies, particularly in methods used to quantify motor performance, the meta-analysis is subject to a moderate degree of heterogeneity ($I^2 = 56.6\%$; $p = 0.002$). Although the study suggested a possible association between in utero exposure to antidepressants and delayed motor development, it could not rule out the influence of different biases or of unmeasured confounding such as confounding by indication.

The results of the observational studies included found no association between antidepressant exposure during pregnancy and intellectual disability outcomes in offspring [45, 49–52]. Nulman et al. conducted a series of studies [49–51] to examine the differences in IQ between antidepressant-exposed and unexposed children, and found no significant association between intellectual disabilities and prenatal exposure to antidepressants. Methodologically, Nulman et al. [50] mitigated the concerns of a previous study [49] by the same authors about exposure misclassification in the first trimester by restricting the study cohorts to women who had used antidepressants throughout their pregnancy. In addition, Nulman et al.'s 2012 study [51] had fewer limitations than their previous studies [49, 50] and was assessed to be at low risk of bias using the ROBINS-I tool. This study overcame confounding by indication by including a control group of depressed mothers who did not receive antidepressants [51].

The findings summarized in this systematic review should be interpreted with caution given the many methodological limitations inherent to the observational studies included. The main problem that limits the validity of most studies is unmeasured confounding, particularly confounding by indication. In only two of the 14 studies, the researchers had an appropriate comparison group of untreated, depressed mothers to address confounding by indication [43, 51]. The risk of residual confounding is another major concern, as these studies had variation in the type of covariates adjusted or controlled for, and most studies did not control for several potential confounders in the analysis, such as the use of psychotropic drugs other than antidepressants, maternal and paternal psychiatric history, or other environmental or genetic factors. Only one study, by Brown et al. [43], controlled for maternal and paternal history of psychiatric diagnoses through matching siblings with discordant exposure status. Notably, sibling design may address time-invariant or shared confounders but may fail to address time-varying

confounders. In comparison to non-sibling design, the risk of bias is higher in sibling design studies when the levels of confounders differ between the siblings [53].

Furthermore, the methods used to assess motor performance, intellectual disabilities, and the severity of the maternal depression varied greatly across studies in terms of validity and internal consistency. The BSID was the most commonly used scale for motor assessment in most studies. Other methods included the NBAS and Movement ABC. Of these, only Movement ABC is a neuropsychological test specifically for motor function impairment and has been reported to have high test–retest reliability and moderate construct validity [54] It was used in one study [45]. In contrast, although the BSID is regarded as the gold standard assessment tool for measuring the developmental functioning of infants and toddlers, its motor subscale is considered a poor predictor of later motor impairments [55].

Measures used to assess intellectual disability outcomes included the WPPSI-III, the Bayley Mental Development Index, and the McCarthy General Cognitive Index. Only the WPPSI-III is a scale specifically designed to provide a full-scale IQ score on general intellectual ability [56]. On the other hand, the type and severity of depression was assessed using a variety of scales, such as the self-rated Edinburgh Postnatal Depression Scale, the Beck Depression Inventory, the Center for Epidemiologic Studies Depression Scale, the Index of Parental Attitudes, the Global Assessment of Functioning Scale, the clinician-rated Hamilton Rating Scale for Depression, and many more. In the studies included, these scales were used either individually or in combination. Taken together, the diverse range of assessment scales and their lack of validity made the results of the studies difficult to compare.

The ascertainment of the timing and duration of the prenatal exposure to antidepressants also differed greatly between studies, leading to exposure misclassification. Because of this, we could not find conclusive evidence on the association between maternal antidepressant exposure and adverse motor or intellectual effects in offspring. The studies used different methods to collect information about antidepressant use during pregnancy, including electronic medical registry data, medical record review, and self-report; however, no study reported adherence in drug use. Hence, there is uncertainty regarding the actual use of the prescribed antidepressants.

5 Conclusion

The studies reviewed were inconclusive in their findings concerning the motor and cognitive neurodevelopmental effects of in utero antidepressant exposure. Furthermore, several methodological limitations, such as confounding by indication and a lack of adjustment for potential confounders, existed in the reviewed studies. Therefore, future studies should use a more robust methodology to help clinicians make better informed risk–benefit assessments concerning the use of antidepressants during pregnancy.

Declarations

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Availability of data and materials Not applicable.

Code availability Not applicable.

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