Antenatal exposure to antidepressant drugs and the risk of neurodevelopmental and psychiatric disorders: a systematic review

Exposição intrauterina a antidepressivos e risco de transtornos de neurodesenvolvimento e psiquiátricos: uma revisão sistemática

Exposición prenatal a medicamentos antidepresivos y riesgo de trastornos psiquiátricos y en el desarrollo neurológico: una revisión sistemática

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Abstract

This study investigated whether antenatal exposure to antidepressants (ADs) increases the risks of autism spectrum disorders (ASD), attention deficit/hyperactivity disorders (ADHD), schizophrenia and other mental illnesses, and cognitive and developmental deficits in infants or preschool children. PubMed, EMBASE, BIREME/BVS databases were searched to identify studies examining associations of ADs in pregnancy with neurodevelopmental and psychiatric disorders. Twenty studies addressed ASD and/or ADHD risks while 30 focused on developmental and cognitive deficits in infants or preschool children. Most studies detected no association of antenatal AD with ASD after adjustment of risk ratios for maternal depression or psychiatric disorders. Some studies showed that maternal depression, regardless of whether it is treated or untreated, increased ASD risks. Seven out of 8 studies found no increase in ADHD risk associated with antenatal exposure to selective serotonin reuptake inhibitors, the most commonly used AD. No consistent evidence was found linking AD in pregnancy to neurocognitive developmental deficits in infants or preschool children. A residual confounding by indication (depression severity) remained in almost all studies. This systematic review found no consistent evidence suggesting that ADs in pregnancy increase risks of ASD, ADHD, and neurocognitive development deficits. Some studies, however, found evidence that maternal depression increases ASD risks.

Antidepressant Drugs; Depression; Autism Spectrum Disorders; Attention Deficit Disorder with Hyperactivity; Pregnancy

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Introduction

Depression is a common but serious disorder characterized by a constellation of symptoms, namely, insomnia or hypersomnia, anhedonia, feelings of worthlessness, deep sadness and excessive guilt, extreme fatigue, loss of energy, diminished ability to concentrate and to make decisions, loss or increase of appetite and/or weight, psychomotor retardation or agitation, and suicidal thoughts and attempts [1].

In 2015, the World Health Organization (WHO) estimated that 322 million people, or 4.4% of world's population, suffered from depression [2]. By 2030 depression will become the leading cause of global burden of disease as measured by the disability-adjusted life years (DALY) [2]. Depression is nearly 1.7-fold more common in females than in males and vulnerability to it increases in pregnancy and puerperium when many women experience their first depressive episode, or have a recurrent manifestation of a previously diagnosed disorder [3]. It affects up to 10%, or even more, of pregnant women and mothers who have recently given birth [4]. Although depression is treatable, only approximately 12% of depressed pregnant women receive adequate treatment [5].

There is little consensus about the management of depression in pregnancy and reluctance to prescribe antidepressants (ADs) to pregnant women arises mostly from unresolved concerns regarding their risks to the unborn child [6]. Accumulated evidence from observational investigations and meta-analyses indicates that maternal use of selective serotonin reuptake inhibitors (SSRI) in the first trimester of gestation entails a slightly higher risk of congenital malformations, particularly of heart defects [7]. Some studies revealed associations of use of non-SSRIs with adverse pregnancy outcomes other than congenital anomalies, such as preterm delivery, low birth weight and perinatal complications [8,9]. A recent systematic review, however, found no consistent differences between AD-treated and untreated patients in the risk level for poor pregnancy outcomes, such as small-for-gestational-age babies, spontaneous abortions and preterm births [10].

Concerns about harmful effects of maternal depression and its pharmacological treatment on the unborn child go beyond the endpoints evaluated at term pregnancy and neonatal period. It is thought, for instance, that antenatal exposure to ADs might increase the risk of neurodevelopmental disorders such as autism spectrum (ASD) and attention-deficit/hyperactivity (ADHD) disorders, and/or cognitive deficits [11]. This notion is plausible because the fetal brain undergoes a process of rapid cell proliferation and migration, synaptogenesis and circuitry formation. Considerable experimental and clinical evidence apparently links dysfunctions of serotoninergic transmission to disruption of neural network shaping and subsequent appearance of neurodevelopmental disorders [12,13]. It is of note that the most commonly prescribed antidepressants inhibit, either selectively or non-selectively, serotonin uptake from the synaptic cleft. Serotonin acts as a nervous tissue growth factor and, by doing this, it modulates neural plasticity and network formation in the developing brain [13]. Serotonin-dependent shaping of neural circuitry provides an insight into a possible mode of action by which antenatal exposure to serotonin reuptake inhibitors might increase the risk of neurodevelopmental disorders. Along this line, Rotem-Kohavi et al. [14] recently reported findings of a possible neural correlate of epidemiologic associations between antenatal exposure to SSRIs and neurodevelopmental disorders. Using a resting-state functional magnetic resonance imaging, the authors noted that, compared with healthy control infants and infants whose depressed mothers did not receive antidepressants, newborns prenatally exposed to SSRIs exhibited a hyperconnectivity in auditory resting-state networks.

Several cohort and case-control studies addressed a potential association between antidepressant drug use by pregnant women and neurodevelopmental disorders such as ASD and ADHD in their children [15]. These studies arrived at conflicting conclusions about whether or not antenatal exposure to antidepressants is associated with ASD or ADHD. There is far less information about risks of neurodevelopmental disorders other than ASD and ADHD, such as mental illnesses of later onset and long-term cognitive deficits.

Eight reviews of observational studies showed a positive association between exposure to ADs (SSRIs) in utero and ASD [16,17,18,19,20,21,22,23], whereas two studies found no evidence of association or inconsistent findings [24,25]. Whether these associations were causal, however, remained unclear. Three reviews evaluated whether prenatal AD exposure was associated with ADHD and found no evidence

of a causal link [25,26,27]. Only one recent review examined whether AD use in pregnancy was associated with neurodevelopmental outcomes other than ASD and ADHD [28].

Autistic disorders are as a rule diagnosed around 3-4 years of age, and last throughout the individuals' life [29]. They are characterized by symptoms such as deficits of social interaction and communication, limited and repetitive patterns of behavior, poor eye contact, lack of response to his/her name and/or indifference to caregivers, difficulty to express his/her emotions or feelings, apparent indifference to the feelings of others, inability to start a conversation or keep one going, and others [29]. Some children with ASD have learning disabilities whereas others show normal to high intelligence, yet having great difficulty to communicate or apply what they learned. Both genetic and environmental factors seem to contribute to ASD susceptibility and severity [29]. According to current estimates, ASD affects approximately 1% of people, being more frequently diagnosed in boys than in girls. There is no effective therapy for ASD, nor are there effective means to prevent it [29]. Identification of environmental risk factors for ASD is, therefore, a public health goal of utmost importance.

ADHD is characterized by difficulty in paying attention and or hyperactivity/impulsivity [30]. It is about 2-fold more frequent in boys than in girls, generally diagnosed in children under the age of 12 years, and lasts throughout the persons' life. Most patients have combined attention deficit and hyperactivity symptoms, and their enhanced distractibility and impulsivity impairs school performance and social skills [30,31]. Although ADHD pathophysiology remains unclear, its symptoms show a good response to treatment with dopaminergic drugs. ADHD is one of the most prevalent childhood psychiatric disorders, affecting 5-7% children, when diagnosed by DSM-IV criteria, and 1-2% when diagnosed by WHO's (ICD-10) criteria [30,31]. Overdiagnosis and overtreatment of ADHD, however, is a matter of debate.

The objective of this review was to answer a question of relevance for both public health and clinical practice: Is there epidemiologic evidence suggesting that prenatal exposure to ADs increases risks of ASD, ADHD, other psychiatric disorders of later onset and neurodevelopmental deficits in the exposed offspring? A well-founded response to this question would enable physicians and health authorities to make informed decisions about the use of antidepressant drugs to treat maternal depression in pregnancy. A corollary aim of the systematic review was to disclose research gaps requiring further epidemiology studies.

This study adds to existing reviews due to its broader research question, encompassing ASD, ADHD, psychiatric disorders of later onset and other neurodevelopmental outcomes, and because it reviewed a greater number of observational studies and critically appraised their methodological limitations.

Methods

This review followed the recommendations of the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32], and was registered with PROSPERO 2018 (CRD42018080950).

Search strategy and study selection

A systematic search on PubMed, EMBASE, BIREME/BVS (Virtual Health Library – Brazil) electronic databases identified epidemiologic studies addressing the association of ADs in pregnancy with neurodevelopmental disorders in the offspring. The search covered the period between the inception of the database and December 2nd, 2018 (PubMed and BIREME/BVS), or January 1st, 2019 (EMBASE). The BIREME/BVS database includes articles published in periodicals indexed in the Latin American and Caribbean Literature on Health Sciences (LILACS). We also conducted a manual screening of reference lists of articles, reviews, and other documents, to identify additional studies potentially eligible for reviewing. There was no restriction regarding the language of the article. The search strategy combined *Medical Subject Heading* (MeSH; https://www.ncbi.nlm.nih.gov/mesh) terms for the pharmacological classes of antidepressants (with their variations) with pregnancy (or gestation) and with MeSH

terms for neurodevelopmental disorders and cognitive skills (and variations). To design the search strings, Boolean connectors "AND" and "OR" were used for combining the search terms. Term combinations and the full search strategy are shown in Figure 1 and Supplementary Material – Appendix 1 (http://cadernos.ensp.fiocruz.br/site/public_site/arquivo/suppl-app1-e00026619_3711.pdf).

• **Inclusion criteria**

Studies were eligible for inclusion if they investigated, in children born to mothers with any exposure to AD in pregnancy, outcomes such as diagnoses of ASD, ADHD, mental disorders (schizophrenic, affective or anxiety disorders), or emotional, internalizing and externalizing behaviors, speech and language, intelligence, neuromotor development, or any other form of cognitive functioning, assessed at least 3-4 weeks after birth, using scales or any other method. Internalizing behaviors (or disorders) are children's negative behaviors characterized primarily by processes focusing inward (on the self) such as anxiety, fearfulness, social withdrawal, somatization and depression. Contrasting with internalizing behaviors, externalizing behaviors are directed outwards (the external world) such as hostility, antisocial behavior, and aggression.

• **Exclusion criteria**

Articles were not eligible for reviewing if they met any of the exclusion criteria, namely, in vivo studies conducted in animals, in vitro/ex-vivo investigations, ecologic and non-analytic epidemiology studies, cross-sectional studies, case-reports, case-series, letters, editorials, reviews, meta-analyses, notes, comments, clinical guidelines, opinion papers, full-paper not available, and articles not available in English, Portuguese, Spanish, German or French.

As shown in Figure 2, selection of retrieved studies (after excluding duplicates) for reviewing was a two-step screening process: at first, publications were screened by titles and abstracts and, if deemed potentially eligible, at a subsequent phase full articles were retrieved and read. Two reviewers independently screened retrieved studies for eligibility and, if they did not reach a consensus after extensive discussion, a third reviewer was asked to resolve it.

Figure 1

Design of systematic review search strings (MeSH terms) with Boolean connectors "AND" and "OR".
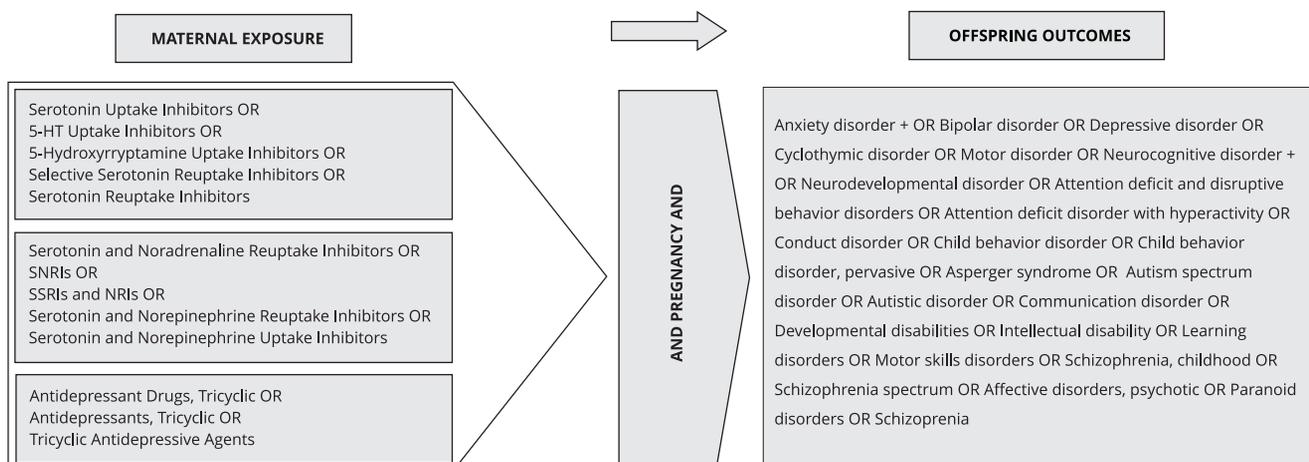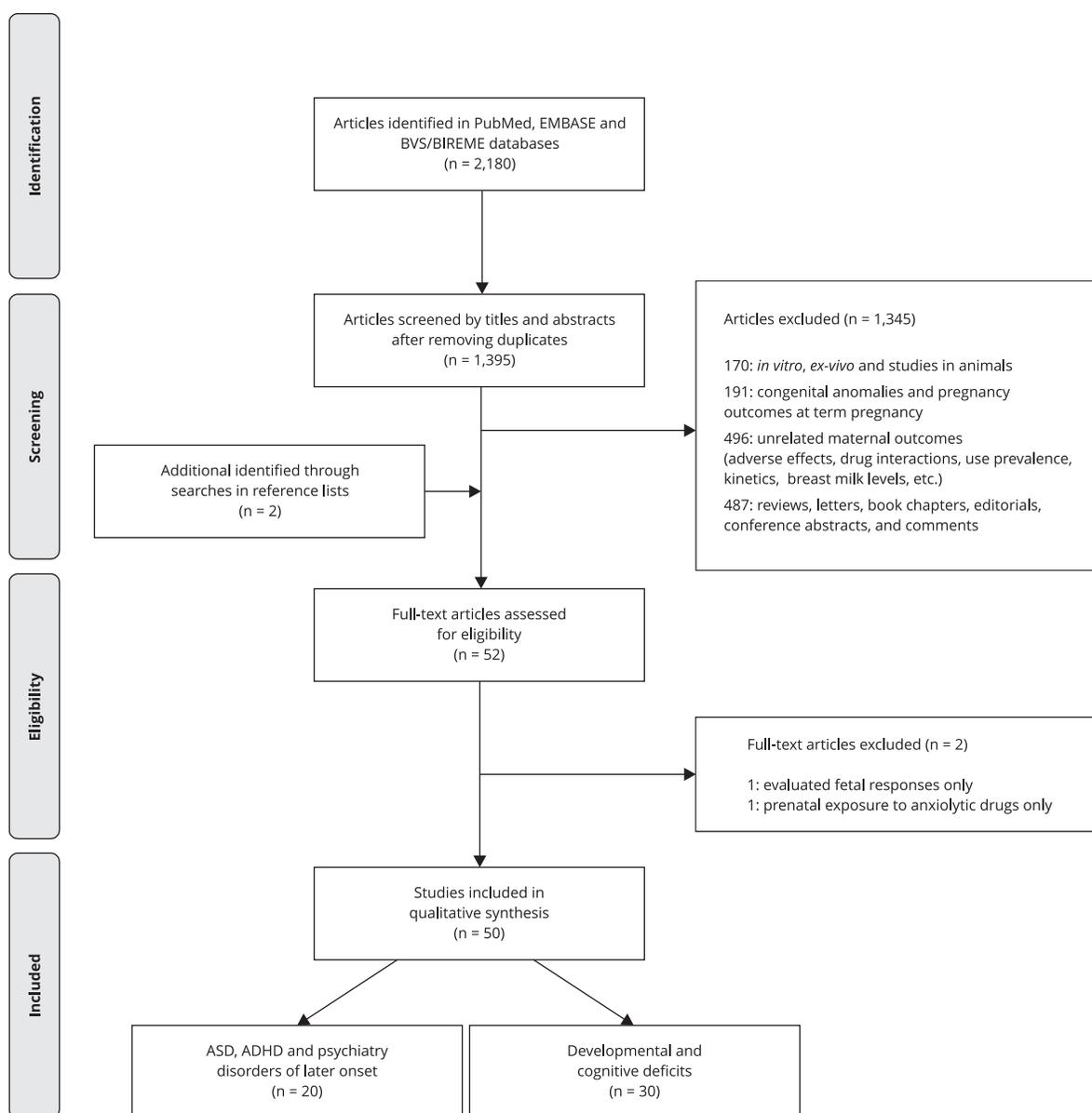
Figure 2

PRISMA flowchart of selection of studies for inclusion in the review.

ADHD: attention deficit/hyperactivity disorder; ADs: antidepressants; ASD: autism spectrum disorders.

Data extraction

Based on the STROBE statement checklist of items that should be included in reports from observational studies [33], two reviewers extracted a predetermined set of data from each study selected for review. Extracted data included first author's name, publication year, geographic location, study period, sample size, drug exposure (type of antidepressant and pharmacological class), period of exposure during pregnancy, strengths and limitations of the study, findings, outcome with risk estimates

and 95% confidence intervals (95%CI), adjusted confounders, and study conclusions. A third reviewer examined the compiled data and study summaries, and differences between reviewers were resolved with discussion.

Assessment of the methodological quality

The assessment of study quality was based on the *Newcastle-Ottawa Scale* (NOS) for observational (case-control and cohort) epidemiology studies [34]. NOS consists of eight items grouped into three domains for selection, comparability and outcome and two reviewers independently assessed each of the studies assigning a score (maximum score = 9) to the study quality. Any discrepancy between reviewers was resolved by a third reviewer.

Data synthesis

For each outcome evaluated, we present the characteristics and findings of all included studies. A qualitative (narrative) synthesis of the evidence for ASD, ADHD and other neurodevelopmental outcomes responded the research question. It took into account not only the results of the reviewed studies but also their methodological limitations and residual confounding. We considered undertaking a quantitative synthesis for ASD and ADHD. Nonetheless, we did not perform a meta-analysis because of the heterogeneity in design and characteristics of the included studies and the fact that several studies (national-based cohorts) used the same national data source (registry) with overlapping of data collection times.

Results

As shown in the PRISMA flow diagram of study selection process (Figure 2), of the 50 studies included in the review, 20 addressed risks of ASD and ADHD while 30 investigated risks of developmental and cognitive impairments in infants, toddlers and preschool children. One Finnish study investigated the impact of gestational exposure to SSRIs on offspring psychiatric disorders including not only ASD and ADHD, but also anxiety and depression in early adolescents [35].

Autism spectrum disorders

Five out of 16 studies evaluating whether prenatal ADs increased risks of ASD found no increase in risk [35,36,37,38,39]. Three studies detected a weak association of AD in pregnancy with ASD that were no longer significant when risk estimates were adjusted for confounding factors such as maternal depression or history of psychiatric disorders [40,41,42]. Hagberg et al. [43] found a significant association of ASD with antenatal AD, when the unexposed offspring (no AD, no history of depression) was compared with a group exposed to both AD and maternal depression in pregnancy. No increase in risk of ASD was evident, however, when unexposed offspring was compared with offspring of pregnant women who received AD for disorders other than depression [43]. Six cohort and case-control (nested in population-based cohorts) investigations, on the other hand, found a modest association of antenatal AD with ASD [44,45,46], ASD in boys [47], and ASD without intellectual disability [48,49]. One of the reviewed studies evaluated whether antenatal exposure to SSRI was associated with higher scores for autistic traits in children [50]. El Marroun et al. [50] found a modest association between maternal (self-reported) use of SSRIs in pregnancy and higher scores for autistic traits in infants assessed by child behavior checklists and a social responsiveness scale. Since depressed women are likely to overestimate problems with their children, and a residual confounding by indication of SSRIs (severity of depression) remained, associations of SSRI use in pregnancy with higher scores for autistic traits in infants may be non-causal.

Attention deficit/hyperactivity disorders

Four out of 8 studies that examined possible associations between AD in pregnancy and ADHD found no association between exposure and outcome [35,37,42,51]. Three studies revealed no association of ADHD with maternal use of SSRIs, yet they found that this disorder was – weakly to moderately – associated with prenatal exposure to non-SSRIs, tricyclic ADs (TCA) and atypical antidepressants.

Figueroa [52] found that maternal use of SSRIs and ADs other than bupropion in pregnancy did not increase the risk of ADHD in children aged 5 years or younger. Antenatal bupropion, on the other hand, was moderately associated with ADHD especially when exposure occurred in the 2nd trimester of gestation. Bupropion inhibits both norepinephrine (NE) and dopamine (DA) reuptakes and, additionally, releases these neurotransmitters into the synaptic cleft. It also acts as a nicotinic receptor antagonist [53]. This atypical antidepressant is used in combination with another AD, when patients are resistant to SSRI, and as an adjunct therapy for smoking cessation, weight loss and ADHD [54,55,56]. Boukhris et al. [57] found that TCA in the 2nd/3rd trimesters of pregnancy was weakly associated with ADHD, even after adjustment for maternal history of depression. A territory population-based study by Man et al. [58] found that non-SSRI use in pregnancy was associated with a modest increase in the risk of ADHD in the offspring, yet a subsequent sibling analysis showed no association.

Finally, a case-control study by Clements et al. [41] found a modest association of ADHD with prenatal exposure to SSRIs & non-SSRIs, especially during the 1st trimester of gestation. This association was significant even after adjustment of risk estimates for maternal history of depression.

Quality assessment

The quality of cohort and case-control studies selected for review ranged from fair to very good (NOS scores 6 to 9), and 16 and 8 of them investigated risks of ASD and/or ADHD, respectively, in children born to AD-treated pregnant women (Tables 1 and 2). The reasons for lower assessments (fair quality) were lower scores in Selection (2) and Comparability (1), and Outcome (1) and Comparability (1) domains for one case-control [44] and one cohort [50] study, respectively (Supplementary Material – Appendix 2: http://cadernos.ensp.fiocruz.br/site/public_site/arquivo/suppl-app2-e00026619_2540.pdf).

Mental disorders of later onset

Malm et al. [35] found that prenatal exposure to SSRIs modestly increased risks of depression in the offspring (SSRI exposed vs. non-exposed, after adjustment for maternal psychiatric disorder; HR = 1.78; 95%CI: 1.12-2.82). In this Finnish national register-based cohort study, cumulative incidence of diagnoses of depression was determined up to adolescence (age of 14) [35]. Notwithstanding the attempt to adjust risk estimates for records of maternal history of psychiatric illnesses, the severity of maternal depressive disorder remained as a residual confounding. It is of note that association of SSRIs with depression among the offspring was also detected (adjusted HR = 1.84; 95%CI: 1.14-2.97) for preconception exposures (i.e., SSRIs discontinued in pregnancy). In this study, the authors found no association of SSRI in pregnant women with anxiety in children prenatally exposed [35]. No other study examined a possible association between antenatal exposure to ADs and psychiatric disorders of later onset (adolescents and young adults) such as schizophrenia [59], and affective and anxiety disorders [60].

Developmental and cognitive deficits

Thirty out of 50 studies selected for review focused on the development and/or cognitive deficits in infants, toddlers and preschool children that might have arisen from prenatal exposures to ADs (Table 3). A majority of these 30 studies found no association between prenatal ADs (mostly SSRIs) and deficits of IQ and/or cognitive [61,62,63,64,65,66,67,68,69], language [70], and behavior development [65,71,72,73,74]. Some studies, however, indicated that the maternal depressive disorder, regardless of whether it is

Table 1

Maternal use of antidepressant medication during pregnancy and risk of autism spectrum disorders in children prenatally exposed.

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR, HR or RR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Croen et al. [44] (2011, USA)	ADs (before pregnant 1st, 2nd & 3rd trimesters)	Population-based case-control study. Kaiser Permanent Medical Care Program in Northern California (KPNC) between January 1995 and June 1999. Cases (n = 298 and their mothers): children with ASD. Controls (n = 1,507 and their mothers): children without ASD randomly selected KPNC in January 1995-November 2002. Exposure: ADs dispensed at a KPNC pharmacy	ASD and maternal use of ADs during the year prior to delivery: 2.2 (1.2-4.3%). ASD and 1st trimester AD: 3.8 (1.8-7.8). No association with history of mental illnesses in the absence of antenatal exposure to ADs	Data on pharmacy dispensing may not reflect actual use. No control of confounders (maternal data/ lifestyle)	6	A 2-fold increase in risk of ASD associated with antenatal exposure to ADs. Risk of ASD was even higher for exposures to ADs in the 1st trimester of pregnancy
Hviid et al. [36] (2013, Denmark)	SSRI (before and during pregnancy)	Population-based cohort (all 626,875 singleton live births in Denmark) January 1996-December 2005, with follow-up until January 1st, 2010, or until the child reached 10 years of age, died or was lost to follow-up, or received a diagnosis of ASD (Danish Psychiatric Central Register)	3,892 ASD cases. No use of SSRIs (before and pregnancy) vs. prenatal SSRI: fully adjusted RR = 1.20 (0.90-1.61). No SSRI vs. use of SSRI before but not during pregnancy: fully adjusted RR = 1.46 (1.17-1.81)	Large cohort. Reduced potential for selection and recall biases. Low prevalence of pregnancy-related use of SSRI. No control of potential confounders (mother data/ lifestyle)	8	No significant association between antenatal exposure to SSRIs and increased risk of ASD in children
Sørensen et al. [40] (2013, Denmark)	ADs (during pregnancy)	Population-based cohort of all children born alive in Denmark (n = 668,468) January 1996-December 2006. ASD diagnosis by December 2010, from Danish Psychiatric Central Register; ICD-10 code F84.0, F84.1, F84.5, F84.8, F84.9). Exposure: women filling a prescription for ADs 30 days before conception to day of birth. From Danish National Prescription Registry (January 1996-December 2006)	Prevalence of ASD = 1.5% (5,437 children), average age of diagnosis 6.7 years. ASD: prenatally AD vs. unexposed: adjusted HR: 1.5 (1.2-1.9). Children born to mothers with affective disorders: AD vs. unexposed; adjusted HR: 1.2 (0.7-2.1). AD vs. unexposed siblings in families with at least one child with ASD: adjusted HR: 0.9 (0.4-2.0)	Large cohort. Low potential for selection, recall and misclassification biases.\n\nPrescription filling data may not reflect actual use. No control of confounding (mother data/ lifestyle)	8	Association of antenatal AD with ASD was not significant when confounding (maternal illness, and family-related factors) was controlled

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Table 1 (continued)

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR, HR or RR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Rai et al. [48] (2013, Sweden)	SSRI & non-SSRI (pregnancy)	Population-based nested case-control study (Stockholm cohort, 589,114 people 0-17 years, 2001-2007). 4,429 ASD cases (2,601 without intellectual disability); 43,277 controls (age and sex-matched). ASD cases: ICD-9 (299.0), ICD-10 (F84.0) and DSM-IV (299). AD use: drug use data from first antenatal interview – Swedish Medical Birth Register	Mother's (but not father's) depression associated with ASD: OR: 1.49 (1.08-2.08). Depression plus prenatal AD (SSRI or non-SSRI) and ASD (adjusted disorders other than depression): 3.34 (1.5-7.47). AD and ASD: 1.90 (1.15-3.14), AD and ASD without intellectual disability: 2.54 (1.37-4.68)	Mother's depression possibly under ascertained. Confounding: AD use may reflect severe depression and thus severe depression (not AD) would be in fact associated with ASD	8	Prenatal AD (SSRI & non-SSRI) associated with ASD without intellectual disability. Association may be non-causal: additional. Further research needed to clarify whether AD use would reflect severe maternal depression
Rai et al. [49] (2017, Sweden)	SSRI & non-SSRI (pregnancy)	Prospective cohort study (Stockholm county, 2001-2011, 254,610 individuals aged 4-17 years, including 5,378 with ASD). ASD: ICD-9 (299.0), ICD-10 (F84.0) and DSM-IV (299). AD use: drug use data from first antenatal interview – Swedish Medical Birth Register. AD use: drug use data from first antenatal interview – Swedish Medical Birth Register	3,342 children prenatally exposed to AD. 4.1% had ASD compared to a prevalence of 2.9% among those not exposed to AD whose mothers had mental illnesses. Adjusted OR: 1.45 (1.13-1.85). Risk increase concerned children with ASD with no intellectual disability	Large sample size (total population of Stockholm county) and multisource ascertainment of cases. Absence of detailed measurements of severity of depression in pregnancy. No trimester assessment	8	Weak (OR = 1.45) association of ASD in pregnancy (particularly ASD without intellectual disability) with AD (SSRI & non-SSRI)
El Marroun et al. [50] (2014, Netherlands)	SSRI (pregnancy)	5,976 children (study embedded in the ongoing population-based cohort: Generation R Study). Births from April 2002 to January 2006. SSRI exposure: maternal self-report assessed by questionnaires, prescription records from pharmacies. Parent reported autistic symptoms (traits) using *Child Behavior Checklists and Social Responsiveness Scale*.	Adjuested (including adjustment for postnatal maternal depression) OR, pervasive develop. problems, prenatal SSRI vs. unexposed: 1.91 (1.13-3.47). Autistic traits (social responsiveness scale) β = 0.15, 95%CI: 0.08-0.22	Prospective study using 2 measures of autistic symptoms. SSRI-treated women may have overestimated problems with their child. No clinical assessments of ASD. Small number of SSRI-exposed children. Residual confounding remained	6	Results suggested association between prenatal SSRI and autistic traits in children

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Table 1 (continued)

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR, HR or RR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Harrington et al. [47] (2014, USA)	SSRI (1st, 2nd & 3rd trimester)	Population-based case-control study. CHARGE (Childhood Autism Risks from Genetics and Environment). Mother-child pairs. Children 2-5 years old from California with ASD (n = 492) or DD other than ASD (n = 154) and typical development, TD (n = 320). Interview (SSRI use, mental health history, sociodemographic information)	OR: among boys (♂) prenatally exposed to SSRI: ASD vs. TD: 2.91 (1.07-7.93). 1st trimester: 3.22 (1.17-8.84)	Relatively large sample of cases. Potential recall bias. Residual confounding by indication of SSRI, no assessment of depression severity. No data on SSRI dosage	8	In boys, prenatal exposure to SSRI increases risk of ASD
Gidaya et al. [45] (2014, Denmark)	SSRI (pre-conception, 1st, 2nd & 3rd trimesters)	Population-based (Danish Civil Registration System) case-control study. All children (singleton or one selected at random from multiple births) born alive in Denmark (n = 628,408) Januarty 1997-December 2006. Cases: ASD diagnosis (Danish National Hospital Register, January 1999-March 2011). Controls without ASD. 10 per case. Exposure: dispensed. From: Danish Drug Prescription Registry	1.5% of cases and 0.7% of controls exposed to SSRI during pregnancy. Adjusted OR, ASD vs. maternal SSRI use (> 45 days); preconception; 2.1 (1.6-2.8); 1st trimester; 2.4 (1.7-3.3); 2nd trimester; 2.4 (1.6-3.5); 3rd trimester; 2.9 (1.9-4.4). Adjusted for: age, child sex, mother depression; other SSRI indications	Large population-based case-control study. Residual confounding by indication of SSRI and severity of maternal depression	8	Study results suggest that antenatal exposure to SSRI increases child's risk associated with ASD
Clements et al. [41] (2015, USA)	SSRI/non-SSRI (pre-conception, 1st, 2nd & 3rd trimesters)	Case-control study. Cases: children from The Partners HealthCare EHR (New England, Boston, Massachusetts) with 2-19 years, if they had at least one ICD-9 code of 299, 1997-2000. Cases: 1,377 children with ASD; Controls: no prior history of ASD, ADHD or intellectual disability; matched (1:3) for birth year, birth hospital, sex, insurance type (proxy for socioeconomic status), ethnicity, preterm vs. full term. AD prescription (outpatient EHR) and dispensing (inpatient pharmacy)	Adjusted OR; pre-pregnancy (adjusted mother's depression) 1.62 (1.17-2.23). Pregnancy (pre-pregnancy-delivery), non-adjusted 1.49 (1.01-2.18), adjuested 1.10 (0.70-1.70), 1st trimester 1.47 (0.81-2.61), 2nd trimester (1.34 (0.77-2.27), 3rd trimester 1.08 (0.61-1.88)	Relatively large sample of cases. Confounding by indication, misclassification bias	7	ASD risk associated with prenatal ADs was no longer significant after controlling for maternal depression

(continues)

Table 1 (continued)

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR, HR or RR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Boukhris et al. [46] (2016, Canada)	ADs (1st, 2nd & 3rd trimesters)	Population-based cohort, January 1998-December 2009. 145,456 full-term singleton infants born alive. ASD: children with at least 1 ASD diagnosis between date of birth and last follow-up	1,054 (0.7%, 4♂:1♀) with ASD. Age of children at the end of follow-up was 6.24 (3.19) years. 2nd/3rd trimester adjuested HR; ADs = 1.87 (1.15-3.04), SSRIs = 2.17 (1.20-3.93). Adjuested for maternal depression: ADs = 1.75 (1.03-2.97)	Large cohort, 11-year follow-up. Prescription filling data (may not reflect actual use), lack of control of potential confounders (mother data/ lifestyle)	8	Antenatal ADs, (predominantly SSRIs), in the 2nd/3rd trimester increases ASD risk
Castro et al. [37] (2016, USA)	SSRI/non-SSRI (pre-pregnancy, 1st, 2nd & 3rd trimester)	Case-control study. Cases: children from The Partners HealthCare EHR with 2-19 years, at least one ICD-9 code of 299. 1997-2010. Cases: 1,245. ASD; Controls: no prior history of ASD, ADHD or intellectual disability; matched (1:3) for birth year, birth hospital, sex, insurance type (proxy for socioeconomic status), ethnicity, preterm vs full term. Mother-child pairs included in the previous report by Clements et al. [41] were excluded. AD prescription (outpatient EHR) and dispensing (inpatient pharmacy)	Adjusted OR; pre-pregnancy (adjusted for maternal depression) 1.54 (1.02-2.30). Pregnancy (pre-pregnancy-delivery), non-adjusted 0.99 (0.63-1.51), adjusted 0.90 (0.50-1.54), 1st trimester 0.89 (0.40-1.78), 2nd trimester (1.11 (0.50-2.26), 3rd trimester 0.85 (0.38-1.74)	Relatively large sample of cases. Some risk of confounding by indication, misclassification bias	7	Pre-pregnancy only use of ADs associated with ASD. No association between mother use of AD in pregnancy and ASD
Sujan et al. [42] (2017, Sweden)	ADs (1st trimmester)	Retrospective cohort study: Swedish offspring born 1996-2012 followed through 2013, death or emigration. Maternal self-reported 1st trimester use and dispensation of ADs; data from Medical Birth Register, and Prescribed Drug Register. ASD inpatient and outpatient diagnoses made by a specialist according to ICD-9 and ICD-10 criteria (Swedish registers)	Analytical cohort (1,580,629 children, 48.6% females), 1.4% were exposed (mother self-report) to ADs during 1st trimester and of these, 82% were exposed to SSRIs. ASD exposed vs. unexposed; HR: 2.0 (1.8-2.3). Siblings analysis adjusted pregnancy, maternal, paternal traits; ASD; 0.8 (0.6-1.1)	Large population based sample (cohort study), Sibling analysis. Exposure conferred both to self-report and dispensation. Recall bias. No assessment of maternal depression severity. 1st trimester exposure only. Mostly SSRIs	8	After taking into account confounding; no association of 1st trimester exposure to ADs with ASD

(continues)

Table 1 (continued)

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR, HR or RR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Malm et al. [35] (2016, Finland)	SSRI (pregnancy)	Population-based cohort study. Data from Finnish National Registers. 845,345 singleton live births in Finland between January 1996-December 2010. Age range from birth to age 14, mother child pairs – National Medical Birth Register. Drug Reimbursement Register (prescription drug purchases). Outcome: ASD	ASD, adjusted HR; SSRI gestation vs. Mother psychiatric disease and no medication, 0.88 (0.65-1.20), SSRI pregnancy vs. SSRI pre-pregnancy only, 1.30 (0.88-1.92), SSRI pregnancy vs. no maternal disease, no medication, 1.40 (1.02-1.92)	Large population based prospective cohort. No pregnancy trimester analysis. No confirmation of adherence to purchased drugs. No information on postnatal environment	7	Taking into account maternal illness, prenatal SSRI was not associated with increased risk of ASD.
Brown et al. [38] (2017, Canada)	SSRI/SNRI (during pregnancy)	Retrospective cohort study using health administrative data from Ontario, Canada, children (35,906 singleton births) born to mothers receiving public prescription drug (4.2% births) from 2002-2010. Outcome followed through 2014. ASD diagnosed after the age of 2 years	ASD adjusted HR; SSRI vs. unexposed 1.59 (1.17-2.17), sibling analysis, 1.60 (0.69-3.74)	No remarkable strength limited to women in Ontario's publicly funded drug plan (lower social class). Potential misclassification bias (filled-out prescriptions not used)	8	Prenatal exposure to SSRI or SNRI was not associated to ASD in children
Viktorin et al. [39] (2017, Sweden)	ADs (pregnancy)	Population based cohort of 179,007 Swedish children born in 2006-2007 followed through 2014 when they were aged 7 and 8. Mother and children identified in the Swedish Medical Birth Register. Exposure: data on prescription drug dispensed – Swedish Drug Register, ASD; ICD-10 codes F84.0, F84.1, F84.2, F84.3, F84.4, F84.5, F84.8, F84.9 – Swedish Patient Register	ASD adjusted RR (95%CI), full sample, ADs vs. unexposed: 1.23 (0.96-1.57). Subsample of mothers with at least one diagnosis of depression or anxiety in their lifetime; ADs (2 dispensations overlapping pregnancy) vs. unexposed: 1.07 (0.80-1.43). citalopram/ escitalopram: 1.47 (0.92-2.35), clomipramine: 2.86 (1.04-7.82)	Nationwide population-based cohort. Severity of maternal mental illness not known	8	Prenatal exposure to ADs was not causally associated with ASD in children

(continues)

Table 1 (continued)

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR, HR or RR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Hagberg et al. [43] (2018, UK)	ADs (pre-pregnancy, 1st, 2nd & 3rd trimester)	Cohort study (with nested sibling case-control analysis) using a population-based electronic medical database (UK Medical Practice Research Datalink, CPRD). Mothers (aged 13 to 44 years) and their live born singleton infants, born between 1989 and 2011. Cohort entry was baby delivery date minus 365 days. Children: at least 3 years of follow-up after birth. 3 cohorts of exposed women (depressed treated with AD); depressed untreated with AD in pregnancy; non-depressed treated with AD in pregnancy). 194,494 mother-baby pairs; 2,154 with ASD	RR; unexposed vs. treated depression: 1.72 (1.54-1.93); unexposed vs. untreated depression: 1.50 (1.28-1.75); unexposed vs. AD for disorders other than depression: 0.73 (0.41-1.29). Sibling analysis yield results similar to those of main study. Additional analysis indicated that risk of ASD increased with increasing severity of depression (duration of last episode of untreated depression; < 12 months vs. 12-35.9 months)	Large population-based cohorts. Assessment of effects of untreated depression and severity of untreated depression. No remarkable weakness	9	Pregnant women with depression have increased risk of having a child with ASD, whether or not she used ADs during pregnancy

95%CI: 95% confidence interval; ADs: antidepressants; ASD: autism spectrum disorders; DD: developmental delays; DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders* – 4th edition; EHR: electronic health record; HR: hazard ratio; ICD: International Classification of Diseases; NOS: *Newcastle-Ottawa Scale*; OR: odds ratio; RR: rate ratio; SNRI: serotonin-norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TD: traditional development.

Table 2

Maternal use of antidepressant medications in pregnancy and risk of attention deficit/hyperactivity disorders in prenatally exposed children.

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR or HR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Figueroa [52] (2010, USA)	ADs (1st, 2nd & 3rd trimesters)	Retrospective cohort study. Claims data (self-insured employers) on 38,074 children born 1997-2002 and their families until they were 4 years old (1997-2006). Data on in/outpatient prescription claims; diagnoses and others. Outcome: ADHD at the age of 5 or earlier	431 children diagnosed or treated for ADHD ≤ 5 years. SSRI in pregnancy OR = 0.91 (0.51-1.60); BUP in pregnancy 3.63 (1.20-11.04); 1st trimester 2.06 (0.35-12.16), 2nd trimester 14.66 (3.27-65.73); other ADs in pregnancy: 0.65 (0.09-4.79)	ADHD typically diagnosed in children > 5 years. Prescription data may not reflect actual use. Failure to control confounding (mother's disease and lifestyle)	7	Prenatal SSRIs and ADs other than BUP not associated with ADHD in children at the age of 5 or younger. Bupropion, especially in the 2nd trimester, increased risks of ADHD
Laugesen et al. [51] (2013, Denmark)	ADs (1st, 2nd & 3rd trimesters)	Cohort of all singletons born alive (N = 877,778) in Denmark (Danish Medical Birth Registry) from 1996 until the end of 2009. Exposure: maternal redemption of an AD prescription through the Danish National Prescription Registry. Outcome: diagnosis of ADHD or prescription for ADHD medication (Danish Psychiatric Registry, Danish National Registry of Patients. Overall median follow up time = 8 years	15,008 (1.7%) were exposed to AD. 12,841 (1.5%) developed ADHD. SSRI the most used (78% of AD users). Adjusted HR any AD pregnancy 1.2 (1.1-1.4), 1st trimester 1.2 (1.0-1.4), 2nd trimester 1.5 (0.9-2.4), 3rd trimester 0.8 (0.3-2.0), pregnancy use: SSRI, 1.2 (1.0-1.5), SNRI 1.0 (0.4-2.5), TCA 1.1 (0.6-20), others 1.6 (0.8-3.0). Sibling analysis: 0.7 (0.4-1.4). Former users vs. never users: 1.6 (1.5-1.8)	Large population-based cohort. No data on actual AD intake by the mother (prescription is a proxy)	8	Long-term follow-up: no evidence of association of prenatal AD with ADHD
Clements et al. [41] (2015, USA)	SSRI/non-SSRI (pre-pregnancy, 1st, 2nd & 3rd trimesters)	Case-control study. Children from The Partners HealthCare EHR (Boston, Massachusetts) with 2-19 years. Cases: 2,243 children with ADHD (but no ASD); Controls (5,631): no prior history of ADHD, ASD or intellectual disability; matched (1:3) for birth year, birth hospital, sex, insurance type (proxy for socioeconomic status), ethnicity, pre-term vs. full term. AD prescription (outpatient EHR) and dispensing (inpatient pharmacy)	Adjusted OR; pre-pregnancy (adjusted history of maternal depression) 1.18 (0.86-1.61). Pregnancy (pre-pregnancy-delivery), non-adjusted 2.30 (1.62-3.24), adjusted 1.81 (1.22-2.70), 1st trimester 2.03 (1.19-3.44), 2nd trimester 0.98 (0.56-1.68), 3rd trimester 1.29 (0.76-2.15)	Relatively large sample of cases. Confounding by indication, misclassification bias	7	Prenatal ADs was associated with a modest increase in risk of ADHD even after adjustment to maternal depression

(continues)

Table 2 (continued)

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR or HR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Castro et al. [37] (2016, USA)	AD (SSRI/ non-SSRI) (pre-pregnancy, 1st, 2nd & 3rd trimesters)	Case-control study. Children from The Partners HealthCare EHR with 2-19 years. Cases: 1,701 ADHD; Controls: no prior history of ADHD, ASD, or intellectual disability; matched (1:3) for birth year, birth hospital, sex, insurance type (proxy for socioeconomic status), ethnicity, pre-term vs. full term. AD prescription (outpatient EHR) and dispensing (inpatient pharmacy)	Adjusted OR pre-pregnancy (adjusted history of maternal depression) 1.50 (1.00-2.20). Pregnancy (pre-pregnancy-delivery), non-adjusted 0.91 (0.56-1.42), adjusted 0.97 (0.53-1.69), 1st trimester 0.69 (0.29-1.49), 2nd trimester 1.11 (0.50-2.26), 3rd trimester 0.73 (0.29-1.62)	Relatively large sample of cases. Risk of confounding by indication, misclassification bias	7	Pre-pregnancy use of ADs modestly associated with ADHD in children. No association between maternal use of AD in pregnancy and ADHD in the offspring
Malm et al. [35] (2016, Finland)	SSRI (during pregnancy)	Population-based cohort study. Data from Finnish National Registers. 845,345 singleton live births between January 1996-December 2010. Age range: birth to age 14, mother child pairs – National Medical Birth Register. ICD-8, ICD-9 and ICD-10 (since 1996) Drug Reimbursement Register (prescription drug purchases). Outcome: ADHD	ADHD, adjusted HR (95%CI); SSRI gestation vs. Mother psychiatric disease and no medication, 0.98 (0.77-1.24), SSRI pregnancy vs. SSRI pre-pregnancy only, 0.98 (0.75-1.27), SSRI pregnancy vs. no maternal disease, no medication, 1.66 (1.27-2.16)	Large population based prospective cohort. No pregnancy trimester analysis. No confirmation of drug adherence. No data on postnatal environment	8	Taking into account maternal disorder, prenatal SSRI was not associated with ADHD in children
Sujan et al. [42] (2017, Sweden)	ADs (pregnancy 1st trimester)	Retrospective cohort study Swedish offspring born 1996-2012 followed through 2013, death or emigration. Maternal self-reported 1st trimester use and dispensation of ADs; data from Medical Birth Register, and prescribed Drug Register. ADHD, inpatient and outpatient diagnoses made by specialist according to ICD-9 and ICD-10 criteria (Swedish registers)	Analytical cohort (1,580,629 children, 48.6% females), 1.4% were exposed (maternal self-report) to ADs during 1st trimester and of these, 82% were exposed to SSRIs. ADHD exposed vs unexposed; HR (95%CI): 2.2 (2.0-2.4). Comparison of siblings, adjusted pregnancy, maternal, paternal traits; ADHD; 1.0 (0.8-1.3)	Large population based sample (cohort study), Sibling comparison. Exposure conferred both to self-report and dispensation. Recall bias. Register-based approach did not assess maternal depression and its severity. 1st trimester exposure only. Mostly SSRIs	8	After accounting for confounding factors; no association of 1st trimester exposure to ADs with ADHD in children

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Table 2 (continued)

Study (year, country)	Drug exposure	Design/Sample characteristics (N)	Main results [OR or HR (95%CI)]	Strengths/ Limitations	NOS	Conclusion/Remarks
Man et al. [58] (2017, China)	ADs (1st, 2nd & 3rd trimesters)	Population-based cohort study (Hong Kong territory wide) nested in Clinical Data Analysis and Reporting System (CDARS). All live born children in Hong Kong from January 2001 to December 2009 (n = 190,618). Exposure: maternal ADs prescribing and dispensing records at CDARS Outcome ADHD after at least 6 years follow-up (ICD-9-CM code 314) until December 2015	5,659 children (3%) had a diagnosis of ADHD. Adjusted HR, ADHD, any AD users in pregnancy vs. non-users: 1.39 (1.07-1.82); 1st trimester 1.43 (1.05-1.95), 2nd trimester 1.50 (1.08-2.09), 3rd trimester 1.43 (1.03-1.98). Prenatal SSRI 1.11 (0.77 to 1.60), prenatal non-SSRI 0.59 (1.19-2.14). 1st trimester 1.64 (1.13-2.38), 2nd trimester 1.72 (1.16-2.53), 3rd trimester 1.65 (1.13-2.40). Sibling analysis: prenatal AD 0.54 (0.17-1.74); AD non-users: maternal mental disease vs. no disease: 1.84 (1.54-2.18)	Relatively large population based cohort. Prescription/ dispensing data may not reflect actual use. Possible misclassification bias. Residual confounding by indication	8	Increased risk of ADHD in children prenatally exposed to ADs and non-SSRIs but not to SSRI. Associations could be at least in part explained by maternal depression or confounding by indication of AD
Boukhris et al. [57] (2017, Canada)	SSRI, SNRI, MAOI, TCA (1st & 2nd/3rd trimesters)	Population-based cohort study with data from ongoing Quebec Pregnancy Children Cohort. All full-term singletons born alive (n = 144,406) in Quebec-Canada in January 1998-December 2009. Exposure: mothers with at least one AD prescription during pregnancy recorded in the Prescription Drug database. Outcome: ADHD diagnosis. Follow-up: birth up to first diagnosis, death or December 31, 2009, whichever occurred first	4,564 infants (3.2%) with a diagnosis of ADHD. Mean age at first diagnosis 6.3 years. Adjusted HR: AD 1st trimester 1.0 (0.9-1.2); 2nd/3rd trimesters 1.3 (1.0-1.6). 2nd/3rd trimesters: SSRI 1.2 (0.9-1.6), SNRI 1.4 (0.8-2.5), TCA 1.8 (1.0-3.1), other ADs 0.5 (0.1-2.2)	Large population based cohort study. Prescription filling data may not reflect actual use. Lack of information on several potential confounders (maternal lifestyle, smoking). Residual confounding by indication remained	8	After taking into account maternal history of depression/anxiety, prenatal exposure to AD, especially in the 2nd/3rd trimesters, was associated with increased risk of ADHD

95%CI: 95% confidence interval; ADHD: attention deficit/hyperactivity disorder; ADs: antidepressants; ASD: autism spectrum disorders; BUP: bupropion; EHR: electronic health record; HR: hazard ratio; ICD: International Classification of Diseases; ICD-CM: International Classification of Diseases – Clinical Modification; MAOI: monoamine oxidase inhibitor; NOS: *Newcastle-Ottawa Scale*; OR: odds ratio; SNRI: serotonin-norepinephrine reuptake inhibitors; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants.

Table 3

Maternal use of antidepressant drugs in pregnancy and developmental and cognitive deficits in infant and toddlers.

Study (year, country)	Drug	Pregnancy exposure	Age at evaluation	Results and conclusions/remarks
Nulman et al. [61] (1997, Canada)	TCA, FLX	1st, 2nd & 3rd trimesters	16 to 86 months	TCA and FLX in pregnancy did not affect global IQ, language development or behavioral development in preschool children
Nulman et al. [62] (2002, Canada)	TCA, FLX	1st, 2nd & 3rd trimesters	15 to 71 months	TCA and FLX in pregnancy did not affect child's global IQ, language development, or behavior development. IQ was negatively associated with duration of maternal depression and language with number of depressive episodes after delivery
Reebye et al. [71] (2002, Canada)	SSRI/ SSRI+CZP	Pregnancy	3 months	Exposure to SSRI and SSRI+CZP in pregnancy did not alter scores for infant development at the age of 2 months as evaluated by the BSID
Casper et al. [64] (2003, USA)	SSRI	Pregnancy	At birth and 6 to 40 months	SSRI exposed newborns showed lower 1 and 5 min Apgar scores. SSRI infants had slightly delayed psychomotor development (adjusted for Apgar). No difference in mental development. SSRI in breast milk not ruled out
Misri et al. [80] (2006, Canada)	SSRI/ SSRI+CZP	Pregnancy	48 to 60 months	Levels of internalizing behaviors (fearfulness, social withdrawal and somatic complaints) did not differ between SSRI and SSRI+CZP and non-exposed at age of 4 years. Increased maternal anxiety/depression associated with increased internalizing behaviors in their children
Oberlander et al. [79] (2007, Canada)	SSRI	Pregnancy	48 months	Externalizing (physical/verbal aggressiveness, disruptive behavior) and attentional behaviors did not differ between prenatal SSRI exposed and non-exposed 4-year-old children. Current maternal mood/stress predicts child externalizing behavior regardless prenatal SSRI and depression
Casper et al. [72] (2011, USA)	SSRI	1st, 2nd & 3rd trimesters	At birth and 14 months	SSRI associated with lower Apgar. SSRI increased risks for lower psychomotor test scores. Mental development and motor function by neurological examination within the normal range
Salisbury et al. [98] (2011, USA)	SSRI	Pregnancy	At birth and 3 weeks	SSRI associated with lower GA at birth. Controlling for GA, SSRI exposed had lower quality of movements and more CNS stress signs
Nulman et al. [63] (2012, Canada)	SNRI (VLX), SSRI	1st, 2nd & 3rd trimesters	36 to 83 months	Offspring from VLX, SSRI and untreated maternal depression groups had similar full-scale IQs. VLX and SSRI had lower IQs than children born to non-depressed women
Weikum et al. [99] (2012, Canada)	SNRI (VLX), SSRI	Pregnancy	Still in utero, 6 and 10 months	As expected, children from non-depressed non-treated mothers succeed the non-native speech and visual language discrimination test at 6 and failed it at 10 months whereas SSRI exposed succeeded it at both ages. As expected, control fetuses responded to vowel but not to consonant discrimination, whereas SSRI-exposed responded for both vowel and consonant
Austin et al. [65] (2013, Australia)	ADs/mostly SSRI	1st, 2nd & 3rd trimesters	17-24 months	ADs (mostly SSRI) not associated (BSID-III) with poorer cognitive, language or motor development outcomes in 18-month-old infants
Batton et al. [73] (2013, Canada)	SSRI	Pregnancy	24-36 months	Cohort of preterm born infants: antenatal SSRI did not increase risk of adverse neurodevelopment (BSID) above the baseline risk for this degree of prematurity
Hanley et al. [100] (2013, Canada)	SRI	Pregnancy	10 months	SRI-exposed 10-month-old infants scored lower than non-exposed on gross-motor, social-emotional and adaptive behaviors (BSID). Controlled for pre/postnatal maternal depression
Pedersen et al. [76] (2013, Denmark)	ADs	1st, 2nd & 3rd trimesters	48 to 60 months	Children behavior assessed by parent reported SDQ. AD not associated with abnormal SDQ scores. Prenatal untreated depression associated abnormal SDQ
de Vries et al. [101] (2013, Netherlands)	SSRI	Pregnancy	2 and 7 days, 3 to 4 months	Prenatal SSRI impaired quality of infant movements (assessed by Prechtl and motor optimality scales) irrespective of maternal depression/anxiety. Severity of maternal depression remained as residual confounding
Santucci et al. [74] (2014, USA)	SRI	Pregnancy	12, 26, 52 and 78 weeks	No impact of prenatal SRI or maternal depression on mental (cognitive) development index scores. Effect of SRI on (first year) psychomotor development scores, a possibly transitory effect

(continues)

Table 3 (continued)

Study (year, country)	Drug	Pregnancy exposure	Age at evaluation	Results and conclusions/remarks
Skurtveit et al. [75] (2014, Norway)	SSRI	Pregnancy up to 6 month old	36 months	SSRI in pregnancy associated with lower language competence (measured by mother's report on language-grammar scale) at 3 years independently of anxiety/depression before/during pregnancy. Anxiety/depression in pregnancy also associated with language competence delay
Eriksen et al. [102] (2015, Denmark)	ADs/ anxiolytics	Pregnancy	60-64 months	No association between children's IQ (*Wechsler Preschool and Primary Scale of Intelligence*) and prenatal exposure to ADs and anxiolytics. Low statistical power study
Hanley, et al. [78] (2015, Canada)	SRI	Pregnancy	36-72 months	SRI in pregnancy was associated with increased internalizing and anxious behavior (after controlling for maternal depression) but not with externalizing behavior in early childhood
Brown et al. [103] (2016, Finland)	SSRI	30 days before, 1st, 2nd & 3rd trimesters	< 14 year old, most < 9 years	Children born to mothers who used SSRI during pregnancy had an increased risk of speech/language disorders compared with the offspring of mothers diagnosed as having depression or other psychiatric disorders not treated with ADs
Grzeskowiak et al. [77] (2016, Denmark)	SSRI, SNRI, TCA	1st, 2nd & 3rd trimesters	48, 60, 84 months	SSRI in pregnancy did not increase risks of behavioral problems (SDQ) in 7-year-old children after adjustment for maternal illness. Untreated prenatal depression increased risks of behavioral problems compared with unexposed children
Handal et al. [104] (2016, Norway)	SSRI	180 days before and pregnancy	36 months	SSRIs during pregnancy was weakly associated with a delayed motor development (*Ages & Stages Questionnaire*) at age of 3 years, but the delay was very short and of no clinical importance
Handal et al. [70] (2016, Norway)	SSRI	Pregnancy	36 months	SSRIs plus folic acid supplementation in pregnancy increased risks of delayed language competence in the offspring. SSRI without folic acid did not alter risks of delayed language competence. Unexpected interaction
Johnson et al. [66] (2016, USA)	SRI	Pregnancy	30-66 months	Prenatal SRI weakly associated with some preschool outcomes (expressive language and behavior problems) but not with cognitive function
Hermansen et al. [67] (2016, Norway)	SSRI	Pregnancy	60-72 months	No effects of prenatal depression or SSRIs upon general cognition or inhibition. Both SSRI and maternal depression associated with higher levels of externalizing behaviors compared to non-exposed controls. SSRI exposed children showed higher levels of internalizing behaviors
Salisbury et al. [105] (2016, USA)	SSRI/ SSRI+BZP	Pregnancy	1st postnatal month	Infants of pregnant mothers treated with SSRI and SSRI+BZP had lower motor scores and more CNS stress signs. Infants of depressed mothers had low arousal throughout the 30-day period. Infants of SSRI+BZP group had the least favorable scores on the *Neonatal Intensive Care Unit Network Neurobehavioral Scale*
Hermansen, et al. [106] (2017, Norway)	SSRI	Pregnancy	Circa 68 months	Prenatal exposure to SSRIs and depression was not directly associated with abilities of interference suppression (behavioral flanker task while recording event-related potential ERPs)
El Marroun et al. [68] (2017, Netherlands)	SSRI	Pregnancy	48, 60 and 84 months	SSRI in pregnancy was not related to maternal reported executive function at 4 years, nor was it related with observed non-verbal intelligence at age 5 or neuropsychological function at 7 years. SSRI and untreated maternal depression in pregnancy had no major impact on child non-verbal cognition
Viktorin et al. [69] (2017, Sweden)	ADs/SSRI	Pregnancy	Circa 96 months	No evidence of association between maternal AD use in pregnancy and child intellectual disability after adjustment for confounding factors
Lupatelli et al. [81] (2018, Norway)	ADs/SSRI	Pregnancy	18 to 60 months	SSRI in pregnancy did not increase risks for externalizing, emotional, or social problems in preschool-aged children

AD: antidepressant drug; BSID: *Bayley Scales of Infant Development*; BZP: benzodiazepine; CNS: central nervous system; CZP: clonazepam; ERP: event-related potentials; FLX: fluoxetine; GA: gestational age; IQ: intelligence quotient; SDQ: *Strengths and Difficulties Questionnaire*; SNRI: serotonin norepinephrine reuptake inhibitor; SRI: serotonin reuptake inhibitor; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressant; VLX: venlafaxine.

treated with ADs or not during pregnancy, may slightly increase the risks of deficits of IQ and language development [62], language competence [75], and/or behavior development [76,77].

Six studies evaluated the impact of prenatal ADs (mostly SSRI) on levels of internalizing and/or externalizing behaviors in preschool children. One study found that both prenatal SSRI and depression increased risks of externalizing behaviors while SSRI increased risks of internalizing behaviors [67]. Another investigation indicated that prenatal SRI predicts internalizing but not externalizing behaviors in early childhood [78]. Oberlander et al. [79] found that antenatal SSRI and depression are not associated with the child's externalizing behavior while current maternal mood predicts it. Two additional studies found no association between prenatal SSRIs or ADs with internalizing [80] and externalizing behaviors [81]. Overall, the foregoing findings showed no consistent association of antenatal SSRIs and depression with children's internalizing or externalizing behaviors.

Discussion

Residual confounding by indication and severity of depression

A residual confounding by indication was a shortcoming with major impact on the interpretation of most research findings. ADs are indicated mainly for the treatment of depressive disorders and so the possibility exists that associations resulted from the maternal depression for which the drug was prescribed and not from the pharmacological intervention. In other words, reported associations between children's neurodevelopmental disorders (ASD and ADHD) and maternal use of ADs in pregnancy may be non-causal. A few studies did not control confounding by indication at all and simply compared the offspring of AD-treated depressed mothers with the offspring of untreated and non-depressed pregnant women. These studies generally found a higher risk of ASD/ADHD among children prenatally exposed to ADs. In most studies, however, investigators made an attempt to control this confounding in the statistical analysis by adjusting risk ratios for effects of dichotomous presence or absence of maternal depression or history of psychiatric disorders, or yet, by also making a maternal sibling sub-cohort analysis.

It is fair to think that depression entailing prescription for AD is probably more severe than the disorder of patients not receiving pharmacological intervention. The lack of adjustment for severity of depression may have led to spurious associations of AD exposure in pregnancy with any analyzed outcome, if there is a causal link between the outcome (ASD, ADHD or other neurodevelopmental disorder) and the mother's major depressive illness.

Depression and risks of ASD, ADHD and neurodevelopmental impairment

The notion that maternal depression might be an independent risk factor for adverse pregnancy outcomes and offspring neurodevelopmental disorders is not only plausible but it is also consistent with findings from observational studies. Systematic reviews, with or without meta-analysis, found that untreated depression, anxiety and/or perceived stress during pregnancy were associated with small increases in the risk of adverse pregnancy outcomes such as preterm births, low birth weights and small-for-gestational-age infants [82,83]. Untreated depression also causes effects on the developing fetus such as hyperactivity, irregular fetal heart rate and altered EEG patterns [84]. The impact of maternal depression on child development and mental health has been far less explored. Nonetheless, some researches provided indirect evidence for such association of unmedicated maternal depression with ASD. A strong evidence along this line was provided by studies showing that preconception-only maternal exposure to ADs increased risks of ASD in the offspring [36,37,41,45]. AD therapy before pregnancy indicates that these women suffered from a depressive disorder severe enough to require a pharmacological intervention. It is difficult to foresee, on the other hand, how a preconception-only exposure to ADs could have any detrimental effect on the further development of the conceptus. Moreover, associations of ASD with AD use in pregnancy detected by several studies proved to be nonsignificant after adjustment for maternal psychiatric disorders. Recently, Hagberg et al. [43] found that untreated depression, but not AD use in pregnancy for disorders other than depression, increased

risks of ASD in the offspring. Using the duration of the last episode of depression as a proxy for disorder severity, the authors noted that risk of ASD increased with increasing severity of maternal depression. Collectively, these findings are consistent with the interpretation that a maternal history of depression might be an independent risk factor for ASD.

Seven studies found that maternal depression in pregnancy and/or after birth, regardless of whether it is treated or untreated, might impair child development [62,67,75,76,77,79,80]. These findings showed that, as noted for ASD and ADHD, the non-adjustment of risk ratios for severity of depression may have led to spurious associations of antenatal AD with deficits in the cognitive and behavioral development of infants and preschool children.

Genetics and mother-child interaction

Both inheritable genetic traits and depression-caused abnormal mother-child interaction might provide plausible explanations for associations between maternal depression and enhanced risks of neurodevelopmental and psychiatric disorders in the offspring.

Affective disorders have well-established genetic components and family studies indicated 2- to 3-fold increases in lifetime risk of major depression among first-degree relatives [85,86]. A recent genome-wide association meta-analysis identified 44 genetic risk loci for major depressive disorders and strongly suggested the existence of biological processes common to major depression and schizophrenia. The genome analysis indicated that some biological processes might be common to major depression and other psychiatric disorders such as ASD and ADHD [86]. In the study by Malm et al. [35], for instance, inherited risk factors for major depression were lurking variables that might have influenced the apparent association between SSRI use in pregnancy and depressive disorders in the adolescent offspring. Although the association was significant after adjustment for maternal psychiatric illness, the authors did not adjust risk ratios for severity of maternal depression. SSRI use in pregnancy could have been a surrogate or marker for more severe maternal depressive disorders and, as mentioned, major depression has a genetic and inheritable component.

Furthermore, various studies provided evidence that depression can adversely affect mother-child bonding as well as the child's development and mental health [87].

Sibling analysis designs are useful to investigate associations thought likely to suffer confounding arising from genetics and environmental postnatal factors, including the detrimental effects of maternal depressive symptoms on mother-child interaction. In principle, such strategy to control potential confounding in the design of the study seems to be better than merely adjusting risk ratios in the statistical analysis using dichotomous data on the presence/absence of maternal history of depression. Nonetheless, a possible disadvantage of sibling analysis in a sub-cohort of population-based cohorts is that it drastically reduces the sample size and thus the statistical power of the analysis. In all sibling analyses conducted by reviewed studies, no association of ADs in pregnancy with ASD was found [38,40,42,43], nor was it detected with ADHD [42,51,58].

Non-differential misclassification of exposure

A notable shortcoming common to all reviewed studies is a potential non-differential misclassification of exposure status due to lack of confirmation of the actual drug intake in pregnancy. Exposure assessment (binary exposure) took into account records of drug prescription and dispensing, but no study confirmed patients' adherence to AD treatment. The exposure status relevant for the outcome of interest is not merely a matter of using or not ADs during pregnancy. The effect of exposure on the outcome is likely to depend on the magnitude (dose), timing and adherence to prescribed pharmacotherapy. Nonadherence to prescribed medication and, particularly, poor AD adherence is a challenging issue in psychiatric practice. It is estimated that up to approximately 50% of psychiatric patients, including those with major depression prematurely discontinue drug therapy [88,89]. Nonadherence with medication is also a common problem among pregnant women whose drug-taking behavior can be negatively influenced by concerns about harmful effects of the pharmacological therapy on the unborn child, among other factors [90]. The influence of concomitant pregnancy and depressive illness on the high rates of nonadherence with medication noted in either

condition alone is unclear. At any rate, non-differential misclassification of exposure is likely to bias towards the null estimates of detrimental effects of prenatal AD exposure on offspring's health.

National scenarios

Another potential drawback of the reviewed cohort or case-control studies is the fact that nearly all of them used data from nationwide (or territory-based) health registries (e.g., Scandinavian countries, Finland, Hong Kong), or large databases from health insurance companies (e.g., United States, United Kingdom). These studies investigated associations between exposure and outcomes in people living in a few highly developed countries and findings might be somewhat different for distinct exposure scenarios and populations from Asia, Africa and Latin America.

Publication bias and searching strategy

In principle, publication biases may misdirect the qualitative and/or quantitative synthesis of any systematic review. It is unlikely, however, that any good quality observational study on the topic addressed by this systematic review would have remained unpublished. The possibility exists, on the other hand, that the adopted searching strategy (search strings and databases) was not effective to identify all relevant studies. To verify whether the search strategy failed to identify articles of interest, we compared the set of studies included in this review with those analyzed by previous systematic reviews. Nine reviews conducted between 2014 and 2018 examined a possible association of ADs in pregnancy with ASD [16,17,18,19,20,21,22,23,24]. Our review about ASD risks covered not only all studies included in the previous reviews but also analyzed two more studies than the most recently published review. Two reviews, both published in 2018, addressed the risks of ADHD [26,27]. Again, this study covered not only all studies included in published reviews but one more than those examined by one of the two previous reviews. Two reviews published in 2011 [91] and 2018 [28], including 5 and 7 studies, respectively, evaluated risks of neurodevelopmental disorders arising from prenatal exposures to ADs. Except for one study [92], this review analyzed all studies included in previous reviews and 23 additional articles. Suri et al. [92] found no association of AD in pregnancy with neurobehavioral outcomes and their study was included in the review by Prady et al. [28].

The foregoing comparison with previous reviews suggests that this updated review, encompassing the three outcomes of interest, did not fail to retrieve and include any relevant study about potential associations between prenatal exposure to AD and risks of ASD, ADHD and neurodevelopmental disorders.

SSRIs and neurodevelopmental outcomes

Studies of associations of ADs in pregnancy with impaired neurocognitive and behavioral development during infancy and early childhood were heterogeneous regarding the design, instruments used to assess neurocognitive development outcomes and child age at assessment. Overall, their findings indicated that antenatal exposure to SSRI did not impair further child development. Many of these studies used scales to assess child development such as the *Bayley Scales of Infant Development* (BSID) for infants with ages ranging from one to 42 months. BSID has high reliability and validity but, unless the scores are very low, its predictive value for long-term intellectual and motor disabilities is questionable [93,94,95]. The clinical relevance of significant yet small differences in BDSI scores detected by some studies is unclear.

Since observational studies have limitations for controlling confounding and making causal inferences, a prospective, randomized, placebo-controlled, double-blinded clinical trial is under way in Sweden to clarify whether a SSRI (sertraline) and/or depression in pregnancy might in fact affect child neurocognitive development. The primary objective of this trial is to assess cognitive development at 2 years of age using the BSID-III scale. The recruitment of pregnant women for this study (MAGDALENA study protocol) will be finished in 5 to 6 years' time [96].

Concluding remarks

This study found no consistent evidence of association between antenatal exposure to ADs and increased risks of ASD, ADHD, psychiatric illnesses, and cognitive and or developmental deficits in preschool children.

The conclusion that prenatal exposure to SSRIs and/or serotonin-norepinephrine reuptake inhibitors (SNRIs) does not predict risks of ASD is particularly robust. It is of note that results from some studies strongly suggested that maternal depression, regardless of whether it is treated or untreated during pregnancy, increases risks of ASD in the offspring. A recent population-based cohort study (mother-newborn pairs from Manitoba, Canada, born 1996-2009 with follow-up through 2014) found no association (HR = 0.92; 95%CI: 0.42-2.03) between antenatal exposure to SSRI or SNRI and ASD [97]. This study was not included because only a conference abstract was available when the review was completed.

As commented before, eight reviews of observational studies found a positive association of ASD with use of SSRIs in pregnancy [16,17,18,19,20,21,22,23]. At least four of these studies highlighted that maternal psychiatric condition was a major confounding [18,20,22,23] or that causality remained to be confirmed [17]. Two additional reviews found no association [24], or pointed out that a residual confounding by indication and inconsistent findings precluded a conclusion about risks of ASD [25]. Along the same line, three reviews concluded that a residual confounding by indication cannot be ruled out as an explanation for observed associations of prenatal AD exposure with ADHD [25,26,27]. Only one review [28] evaluated studies that compared behavioral and neurodevelopmental outcomes for children whose mothers took ADs during pregnancy with those whose mothers suffered from mental disorders but did not take medication. This study [28] found very limited evidence indicating that gestational use of ADs might impair behavioral and neurodevelopmental outcomes in the offspring.

Overall, findings from this study and those from other systematic reviews addressing risks of poor pregnancy outcomes and developmental disorders do not support concerns on the risks of SSRIs/SNRIs for the unborn child.

Contributors

J. S. A. Araujo contributed to the conception and study design, data collection and analysis, and drafting of the manuscript. I. F. Delgado contributed to the study design, data analysis, and review of manuscript. F. J. R. Paumgartten conceived and designed the study, contributed for data collection and interpretation and wrote a first draft of the manuscript. The final version of the article submitted for publication was approved by all authors.

Additional informations

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Resumo

O estudo teve como objetivo investigar se a exposição intrauterina a antidepressivos (ADs) aumenta o risco de transtornos do espectro autista (TEA), transtorno de déficit de atenção e hiperatividade (TDAH), esquizofrenia e outros transtornos mentais e déficits cognitivos e de desenvolvimento em lactentes e pré-escolares. Foram realizadas buscas nas bases PubMed, EMBASE e BIREME/BVS para identificar estudos sobre associações entre o uso de ADs durante a gestação e transtornos de neurodesenvolvimento e psiquiátricos. Vinte estudos trataram de riscos de TEA e/ou TDAH, enquanto 30 focaram em déficits cognitivos e de desenvolvimento em lactentes ou pré-escolares. A maioria dos estudos não detectou associação entre AD na gestação e TEA, depois de ajustar as razões de risco para depressão ou outros transtornos psiquiátricos maternos. Alguns estudos mostraram que a depressão materna, quer tratada ou não, aumenta o risco de TEA. Sete entre oito estudos não detectaram aumento de risco de TDAH associado à exposição intrauterina a inibidores seletivos da recaptação da serotonina, o AD mais comumente utilizado. Não foram encontradas evidências consistentes entre o uso de AD na gestação e déficits de desenvolvimento neurocognitivo em lactentes ou pré-escolares. Em quase todos os estudos, permaneceu um confundimento residual por indicação (gravidade da depressão). A revisão sistemática não encontrou evidências consistentes de que os ADs na gestação aumentassem o risco de TEA, TDAH ou déficits de desenvolvimento neurocognitivo. Entretanto, alguns estudos evidenciaram que a depressão materna aumenta o risco de TEA.

Antidepressivos; Depressão; Transtorno do Espectro Autista; Transtorno do Déficit de Atenção com Hiperatividade; Gravidez

Resumen

Este estudio investigó si la exposición prenatal a antidepresivos (ADs) incrementa los riesgos de trastornos del espectro autista (TEA), trastornos de déficit de atención/hiperactividad (TDAH), esquizofrenia, así como otras enfermedades mentales, cognitivas, y déficits en el desarrollo de niños de primaria o preescolares. Se consultaron las bases de datos PubMed, EMBASE, BIREME/BVS para identificar estudios de asociaciones de ADs durante el embarazo con trastornos de desarrollo neurológico y psiquiátricos. Veinte estudios estaban centrados en riesgos de TEA y/o TDAH, mientras que 30 se centraron en déficits de desarrollo y cognitivos en niños de primaria o preescolares. La mayor parte de los estudios no detectaron asociación de AD, durante la etapa prenatal, con TDA tras el ajuste de las ratios de riesgo para depresión materna o trastornos psiquiátricos. Algunos estudios mostraron que la depresión materna, independientemente de si es tratada o no, incrementó los riesgos de TEA. Siete de los 8 estudios no encontraron un incremento en el riesgo de TDAH, asociado con la exposición prenatal a inhibidores selectivos de la recaptación de serotonina, el antidepresivo más usado habitualmente durante el período prenatal. No se encontraron evidencias consistentes relacionando AD durante el embarazo y déficits en el desarrollo neurocognitivo de niños de primaria o preescolares. En casi todos los estudios hubo una desviación residual señalada como gravedad de la depresión. Esta revisión sistemática no halló evidencias consistentes, sugiriendo que el consumo de ADs durante el embarazo incremente el riesgo de TEA, TDAH, y déficits en el desarrollo neurocognitivo. Algunos estudios, no obstante, encontraron evidencias de que la depresión materna incrementa riesgos de TEA.

Antidepresivos; Depresión; Trastorno del Espectro Autista; Trastorno por Déficit de Atención con Hiperactividad; Embarazo