Long-term effects of intra-uterine exposure to antidepressants on physical, neurodevelopmental and psychiatric outcomes: a systematic review

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Abstract

Objective. Reviews on child outcomes following in utero antidepressant exposure have focused on short-term outcomes. However, several recent individual studies reported on adverse physical, neurodevelopmental and psychiatric outcomes beyond infancy and early childhood. The objective of this systematic review was to establish the long-term effects of prenatal antidepressant exposure on physical, neurodevelopmental and psychiatric outcomes in individuals aged four and older. **Data sources.** Embase, Medline Ovid, Web of Science, Cochrane Central and Google Scholar were systematically searched for all relevant articles, written in English, published prior to November 2018, using terms describing antidepressants, pregnancy, and developmental outcomes. **Study selection.** All original research articles on long-term outcomes of prenatal antidepressant exposure were eligible for inclusion. After screening and removal of duplicates, a total of 34 studies were identified. **Data Extraction.** Included articles were qualitatively analyzed to determine inconsistency, indirectness, imprecision and study bias. **Results**. The identified studies demonstrated statistically significant associations between prenatal antidepressant exposure and a range of physical, neurodevelopmental, and psychiatric outcomes. Yet, the risk of confounding by indication was high. When controlling for confounders, five studies investigating physical outcomes (asthma, cancer, BMI, epilepsy) found no association, except conflicting outcomes for BMI. Eighteen studies examining neurodevelopmental outcomes (cognition, behavior, IQ, motor development, speech, language and scholastic outcomes) found no consistent associations with antidepressant exposure after taking confounders into account. Eleven studies investigated psychiatric outcomes. After adjusting for confounders, prenatal antidepressant exposure was associated with affective disorders, but not with childhood psychiatric outcomes (autism spectrum disorders, attention-deficit/hyperactivity disorder). **Conclusion.** Reported associations between in utero exposure to antidepressants and physical, neurodevelopmental, and psychiatric outcomes, in large parts, seem to be driven by the underlying maternal disorder. When limiting confounding by indication, prenatal exposure to antidepressants was only significantly associated with offspring BMI and affective disorders.

Key words: Antidepressants, perinatal psychopathology, depression, pregnancy, development, neurodevelopment

Introduction

Depression and anxiety are highly prevalent mental disorders and the leading cause of disability worldwide[1]. Perinatal depression, defined as depression during pregnancy and after delivery, affects approximately 11.5% of new mothers annually in the United States[2]. If left untreated, perinatal depression puts mothers at increased risk of experiencing negative mental and physical health outcomes[3,4]. Moreover, perinatal depression has been linked to poor child outcomes, including adverse birth outcomes, poorer long-term cognitive and social development, and the risk of future psychopathology[5]. Antidepressants are usually given as first-line treatment for depression and anxiety[6,7] and many patients continue to take their antidepressants for long periods of time as maintenance treatment to prevent relapse[8]. As a result, antidepressant use during pregnancy is common, with estimated prevalence rates ranging between 2% and 13%[9-12].

However, since antidepressants cross the placenta, as well as the blood-brain barrier[13], concern is growing about sequelae of in utero antidepressant exposure on the unborn child. Many antidepressants target the serotonergic system, and modifications of serotonergic signals are thought to influence brain development and subsequent functioning[14]. Moreover, the serotonergic system is involved in mechanisms besides brain functioning, including motor control, food intake, and body weight regulation[15,16]. Consequently, approximately 50% of women decide to discontinue their antidepressants, either before or during pregnancy[17].

A substantial number of observational studies has examined the use of antidepressants during pregnancy, with inconsistent results. Observational studies always carry the risk of confounding, particularly confounding by indication. Some of these studies found associations between in utero exposure to antidepressants and adverse neonatal outcomes, including low birth weight, preterm birth, persistent pulmonary hypertension of the neonate (PPHN) and poor neonatal adaptation[18-25], as well as associations between prenatal antidepressant exposure and poorer neurodevelopmental and neurobehavioral outcomes in early childhood[26-28]. While these short-term outcomes have frequently been investigated and subsequently consolidated in systematic reviews (e.g.[29-32]), very few long-term child outcomes were included in these reviews. Recently several individual studies have reported on adverse long-term outcomes beyond infancy and early childhood, including studies on intellectual disability at age eight years, as well as childhood cancer and psychiatric disorders over 15 and 17-year follow-up periods respectively[33,34].

Our aim was to systematically evaluate the literature, examining the long-term effects of in utero exposure to antidepressants on child outcomes including and beyond the age of four years, and untangling the results from confounding factors, such as confounding by indication, socioeconomic status, untreated mood/anxiety symptoms, and exposures to other substances. We chose to focus on outcomes from age four onwards because the short-term effects of in utero exposure to antidepressants have been well established in a plethora of reviews focusing on infancy and very early childhood. Yet, it is paramount to also understand the long-term health effects of prenatal antidepressant exposure. Furthermore, many children start preschool at age four and measurements of childhood psychiatric disorders, learning disabilities and cognitive development become more reliable. Due to the nonspecific action of antidepressants, we included all investigated developmental outcomes, including physical, neurodevelopmental, and psychiatric outcomes.

Methods

Literature search and data sources

The systematic electronic literature search was performed by a medical information specialist (WB) on November 8th, 2018. All large databases, including embase.com, Medline Ovid, Web of Science, Cochrane Central and Google Scholar were searched, using search terms describing: types of antidepressants (e.g. selective serotonin reuptake inhibitor, tricyclic antidepressant), the target population (e.g. pregnancy, pregnant women, maternal exposure), and outcome measurement timing (e.g. childhood, child development, adolescent). A complete overview of the search terms used is depicted in Supplementary Appendix 1. This systematic review was registered in PROSPERO under the number CRD42019116981.

Selection criteria

The selection procedure was conducted according to the guidelines described in the PRISMA statement[35]. Studies were eligible for inclusion if they were peer-reviewed, written in English and if they described a population of women using any antidepressants, including: Serotonin reuptake inhibitors (SRIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and other antidepressants during pregnancy. We defined long-term outcomes as any child outcome

from the age of four years onwards, not restricting our search to a maximum follow-up period. All original research articles were eligible for inclusion.

Study selection and data extraction

Duplicate manuscripts were screened and removed with the citation manager EndNote. Two reviewers (NMM, RC) independently screened the titles and abstracts and assessed the full text of potentially eligible studies. Disagreements between reviewers' selection were resolved by discussion among the reviewers and authors. When multiple papers reported on the same cohort and the same outcome measurement, the manuscript with the highest level of detail was included. Data were extracted using a standardized data extraction form by two reviewers (NMM, ASR, see Supplementary Appendix 2). Two reviewers (NMM, ASR) independently assessed the quality of the studies using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Institutes of Health; NIH). The overall quality of evidence per outcome was summarized according to the GRADE guidelines only for those outcomes reported in five or more studies[36].

Data synthesis

Here, we report a narrative synthesis of the evidence and present extracted adjusted relative risks and 95% confidence intervals where possible. We did not perform a meta-analysis of the results because the physical health and neurodevelopment outcomes assessed in the included studies were too varied and biased to be pooled. Moreover, a meta-analysis of the psychiatric outcomes was futile because not enough research has investigated psychiatric disorders manifesting in adolescence and adulthood and childhood psychiatric outcomes have been meta-analyzed extensively.

Results

Identified and included articles

Thirty-four studies met the predefined inclusion criteria and were included in this review (Figure 1, Supplementary Appendix 3). Interrater reliability was high (raw interrater agreement 98.9%). Studies reported on physical health outcomes (N=5), neurodevelopmental outcomes (N=18) and psychiatric disorders (N=11). Fifteen studies (42.9%) were prospectively designed. Sample size per study ranged between 36 and 1,580,629 children. All studies included SSRIs, while some also focused on SNRIs

(N=19), TCAs (N=13) and MAOIs (N=10). Detailed characteristics of all studies, including the quality assessment per study, are provided in Table 1.

Physical health outcomes (Table 2)

Four retrospective studies reporting on physical health outcomes were identified and their quality rated fair to good. Two studies by Grzeskowiak et al.[46,47] focused on childhood overweight, classified as a body mass index >85th percentile. In an Australian cohort of 6,560 women[46], an association between SSRI exposure and childhood overweight at the age of four to five years was found for female, but not male offspring. In contrast, in a Danish cohort of 36,185 pregnancies[47], an association between SSRIs and childhood overweight was found for male, but not female offspring at the age of seven. The authors assign the inconsistent results to the differences in study methods, and indicate a higher accuracy in the Danish study.

Liu et al. [55] did not find an association between antidepressant use and asthma in a large Danish population-based cohort. Only use of older antidepressants (mainly TCAs) was associated with an increased risk of asthma when compared to an untreated control group. However, this finding could reflect confounding by the severity of maternal depression, which cannot be assessed directly in register-based studies.

Momen et al.[61] examined the association between in utero antidepressant exposure and childhood cancer. No association was found between antidepressant use during pregnancy and childhood cancer in general, leukemia and nervous system tumors.

Mao et al.[59] examined the association between antidepressant exposure and epilepsy. Children exposed to antidepressants in utero (n=12,438) had a higher overall risk of epilepsy compared to unexposed children, but this difference was not significant when compared to mothers who discontinued antidepressants shortly before pregnancy, indicating that the underlying maternal disease plays a role in the observed association.

Neurodevelopmental outcomes (Table 3)

<u>Cognition</u>

None of the five studies[43,45,51,52,62] investigating cognitive-neurophysiological outcomes following in utero antidepressant exposure found a significant association between prenatal exposure to

antidepressants and cognitive performance in a total of 274 antidepressant-exposed children, 818 children exposed to untreated maternal depression, and 7,142 unexposed children.

Internalizing and externalizing behavior

We identified seven studies examining both externalizing and internalizing behavior[45,48,49,56,62-64], four studies investigating externalizing behavior only[28,42,51,65] and one study[60] assessing internalizing behavior only, following in utero antidepressant exposure. Except for three case-control studies[45,49,60], all studies were longitudinal cohort studies[28,42,48,51,56,62-65]. Two analyses used the Health and Behavior Questionnaire to assess externalizing and internalizing behavior[49,62], one study used the Strength and Difficulties Questionnaire (SDQ)[48] and nine studies assessed externalizing and internalizing behavior using the Child Behavior Checklist (CBCL)[28,42,45,51,56,60,63-65].

A positive association between antidepressant exposure and externalizing behavior was reported in three studies[28,42,62], including a total of 198 individuals prenatally exposed to SRIs and 5,647 unexposed individuals. One study, including 44 individuals exposed to SRIs in utero and 66 unexposed individuals, showed a positive association between antidepressant exposure and internalizing behavior as assessed by the CBCL[49]. Eight other studies, including a total of 1,216 children exposed to antidepressants, 474 children exposed to untreated depression and 87,022 unexposed children, did not show a relationship between in utero antidepressant exposure and internalizing and/or externalizing behavior[45,48,51,56,60,63-65].

Intelligence Quotient (IQ)

Out of the five prospective studies that examined IQ scores[43,45,51,63,64], only one study showed a small significant difference in IQ scores in children exposed to antidepressants in utero[64]. Nulman et al.[64] compared children of depressed women using venlafaxine during pregnancy (N=62) and children of depressed women using SSRIs during pregnancy (N=62) to children of untreated depressed pregnant women (N=54), and children of non-depressed, healthy pregnant women (N=62). Children of non-depressed mothers had significantly higher full-scale and verbal IQs than those in the venlafaxine and SSRI group. However, after correcting for covariates, dose and duration of antidepressant use during pregnancy did not predict child IQ score. This suggests that factors other than antidepressant exposure during pregnancy predict children's intellect, including maternal IQ and gender of the child.

The other four studies, together reporting on 176 children exposed to antidepressants in utero, observed no association between antidepressant exposure and IQ scores in children between 2.5 and 7 years of age[43,45,51,63].

Viktorin et al.[33] examined the association between antidepressant exposure in utero and intellectual disability (ICD-10 codes F70-F79). No significant association was observed after adjustment for potential confounding factors.

Motor development

Five studies examined motor development in the offspring; four prospective studies[43,45,65,66] and one retrospective study[39]. Brown et al.[39] used an ICD-10 diagnosis of specific developmental disorders of motor development as outcome, while the prospective studies used a kinematic task of visual motor and fine motor function, the Movement Assessment Battery for Children (Movement ABC-2), the sensorimotor function of the NEPSY-II and the movement subscale of the Crowell procedure[43,45,65,66]. Of the four prospective studies, together reporting on 140 antidepressant-exposed children between the ages of 4 and 7 years, only one study reported significant findings. Partridge et al.[66] performed a kinematic task of visual motor and fine motor functions at ages 4-5 years in SRI exposed children (n=15), children of untreated depressed pregnant women (n=10) and a control group (n=15). Children with prenatal SRI exposure had poorer fine motor control compared with children who were not exposed to SRIs.

Speech, language, and scholastic outcomes

One prospective[28] and two retrospective studies[39,53] reported on speech, language and scholastic outcomes. Johnson et al.[28] examined 178 mother-child dyads, including 102 dyads with in utero SRI exposure, with the Expressive Language subtest of the Test of Early Language Development, 3rd edition (TELD-3). There was a modest mean difference of approximately five points in Expressive Language scores in favor of non-SRI exposure. Brown et al.[39] examined specific developmental disorders of speech and language and specific developmental disorders of scholastic skills according to ICD-10 diagnosis. Children exposed to SSRIs in utero had a significant increase in the risk of speech-language disorders compared to unexposed children. No overall association was found between in utero SSRI exposure and special education needs or delayed school start[53].

Psychiatric disorders (Table 4)

Autism Spectrum Disorders (ASD)

We identified seven studies, one case-control study[50], two health record analyses[40,41], and four register-based cohort studies[34,37,57,67], which reported on the association between in utero antidepressant exposure and ASD. All four register-based cohort studies reported a significant association between in-utero antidepressant exposure and risk for ASD, with relative risks (RRs) ranging from 1.23 to 4.39[34,37,57,67]. Three studies did not find a significant association[39,41,50]. All, except one study[50], based their outcome definition on the ICD diagnoses of ASD. Harrington et al.[50] employed the Autism Diagnostic Interview–Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS).

The case-control study[50] compared children with ASD (n=492) to typically developing controls (n=320) on self-reported maternal SSRI use during pregnancy. Children with ASD were not more likely to have been exposed to SSRIs during pregnancy (5.9%) than typically developing children (3.4%). Restricting the analysis to boys produced a significant association (OR=2.92; 95% CI:1.07–7.93), but further reduced the already small number of children exposed to SSRIs in-utero (N=40, N for boys only=32).

The two health record analyses employed diverging methods. One study[41] identified individuals with an ASD diagnosis (n=1,245) and compared them to typically developing controls (n=3,405). The other study[40] compared individuals prenatally exposed to SSRIs (n=2,837) both to unexposed controls (n=33,069) and to their unexposed sibling (n=620). Neither of these studies reported a significant association between in-utero antidepressant exposure and risk for ASD.

The four register-based cohort studies[34,37,57,67] reporting a significant association included a total of 58,365 individuals prenatally exposed to antidepressants and compared them to a total of 2,586,644 unexposed individuals. To control for confounding by indication, Liu et al.[34] and Malm et al.[57] further compared the antidepressant-exposed individuals to a total of 30,079 individuals whose mothers had used antidepressant medication before, but not during, pregnancy (discontinuation group). Malm et al.[57] added an additional comparison group of 9,651 individuals who were exposed to untreated mental illness in utero. Sujan et al.[67] carried out a discordant sibling analysis. These attempts at controlling for confounding by indication yielded mixed results. While Liu et al.[34] reported a

small significant association between antidepressant exposure and ASD, Malm et al.[57] and Sujan et al.[67] did not find significant associations.

Attention Deficit Hyperactivity Disorder (ADHD)

We identified seven studies, one insurance data analysis[44], two health record analyses[41,58], and four register-based cohort studies[38,54,57,67], which examined the association between ADHD and in utero antidepressant exposure. Three of the four register-based cohort studies[54,57,67] and one health record analysis[58] reported a significant association between in utero antidepressant exposure and risk for ADHD, with RRs ranging from 1.2 to 1.66. Three studies did not report a significant association[38,41,44]. All, except one study[44], based their outcome definition on the ICD diagnoses of ADHD. Figueroa et al.[44] based ADHD diagnoses on insurance and prescription claims.

Figueroa et al.[44] investigated the association between in utero SSRI exposures and the presence of ADHD in the child by the age of 5 years (N=38,074) and found that, while maternal ADHD, depressive disorders and prenatal bupropion exposure increased the risk for ADHD, in utero SSRI exposure did not.

The two health record analyses employed diverging methods. One study[41] identified individuals with an ADHD diagnosis (n=1,701) and compared them to typically developing controls (n=3,405). The other study[58] compared individuals prenatally exposed to antidepressants (n=1,252) to unexposed controls (n=189,002) and a discontinuation group (n=1,486). In addition, they conducted a post hoc sibling-matched analysis to control for shared genetic and social confounding, including 53,616 children of 26,049 mothers. Castro et al.[41] did not find a significant association between risk for ADHD and prenatal antidepressant exposure. Man et al.[58] found a significant association only when comparing the exposed children to unexposed controls, but not when comparing the exposed children to the discontinuation group or in the sibling-matched analyses, which aimed to control for confounding by indication.

The three register-based cohort studies[54,57,67] reporting a significant association compared a total of 52,310 individuals prenatally exposed to antidepressants to 2,407,290 unexposed individuals. One register-based cohort study[38] not showing a significant association included 1,561 individuals exposed to SSRIs in the second and/or third trimester and 141,905 unexposed individuals. To control for confounding by indication, Malm et al.[57] further compared the antidepressant-exposed individuals

to a total of 7,980 individuals whose mothers had used antidepressant medication before, but not during, pregnancy and 9,651 individuals who were exposed to untreated mental illness in utero. In addition, Sujan et al.[67] and Laugesen et al.[54] carried out discordant sibling analyses. These attempts at controlling for confounding by indication resulted in the loss of the significant associations between antidepressant exposure and increased risk for ADHD in all three studies.

Affective disorders

Two studies report on affective disorders diagnosed in adolescence[34,57], taking advantage of the long-term follow-up of the Scandinavian national registers. Malm et al.[57] assessed depression and anxiety (ICD diagnoses) in SSRI-exposed offspring compared to unexposed offspring, offspring exposed to untreated mental illness in utero and offspring whose mothers had used antidepressants before, but not during, pregnancy. Children exposed to SSRIs during gestation (n=15,729) were at increased risk of developing depression compared to the other exposure groups. There was no association between SSRI exposure and a diagnosis of anxiety disorders.

Liu et al.[34] investigated the overall risk of psychiatric disorders, as well as affective disorders more specifically, (ICD-10 diagnoses) over a maximum follow-up of 16.5 years. Increased risks for affective disorders were seen in children exposed to antidepressants in utero compared to children whose mother discontinued antidepressants before pregnancy.

Quality of evidence (GRADE assessment)

The quality of evidence was summarized for all outcomes reported in five or more studies. According to GRADE criteria, the overall quality of evidence was considered low for ASD and ADHD and very low for cognition, behavior, IQ and motor development.

Discussion

Based on our comprehensive systematic review of the literature, we found statistically significant associations between in utero exposure to antidepressants and a wide range of physical, neurodevelopmental, and psychiatric outcomes. Yet, the evidence is inconsistent and the risk of residual confounding, particularly confounding by indication, is high. Across all identified and included studies, the quality of evidence of the examined outcomes was rated low to very low (GRADE[36]).

In studying the effects of prenatal antidepressant exposure, it is crucial to consider that the indication for antidepressant use, namely maternal psychopathology, has also been shown to increase the risk of adverse outcomes in the child[68]. This issue is known as confounding by indication. Maternal psychopathology may assert its effect on the offspring via shared genetic susceptibility, environmental stress, and/or parenting practices[69-71]. All but nine studies[44-46,51-53,55,59,65] statistically controlled for some form of maternal psychopathology. Because these statistical adjustments are unlikely to fully control for the source of confounding, some studies have used additional strategies to disentangle the effects of antidepressant use from the effects of the underlying maternal illness. These strategies include comparing antidepressant-exposed individuals to individuals born to mothers who discontinued antidepressants or to individuals born to mothers with untreated mental illness. In addition, discordant sibling designs, which compare exposed individuals to their unexposed sibling, aim to address this issue by controlling for all genetic and environmental factors shared between siblings. In general, attempts to control for confounding by indication led to a decrease in the magnitude of the association between in utero antidepressant exposure and adverse child outcomes. Below we discuss studies where the association persisted.

Physical health outcomes

Two small studies found sex-related decreases and increases in the risk of childhood overweight following in utero antidepressant exposure[46,47]. Prenatal SSRI exposure can alter postnatal components of central serotonergic signaling, a pathway that plays a critical role in regulating mammalian energy homeostasis[72]. In animals, fetal and neonatal SSRI exposure has been shown to result in changes consistent with Type 2 diabetes and its comorbidities[73]. Previous studies on short-term outcomes in humans have also repeatedly found associations of in utero exposure to antidepressants and decreased birth weight[18]. Decreased birth weight, in turn, may reflect altered programming of organ structures and associated functions, which can lead to changes that carry into adulthood, including increased risk of diabetes and heart disease[74,75].

Interestingly, both animal and human studies indicate a gender difference. In theory, this gender difference could be related to sex hormones, because estrogen is known to influence the serotonergic system[76,77] and regulates serotonin transporter (SERT) expression, enhancing serotonergic signaling pathways[78,79]. Indeed, a study in rats demonstrated that genes that regulate

serotonin signaling and action in the ovary are altered in prenatally SSRI-exposed offspring. These rats had impaired reproductive cycling and an increased number of follicles in the ovary[80]. In humans, menstrual cycling and fecundity have not yet been investigated.

Psychiatric disorders

Childhood psychiatric disorders, particularly ADHD and ASD, have received the majority of attention from researchers. At least a dozen systematic reviews and meta-analyses have attempted to examine a causal link between exposure to antidepressants in utero and ADHD and/or ASD in the offspring, often with inconclusive results (e.g.[81,82]). This popularity likely results from methodological considerations since ADHD and ASD usually manifest early in life, and may thus be assessed after a relatively short follow-up period[83]. An increased risk for ADHD following prenatal exposure to antidepressants was found in four large cohort studies when comparing exposed to unexposed individuals. This significant association disappeared when these studies attempted to address confounding by indication in their study designs. Moreover, four large register-based cohort studies reported a significant association between in utero antidepressant exposure and risk for ASD. Only one of these studies [34] found that a small but significantly increased risk for ASD remained in individuals exposed to antidepressants in utero when comparing them to individuals born to mothers who discontinued antidepressants before pregnancy. For all other studies, the significant association between prenatal antidepressant exposure and ASD disappeared when exposed individuals were compared to individuals born to mothers who discontinued antidepressants, to individuals born to mothers with untreated mental illness or to unexposed siblings. Moreover, none of these studies were able to take the severity of the underlying maternal illness into account. These results, therefore, suggest that the underlying maternal disorder, rather than in utero antidepressant exposure, may be driving the association between in utero exposure to antidepressants and childhood psychiatric disorders. This is conceivable, given that psychiatric disorders are highly heritable[84], and maternal psychopathology may assert its effects via environmental stress, and suboptimal parenting practices[69-71].

The average age of onset of most psychiatric disorders, including depression, anxiety, psychosis and mania, is around late adolescence/early adulthood. This makes it harder to assess these disorders, because longitudinal and register-based studies in existence today have limited

follow-up durations. Consequently, only two studies thus far have reported on affective disorders[34,57]. Interestingly, both studies found that the risk for depression was increased in individuals prenatally exposed to antidepressants, even compared to individuals born to mothers who discontinued antidepressants before pregnancy or individuals born to mothers with untreated mental illness. These findings point to a putative causal relationship between in utero antidepressant exposure and depressive disorder in the offspring. However, comparing antidepressant-exposed individuals to individuals born to mothers who discontinued antidepressants before pregnancy or individuals born to mothers with untreated mental illness may still not be sufficiently addressing confounding by indication, because women who continue antidepressants throughout pregnancy may be fundamentally different from women who discontinue or women who have never used antidepressants. In particular, mothers with severe symptoms are more likely to continue treatment during pregnancy[85], and the severity of symptoms may differ between pregnancies. To address residual confounding by indication, randomized controlled trials, in which women are randomly assigned to an antidepressant continuation or discontinuation (plus cognitive therapy) group, are needed. This approach will ensure that all potential confounding factors are distributed equally among the groups to be compared.

Strengths and Limitations

The literature search was performed by an experienced medical information specialist. Study selection, data extraction and risk of bias assessments were conducted by two reviewers, ensuring validity and accuracy. However, due to resource limitations, we were unable to include articles published in languages other than English. Moreover, the clinical implications of our findings are limited by the quality of the reviewed studies, including their selection of confounding factors, and the heterogeneity of the investigated outcome measures.

Implications

Approximately 50% of women who use antidepressants before pregnancy decide to discontinue their antidepressants, either before or during pregnancy, due to concerns about the negative consequences for the child. However, evidence indicating a causal relationship between in utero exposure to antidepressants and long-term health of the offspring is limited. Concerns remain given

the significant associations of prenatal antidepressant exposure with BMI and affective disorders, the heterogeneity of the literature and the scarcity of findings on long-term outcomes. As potential negative consequences of psychiatric illness during pregnancy may transcend potential negative consequences of in utero exposure to antidepressants, women and their health care providers must carefully weigh the risks and benefits of antidepressant (dis)continuation during pregnancy. Treatment decisions will need to be tailored to the individual patient, taking her disorder severity, the course of her illness and psychiatric history, previous experiences with antidepressant discontinuation and her treatment preferences into account. Substantial evidence points to the efficacy of alternative non-pharmacologic interventions, such as cognitive behavioral therapy and interpersonal therapy, in preventing perinatal depression in at-risk women[86]. Women may, therefore, capitalize on these treatment options in order to minimize risks of exposure to antidepressants and untreated illness and maximize treatment of the disorder. However, judicious use of pharmacotherapy is recommended for women with severe mental illness or a high risk of relapse based on psychiatric history in order to avoid under-treatment and the resulting exposure to untreated illness.

To date, most clinical guidelines do not give any clear recommendations on antidepressant management during pregnancy[87]. It is challenging to formulate such guidelines when the evidence base is weak and inconsistent, and confounding by indication is difficult to avoid. Consequently, future research may use randomization to not only limit confounding by indication but also to identify women who may discontinue antidepressant use during pregnancy with a low risk of relapse and women for whom antidepressant treatment is indicated in order to remain euthymic[88].

Conclusion

Our comprehensive systematic review of the literature revealed statistically significant associations between in utero exposure to antidepressants and a wide range of physical, neurodevelopmental, and psychiatric outcomes. However, rather than reflecting a causal relationship, most of these associations seem to be driven by the underlying maternal disorder. After limiting confounding by indication, in utero exposure to antidepressants remained significantly associated only with BMI and increased risk for affective disorders.

The literature is heterogeneous and findings on long-term outcomes are scarce. As time goes on, more data will become available on the long-term effects of prenatal antidepressants exposure,

including on physical and mental health outcomes. These data will help to clarify the relationship between prenatal antidepressant exposure and BMI. Future research must also substantiate the association between in utero antidepressant exposure and affective disorders in adolescence and adulthood and investigate the associations between prenatal antidepressant exposure and other psychopathologies arising later in life.

Clinical Points

- There are no clear recommendations on antidepressant management during pregnancy, because the evidence base, especially on long-term outcomes, is weak and inconsistent. Evidence indicating a causal relationship between in utero exposure to antidepressants and long-term health of the offspring is limited but concerns remain
- Treatment decisions must take disorder severity, the course of illness and patient preferences into account

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