Original Article

The Effect of Antipsychotic Treatment, During the Perinatal Period, on the Neurodevelopment of Children: A Systematic Review and Meta-Analysis

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Abstract

Background: Managing mental disorders in the perinatal period is a challenge. The most common mental disorders encountered in this period are major depression, bipolar disorder, anxiety and psychotic disorders.
Purpose: This study aimed to investigate the neurodevelopmental effects in children born to mothers who were on antipsychotic medication, during pregnancy.
Methodology: Databases MEDLINE, Embase, Cochrane, PsychInfo, Google Scholar and Scopus searched according to inclusion and exclusion criteria. The studies involved mothers with preconception or relapsed mental illness receiving antipsychotic medication during the perinatal period and their children were screened for any neurodevelopmental disorders. From the initial search of the literature, 277 articles emerged and applying the criteria, according to the methodology, we identified 15 articles.
Results: Three studies were identified in which children were exposed and developed ADHD with a pooled odds ratio of 2.33 (95% CI = 1.69 – 3.20, $p<0.001$) indicating that children exposed to antipsychotics are more likely to develop ADHD than unexposed children. Regarding socio-emotional and mental development, it was found that the pooled odds ratio was 2.33 (95% CI = 1.68 – 3.22, $p<0.001$) indicating that exposed children are more likely to show delay compared to unexposed children. This relationship was statistically significant. Finally, it was found that children who were exposed and showed a delay in motor development had a pooled odds ratio of 2.93 (95% CI = 1.86 – 4.61, $p<0.001$).
Discussion: Fetal exposure to antipsychotic medication can cause short-term developmental delays in motor, social-emotional, and adaptive behavior. However, further investigation is needed since the number of studies.

Keywords: antipsychotic treatment; pregnancy; neurodevelopmental disorder

Introduction

Managing mental disorders in the perinatal period is a challenge. Perinatal mental disorder is defined as the recurrence of a known mental disorder of the mother or the first episode of its occurrence, when this occurs during pregnancy. It is dated from the moment of conception to one year after delivery (O'Hara & Wisner, 2014). The postpartum time frame is debatable, as most researchers use a period ranging from 4 weeks to 3 months postpartum, while the current literature suggests that depressive and anxiety disorders may appear up to a year postpartum (Mughal, Azhar & Sibbiqui, 2022). A10 to 20%

of women constitute a high-risk population for the occurrence of mental disorders, they already suffer from some symptoms or show vulnerability that remains stable up to 25 years after childbirth (Schmied et al., 2013). Women who go through the perinatal period are likely to experience disorders from the entire spectrum mental disorders, with depression and anxiety disorders being more common, affecting 20% of them (O'Hara & Wisner, 2014). Women with pre-existing psychiatric disorders, such as bipolar disorder, the risk of a manic or depressive episode in the postpartum period is 40- 50%, compared to the risk in the general female population of 0.1 to 0.25% (Akdeniz et al, 2003). The most common mental disorders encountered in this period are major depression, bipolar disorder, anxiety and psychotic disorders (Howard & Khalifeh, 2020).

Psychotropics, such as antipsychotics, anxiolytics, and antidepressants, are among the most prescribed medications (Houben et al., 2020). In the US, between 2006 and 2011, over 10% of pregnant women received at least one psychotropic drug (Hanley & Mintzes, 2014). In the Netherlands, from 1994 to 2003, the rate of prescription of antipsychotics during the perinatal period ranged from 0.09 to 0.19 per 1,000 women (Bakker et al., 2006). They are mainly prescribed for patients with schizophrenia, bipolar disorder, and to a lesser extent for depression, anxiety, insomnia, autism and nausea in early pregnancy (Edinoff et al, 2022).

Most of the psychotropics fall to a pregnancy category C. Although the long-standing pregnancy risk categories A, B, C, D, and X offer a tenet for the relative protection of medicinal drugs, greater distinct facts are important so that one can completely recognize the efficacy and protection of medicine use for the duration of being pregnant and lactation. In 2009, the FDA performed a look at to recognize higher how healthcare companies make choices concerning their pregnant sufferers. Researchers discovered that physicians relied more heavily on the Drug Authorities (e.g., the FDA, EMA) pregnancy categories than they did on any other available resource, leading the FDA to replace the overly simplistic pregnancy risk categories with a new system entitled the Pregnancy and Lactation Labeling Rule (PLLR). The cause became to develop a system that might decrease incorrect information and could higher help physicians and their sufferers in making evidence-primarily based totally scientific choices. However, the lack of robust evidence, from clinical trials and controversies lead to inexplicit results (FDA, 2014; Leek & Arif, 2023; Pernia & DeMaagd, 2016).

The decision, whether to prescribe psychotropics to pregnant women before childbirth, remains a dilemma for many psychiatrists, regardless the relative guidelines. There is a strong evidence that the relative risks of not receiving treatment while needed, are greater than the potential for developmental toxicity due to mother's low self-care, including self-destruction and attempted suicide by the mother (Ayers, Bond, Webb et al, 2019; Howard & Khalifeh, 2020; Knight, Bunch, Tuffnell et al, 2021). In addition, the possibility of improper fetal development and a weak mother-fetus connection/relationship increases (Menon, 2008; Solari et al,2009). On the other hand, treating the mother with antipsychotics involves exposing the fetus to substances, that easily cross the placenta (Tosato et al, 2017). According to a study by Babu et al (2015), olanzapine and haloperidol have the highest placental crossing ratio, with a mean value of 72.1% and 65.5%, followed by risperidone (49.2%) and quetiapine (23.8%) respectively.

Fetal exposure to antipsychotic medication is associated with an increased risk of obstetric and neonatal complications, including preterm births and foetal growth impairments (Howard & Khalifeh, 2020). Antipsychotic medications are being more commonly prescribed to women during pregnancy who have bipolar disorder and schizophrenia. Research on the occurrence of congenital malformations, cardiac anomalies, extrapyramidal symptoms, neonatal withdrawal/abstinence syndrome, and the enduring neurodevelopmental consequences resulting from exposure to these medications has been limited (Batt et al, 2022; Clark, 2020).

Neurodevelopmental disorders include a range of neurological and psychiatric conditions, different in terms of their clinical

picture and etiology. More specifically, according to the authors, the term "Neurodevelopmental disorders" is used in two different ways. The first concerns conditions that affect the child's neurological development due to genetic and acquired factors, such as fetal alcohol syndrome. Conversely, the second way is related to conditions of multifactorial etiology, such as dyslexia or autism (Bishop, 2010). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, DSM-5 (2013), does not include disorders that have a known genetic etiology and disorders that are environmentally driven. In contrast, in the Neurodevelopmental Disorders chapter, the Handbook includes multifactorial disorders, in which genetic, biological, psychosocial and environmental factors usually interact. The Neurodevelopmental Disorders included in the DSM-5 are the following: Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), Specific learning disorders, Mental retardation, Communication disorders, Movement disorders and Tic disorders.

The purpose of this systematic review and meta-analysis is therefore to identify and present possible negative neurodevelopmental consequences of taking antipsychotic medication during pregnancy to the child.

Methodology

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Post-Analyses (PRISMA), searching in MEDLINE, Embase, Cochrane, PsychInfo, Google Scholar and Scopus. We included studies published in English without time limit. The keywords used in the search were: ((((antipsychotics medication) OR (therapy)) OR (treatment)) AND (perinatal period)) AND (neurodevelopmental disorders), ((antipsychotics) AND (utero exposure)) AND (neurodevelopmental disorders).

The included studies referred to female populations, regardless of age and ethnicity, mothers who had a mental illness before conception or mothers who experienced a relapse of bipolar disorder into postpartum psychosis during pregnancy and received antipsychotic treatment during the perinatal period. Also, the studies concerned children, regardless of their nationality, who were investigated for any neurodevelopmental disorders due to exposure to antipsychotic treatment during pregnancy (neurodevelopmental disorders: mental disability, communication disorders, autism spectrum disorder, attention deficit hyperactivity disorder, learning disabilities and movement disorders). Diagnoses of maternal and/or child mental disorders were based on the following DSM -5, ICD 10, and ICD 11 diagnostic criteria. Studies were excluded from the review, which involved a population of women first ailed or diagnosed with a mental disorder during or after pregnancy (postpartum depression, postpartum psychosis, postpartum depression, anxiety disorders, and major depression) and receiving only antidepressants, anxiolytics, or antiepileptic treatment before or during pregnancy. Also excluded, were studies related to mental disorders in the postpartum period, studies that related to breastfeeding and taking antidepressant, anxiolytic, and antiepileptic medication, and studies with a population sample of substance-using mothers. Finally, with reference to the child's development, studies related to congenital malformations, residual growth, prematurity, neonatal complications/outcomes, and studies investigating the relationship of receiving antipsychotic treatment with perinatal complications, for example gestational diabetes mellitus, were excluded.

The data to be retrieved selected by two independent researchers and any disagreements resolved by a third researcher. The data to be extracted from each article are the main author - the year of publication, the country of the study, the type of study, the time of data collection, the total number of children in the study, the population of children exposed to antipsychotic treatment, the type of treatment (formal and/or informal) and the outcome.

After the final selection of studies and data to be recorded, their quality assessed as it in turn affects the quality and results of the systematic review and meta-analysis. This process was carried out by two independent researchers. It was blinded to the authors, organization and funder of each trial. The review is likely to have included studies that

emerge as citations of the studies from the search. By completing the search and removing duplicate references of studies in the same or different databases, studies were blindly selected by two independent researchers. Initially, the selection of studies was based on the titles and abstracts of the studies, those studies that were not relevant to the issue under study were excluded, as well as those that did not meet all the inclusion criteria or any of the exclusion criteria apply. In a second time, for the studies that were relevant to the topic, or the initial criteria were not sufficient to decide whether to include or exclude, a full reading and study of the articles were carried out. Upon completion of the process, the selected studies were reviewed by a second researcher. In case of disagreement between the two researchers during the selection, a third independent researcher intervened to resolve the problem by including or not the respective study in the review. The flowchart was also displayed.

Meta-analysis was performed, in the case that there were data for at least three studies. The following data were recorded in each study: the number of children who were not exposed to a drug and did not develop a disorder, the number of children who were not exposed to drug who developed a disorder, the number of children exposed to a drug who did not develop a disorder, the number of children who were exposed to a drug and developed a disorder, the total number of children not exposed to a drug, and the total number of children exposed to a drug. In the meta-analysis models, we calculated the pooled odds ratio, the 95% confidence interval (CI), and p-values. Moreover, we calculated the degree of heterogeneity by calculating the I^2 index and the p-value for the Hedges Q statistical test. I^2 values > 75% indicate high heterogeneity and $p < 0.1$ indicates statistically significant heterogeneity (Higgins, 2003). If the heterogeneity was large, the random effects model was used, while when it was small, the fixed effects model was used (Higgins, 2003). In addition, it was also investigated whether there is a publication bias. In this case, the "funnel" plot is presented, and the trim and fill method were used with the presence of absent studies indicating the existence of publication error. Finally, the p-value of Egger's test was calculated with values <0.05 indicating a publication bias (Egger et al., 1997). Meta-analysis was performed with OpenMeta[Analyst] software (Wallace et al., 2009).

Results

Flow Chart

The flow chart of the Systematic Review is shown in figure 1. From the initial search of the literature, 277 articles emerged and applying the criteria, according to the methodology, we identified 15 articles.

Characteristics of the Studies

After searching the literature, we identified 15 studies, involving over 50,000 pregnant women during the perinatal period and monitoring/examining over 9,000,000 children in total. Specifically, the children who were exposed to antipsychotic treatment, during pregnancy, were 344 on atypical antipsychotics and 32,012 children on a combination of typical and atypical antipsychotic drugs.

Seven studies concern exposure to typical and atypical antipsychotics (Hálfdánarson et al., 2021; Johnson et al., 2012; Petersen et al., 2016; Schrijver et al.,2022; Straub et al., 2022; Wang et al.,2021; Wibroe et al., 2017), four studies on atypical antipsychotics (Peng et al.,2013; Shao et al., 2015; Ta-Chuan et al.,2021; Wichman, 2009), three in drug group (Delarue et al.,2016; Janecka et al.,2018; Stika et al.,1990) and one in typical antipsychotics (Dennis et al,1977).

The main diagnoses concerning the mothers were schizophrenia, bipolar disorder, depression, anxiety disorder, schizoaffective disorder and obsessive compulsive disorder. Also, it is worth mentioning that the studies of the last six years examined the possibility of the occurrence of ASD and ADHD as a result of receiving antipsychotic treatment by the mother during the perinatal period (Hálfdánarson et al, 2021; Janecka et al., 2018; Straub et al., 2022; Ta -Chuan et al, 2021; Wang et al., 2021), while there were several that assess cognitive, language and psychomotor development (Delarue et al,2016; Peng et al,2013; Shao et al., 2015; Stika et al,1990; Wibroe et al,2017). Finally, in recent years there has been increasing

interest in the search for a relationship between the mother's antipsychotic treatment and the child's low or high IQ (Dennis et al, 1977; Schrijver et al, 2022; Straub et al., 2022).

Regarding the general characteristics of the studies, four studies were conducted in China, two in the Nordic countries, four in the USA, one in Israel, one in England, one in the Netherlands and one in France. Data collection time varied. In the most recent studies, the time ranged from 1997 to 2016. Finally, most studies were cohort and case control studies, except for 2 studies (Table 1).

Despite differences in methodology, the clinical studies included in the systematic review report adverse neurodevelopmental and behavioral effects due to fetal exposure to antipsychotics.

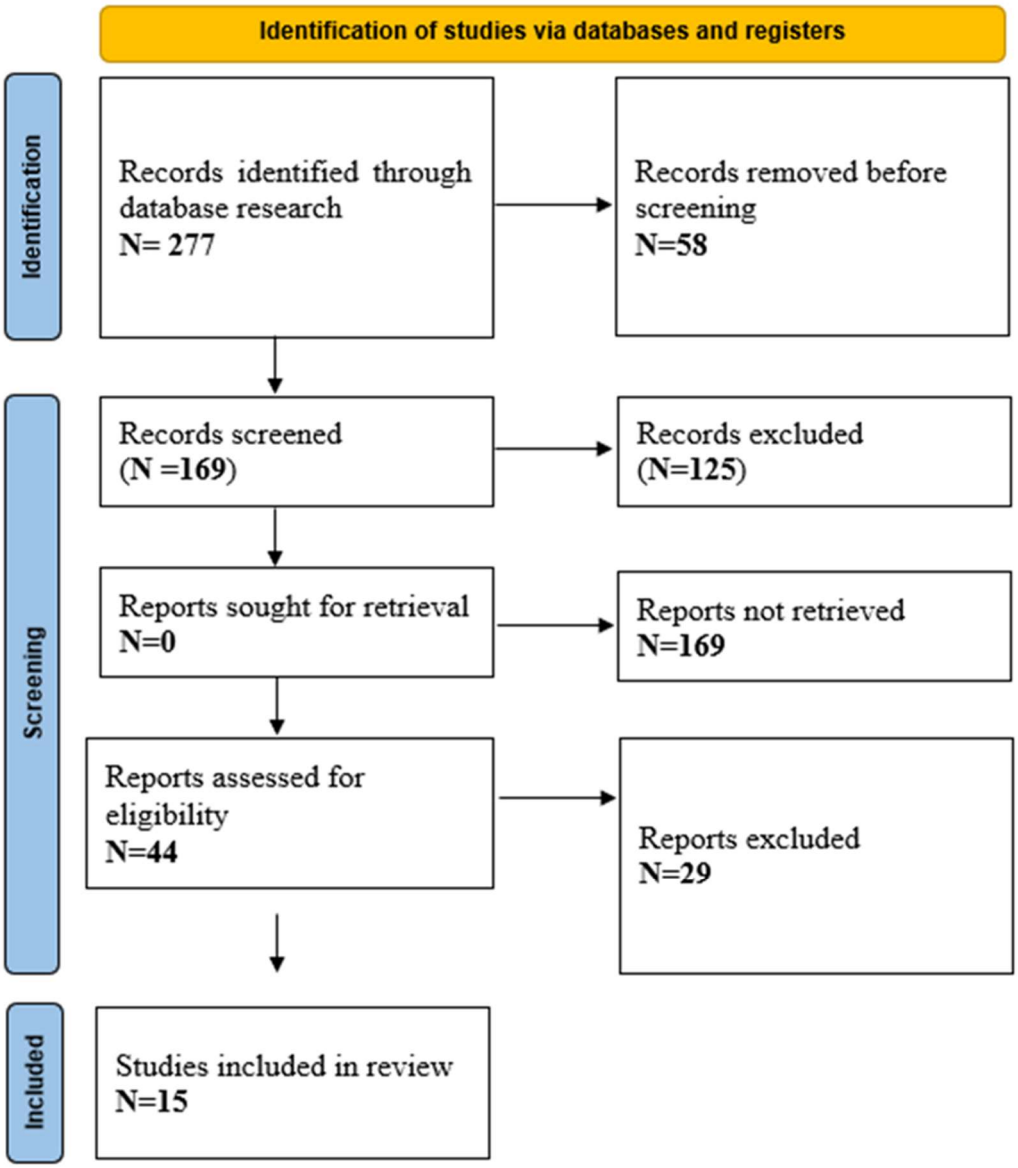

Figure 1. PRISMA flowchart diagram of the systematic review

Table 1. Overview of the studies included in this systematic review.

Reference	Country	Type of Study	Data Collection Time	Sample Size	Number of Exposed Children	Pharmaceutical exposure	Evaluation
Straub et al. **(38)**	USA	Cohort study	2000-2015	3.352.063	10.772	Typical and Atypical antipsychotics (olanzapine, aripiprazole, quetiapine, risperidone and aripiprazole)	Autism, ADHD, Mental Retardation, Learning Disabilities, Speech Disorders, Mood Disorders
Schrijver et al. **(33)**	Netherlands	Cohort study	NR	91	17	Typical and Atypical antipsychotics	Mental retardation, Learning disabilities, Mental development
Ta-Chuan et al. **(39)**	China	Case control study	2002-2011	11.338	188	Atypical Antipsychotics Antidepressants and Mood Stabilizers	Autism and ADHD
Wang et al. **(42)**	China	Cohort study	January 2001-2015	74.500	1.253	Typica and Atypical antipsychotics	Autism and ADHD
Hálfdánarson et al. **(14)**	Scandinavian Countries	Cohort study	Denmark (1997-2017),Finland (1996-2016), Iceland (2004-2017), Norway (2004-2017), Sweden (2006-2016)	4.324.086	15.466	Typical and Atypical antipsychotics	Autism and ADHD
Janecka et al.**(19)**	Israel	Case control, cohort study	January 1997-December 2007	96.270	4.105	Drugs affecting the Central Nervous System (dopamine receptor D2, 5HT2, etc.)	Autism
Wibroe et al. **(43)**	Denmark	Cohort study	1995-2008	868.159	3887	Antipsychotics, anxiolytics, hypnotics	Cognitive and Mental Development
Delarue - Hurault et al. **(9)**	France	Cohort study	July 2004-December 2009	32.796	70	Antipsychotics, anxiolytics, antiepileptics and antidepressants	Psychomotor Development
Petersen et al. **(30)**	England	Comparative cohorts studies	January 1995-December 2012	212.575	595	Typical and Atypical antipsychotics	Muscle tone, tremors

Reference	Country	Type of Study	Data Collection Time	Sample Size	Number of Exposed Children	Pharmaceutical exposure	Evaluation
Shao et al. **(34)**	China	Post-Hoc analysis	October 2007-December 2010	63	63	Atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine)	Cognitive, language, motor, social-emotional development and adaptability
Peng et al. **(24)**	China	Case controlled, prospective study	October 2007-December 2010	152	76	Atypical antipsychotics (clozapine, risperidone, olanzapine, quetiapine and sulpiride)	Cognitive, linguistic, motor, social-emotional and adaptability
Johnson et al. **(20)**	USA	Prospective controlled study	December 1999-June 2008	309	22	Typical (haloperidol) and atypical antipsychotics (aripiprazole, olanzapine, risperidone, ziprasidone)	Muscle tone, posture, reflexes, motor development and visual skill
Wichman **(44)**	USA	Retrospective cohort study	January 1993-December 2007	17	17	Atypical antipsychotics (clozapine, olanzapine, risperidone, aripiprazole, quetiapine, and ziprasidone)	Description of symptoms
Stika et al. **(37)**	Czech Republic	Retrospective case control study	1974-1975	145	68	Neuroleptics	Assessment of school performance and behavior
Slone et al. **(35)**	USA	Cohort study	NR	28.358	2.141	Phenothiazine	Intelligence quote

NR, not reported

Autism and ADHD

Three studies, attempted to investigate the relationship of Autism and ADHD with fetal exposure to antipsychotics. The first study looked at the association between exposure to psychotropic drugs and the offspring's risk of being diagnosed with Autistic disorder and ADHD. Their mothers suffered from bipolar disorder and were or not under treatment with any medication. Exposure to psychotropic medications (atypical antipsychotics, mood stabilizers, and antidepressants) was assessed in the first, second, third trimester, and 3 months prior to pregnancy. According to the study, children who were exposed, during the 3rd trimester, to atypicals were 3.83 times more likely to be diagnosed with ADHD and 5.42 times more likely to be diagnosed with Autism, compared to non-exposed children. Also, regardless of exposure time, a statistically significant relationship was shown between exposure and the development of Autism and ADHD. However, the article does not mention the total number of children exposed to SGAs, whether there was a sample of children exposed only pre- or perinatally, and specifically, to which substance (aripiprazole, risperidone, paliperidone, olanzapine, amisulpride,

clozapine and quetiapine) (Ta -Chuan et al, 2021).

The study by Wang et al (2021) observed children exposed only to antipsychotic drugs and concluded that children born to mothers with a psychiatric disorder had a higher risk of developing ASD and/or ADHD, against children whose mothers did not have a mental illness. Of the 706 prenatally exposed children, 27 were diagnosed with Autism, while of the 547 perinatally exposed, 45 were diagnosed with ADHD. There was no statistically significant difference between prenatal and perinatal exposure in the development of any neurodevelopmental disorder. Finally, according to the study, the risk for ADHD was statistically significantly greater when children were prenatally exposed to antipsychotics, compared to unexposed children. In the same year, opposite results are published. According to a cohort study (Hálfdánarson et al., 2022) of approximately 4,000,000 births, no increased risk of developing Autism or ADHD was found in exposed children. They only highlighted a slightly increased risk estimate for ASD when using atypical antipsychotics, which indicates the need for further investigation.

Cognitive and Language Development

Regarding the evaluation of the Cognitive and Language development of the exposed children, 2 studies were found that included it as a parameter. One study followed a total of 63 children, of which 33 were perinatally exposed to clozapine and the rest to risperidone, olanzapine and quetiapine. Children were assessed at 2, 6 and 12 months of age, based on the Bayley -III scale. No statistically significant difference was observed between the two groups, regarding Cognitive and Language development (Shao et al., 2015). Additionally, another study conducted in China evaluated 73 children who were perinatally exposed to clozapine, olanzapine, risperidone, sulpiride, or quetiapine and 73 children who were not exposed to any drug. The evaluation of Language and Cognitive development was done based on the same scale, at the age of 2, 6 and 12 months. More specifically, according to the study by Peng et al. (2013), at 2 months of age, 18.4% of exposed children had a lower score in the Cognitive Development assessment, compared to non-exposed children (6.6%). In contrast, the number of exposed children with delayed language development did not differ significantly compared to the control group, 12 and 10 respectively. Subsequently, at 6 months, the researchers highlighted that the percentage of infants with delayed Cognitive and Language development did not differ significantly between the two groups, likewise at 12 months.

Adaptability, Socio-emotional and Mental development

First, based on the study by Peng et al. (2013), which was also mentioned previously, at 2, 6 and similarly at 12 months it was found that the percentage of children exposed to atypical antipsychotics who showed a delay in Social-Emotional Development and Adaptability, was higher compared to the control group. However, at 6 and 12 months there was no statistically significant difference between the two groups. In addition, the study by Shao et al. (2015) adds that most infants exposed to clozapine, aged 2 and 6 months, met the criteria for delayed development in Adaptive Behavior, compared to the group exposed to the other antipsychotics. This difference disappeared at 12 months and the rate of delayed social-emotional development did not differ between the two groups at any age. Finally, Wibroe et al (2017). suggested that children exposed to antipsychotics had a higher risk to develop mental retardation compared to children not exposed. It is worth noting that the relative risk increased slightly as the exposure took place at an advanced stage of pregnancy. However, no statistically significant relationship was found, and the categories of antipsychotics administered to the mother were not reported in detail.

The study that examined mental development as a primary childhood outcome due to fetal exposure to antipsychotics is by Delarue et al (2016). The research evaluated a total of 32,796 children, aged 9 and 24 months, of which 493 were exposed to a group of psychotropic drugs, during the 2nd and 3rd trimester. Of the 493 children, 70 were exposed to antipsychotics (chlorpromazine, cyamemazine, and sulpiride). In this study, the motor development of the infants was also

evaluated. According to the article, fetal exposure to antipsychotics was more likely to result to motor deficits at nine months of age compared to no drug exposure (13.9% vs. 6.1%). Also, six of the nine children exposed to chlorpromazine showed some delay in psychomotor development.

Kinetic development

The clinical study by Peng et al (2013) evaluating, at the same time, Motor development as a parameter, observed that at 2 months, the average value of the score, based on the Bayley -III scale, was lower in exposed children, with the result that the percentage of exposed children with delays was significantly higher (19.7% vs. 6.6%). On the contrary, at 6 and 12 months, both the mean values of the score and the percentage of children with motor difficulties did not differ statistically significantly between the two groups. Different conclusions are presented by the study by Shao et al. (2015), which was similar in its methodology to the previous one. The researchers observed that the mean score values and percentage of delayed development of motor skills did not differ between the two groups at 2, 6 and 12 months of age.

One study compared Cohort studies based on whether the mother received antipsychotic medication (typically or atypically) and the time frame of administration. In study A, mothers were treated with antipsychotics. In Cohort B, women discontinued treatment before pregnancy and in Cohort C did not receive an antipsychotic. Thus, it was observed that 6% of women who received antipsychotic treatment, during the 3rd trimester of pregnancy, gave birth to a child who experienced deficits in muscle tone, compared to 4.7% (B) and 2.5% (C). When confounding factors were excluded, there was no statistically significant difference between the comparable studies (Petersen et al., 2016).

Finally, it is worth mentioning the research by Johnson et al. (2012), which evaluated the motor performance of children, aged 6 months, after their in-utero exposure to antipsychotic treatment. The researchers followed a total of 309 children, of which 22 were exposed to haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, etc. and 202 on antidepressant treatment. Children's exposure occurred at a different stage of pregnancy (either during the 1st trimester, or during the 2nd and 3rd trimesters) and were examined based on the Infant Neurological International Battery (INFANIB). Posture, muscle tone, reflexes, motor, and visual skills were assessed. According to the article, infants within utero exposure had significantly lower INFANIB scores (mean = 63.86) than infants exposed to antidepressants or no medication. However, the small sample size provides significantly limited statistical power. Thus, given the limited sample, the researchers sought to compare the effect of exposure to atypical and typical antipsychotics. They highlighted a modest but non-significant difference, with adjusted means indicating lower scores in children exposed to atypicals (average = 62.9), versus children exposed to 1st-generation antipsychotics (average = 67.1).

Meta-analysis

Figure 2. We found three studies that investigated the relationship between the children in utero exposure to antipsychotic medication and the onset of ADHD (Figure 2), with a pooled odds ratio of 2.33 (95% CI = 1.69 – 3.20, $p<0.001$). This suggests that drug-exposed children were 2.33 times more likely to develop ADHD than non-exposed children. Also, the heterogeneity in the meta-analysis was large ($I^2=78.8\%$) and statistically significant ($p=0.009$).

Figure 3. The “funnel” plot for estimating publication error indicated that publication error was present, with the trim and fill method indicating that a study was missing (Figure 3). Finally, Egger's test p-value confirmed that publication error existed ($p=0.043$).

Figure 4. Funnel plot for estimating publication error in studies in which children were exposed to drugs and developed ADHD. Three studies were identified that examined the delay in socio-emotional and mental development due to in-utero exposure to antipsychotic medication (Figure 4). The pooled odds ratio was 2.33 (95% CI = 1.68 – 3.22, $p<0.001$) indicating that children exposed to antipsychotic drugs were 2.33 times more likely to have delayed social-emotional and mental development than the unexposed children. There was low

heterogeneity in meta-analysis (I^2=24.3%, p=0.027).

Figure 5. The funnel plot for the estimate of publication error suggested that there was publication bias with the trim and fill method indicating that a study was missing (Figure 5). Egger's test p-value confirmed publication bias (p=0.041).

Figure 7. Finally, the meta-analysis of the studies in which the children were exposed to antipsychotic treatment and showed a delay in motor development is presented in Figure 6. A total of three studies were found with a pooled odds ratio of 2.93 (95% CI = 1.86 – 4.61, p<0.001), highlighting that children exposed to antipsychotics were 2.93 times more likely to have delayed motor development than children not exposed. There was no heterogeneity in meta-analysis (I^2=0%, p=0.76). The "funnel" plot for the estimate of publication error suggested that there was no publication bias, with the trim and fill method demonstrating that no study was missing (Figure 7). Furthermore, Egger's test p-value confirmed no publication error (p=0.17).

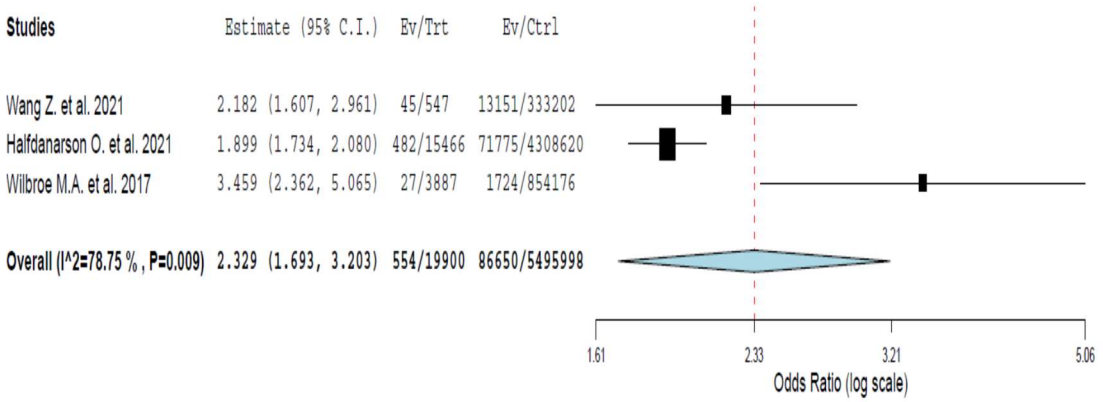

Figure 2. Meta-analysis of studies in which children were exposed to antipsychotics and developed ADHD

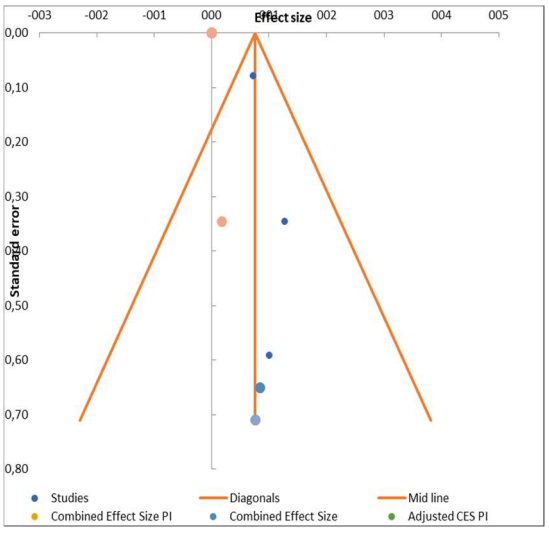

Figure 3. Funnel plot for estimating publication error in studies in which children were exposed to drugs and developed ADHD

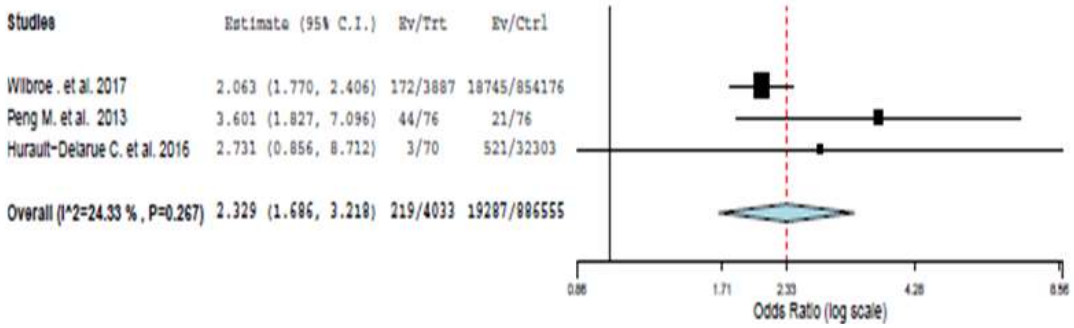

Figure 4. Meta-analysis of studies in which children were exposed to drugs and showed delay in Social-emotional and Mental development.

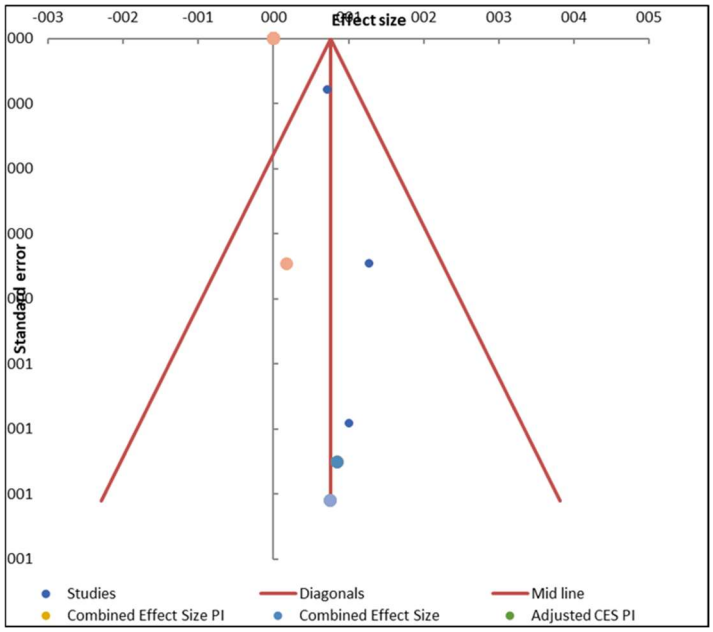

Figure 5. Funnel plot for estimating publication error in studies in which children were exposed to drugs and had delayed Social-Emotional and Mental Development.

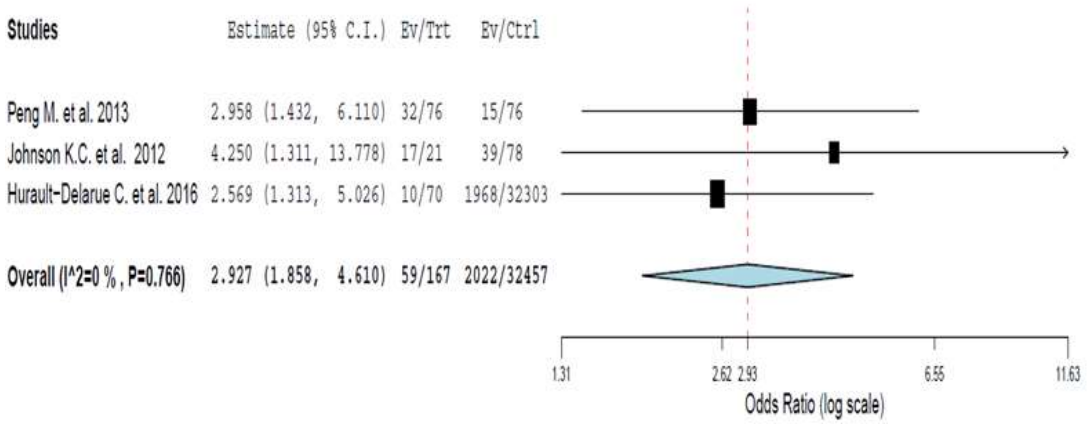

Figure 6. Post-analysis of studies in which children were exposed to drugs and showed delayed motor development.

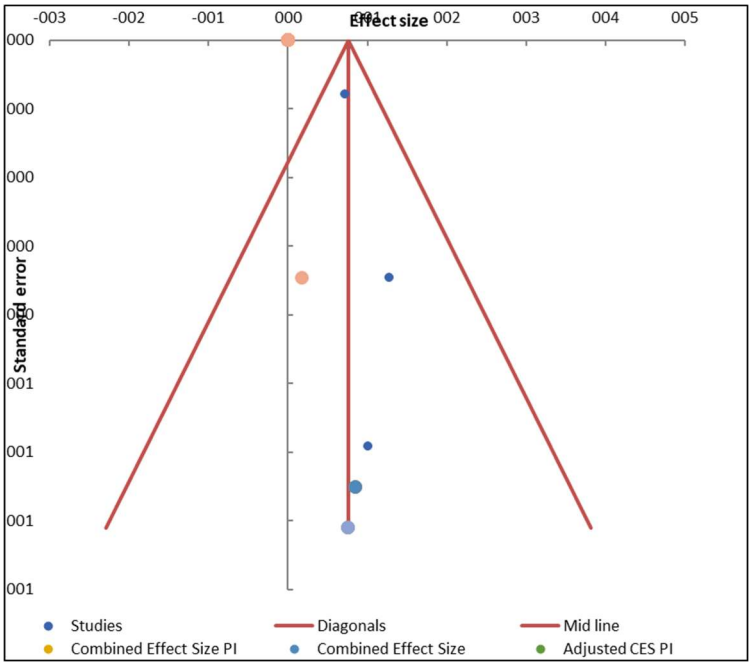

Figure 7. Funnel plot for estimating publication error in studies in which children were exposed to drugs and had delayed motor development.

Discussion

In this systematic review and meta-analysis, we present an overview of the current literature on the long-term neurodevelopmental effects of perinatal exposure to antipsychotic medications. Our interest was limited to human clinical studies. Little information is available on neurodevelopmental teratogenicity since pre-clinical studies in animals highlights this risk. On the other hand, longitudinal studies, which assess in humans the same association as us, face high challenges in drawing conclusions, as they require large cohort studies over long periods of time, resulting in the possibility of confounding factors. It is worth noting that until recently, the available data came mainly from case reports and small case series.

Furthermore, during the search of the literature, we noticed that the interest in investigating this relationship has grown substantially in recent years, as most studies had focused on the relationship of antidepressants and mood stabilizers, especially SSRIs and lithium, with the appearance of a neurodevelopmental disorder in the child (Andrade,2022; Fatima et al.,2018; Jordan et al.,2022; Liew et al., 2023; Poels et al.,2018). Finally, studies that investigated the same concern as ours were observed not to focus only on antipsychotic drugs (typical and/or atypical). Instead, they look at groups of psychiatric drugs, such as anxiolytics, antidepressants, anticonvulsants, mood stabilizers, and antipsychotics.

The most common way to collect data for these studies is through medical records and prescribing record systems. There are few studies that monitor the course of pregnancy and the outcome because they are time-consuming and many children are "lost" in the follow-up, as well as in many cases the design of the study does not meet the rules of Ethics and Deontology, due to "sensitive population" issues.

Neurodevelopmental disorders, which have been associated with maternal antipsychotic treatment during the perinatal period, are mainly Autism and ADHD (Hálfdánarson et al, 2021; Janecka et al., 2018; Straub et al., 2022; Ta -Chuan et al, 2021; Wang et al., 2021). At the same time, the most recent studies emphasize both mental retardation, and the acquisition of learning difficulties and speech-communication disorders, after prenatal exposure of children to antipsychotic treatment (whether formal or atypical). However, there are several studies that generally investigated the linguistic, cognitive, and socio-emotional development of the child, based on developmental milestones (Delarue et al,2016; Peng et al,2013; Shao et al., 2015; Stika et al,1990; Wibroe et al,2017). In contrast, there is a small number of studies that exclusively investigate movement disorders and mainly concern younger ages (newborns or months old).

Our meta-analysis showed a significant association between prenatal exposure to antipsychotics and an increased risk of adverse outcomes in the child related to attention deficit hyperactivity disorder, social-emotional-mental development and motor delay. Although we believe that the current data are insufficient to conclude that antipsychotics in the perinatal period cause increased morbidity, these results highlight that women receiving antipsychotic drugs in the perinatal period represent a population at higher risk for adverse outcomes for their children. Our findings, therefore, come to complement those of recent studies, suggesting that women with mental illnesses such as Schizophrenia and Bipolar disorder and taking antipsychotic drugs at the same time, have an increased risk of negative effects on neurodevelopment of their children.

Limitations: Our study is subject to some limitations. Data taken from databases may not provide the most up-to-date evidence. This limitation is of particular importance in the present review, as the data have been constantly increasing. Moreover, data collection time among studies ranged from 2021 to 2022 whereas evidence regarding safety and efficacy of antipsychotics in pregnant women has been significantly increasing on an ongoing basis. Thus, we should interpret the results of this review with care because they may not directly predict the future behavior of pregnant women.

Conclusions: Managing mental disorders during pregnancy is demanding. There is a need to balance maternal well-being considering the risk of later adverse outcomes to the child due to exposure, and ideally should be based on evidence-based research. The long-term neurodevelopmental outcome after in utero exposure to antipsychotics is not yet fully understood, as most of the cases deal with drug combinations. Furthermore, we lack sufficient data on the impact of substance use and potential interactions with genetic and environmental factors.

In addition, the findings of our study identify a subgroup that may benefit from additional guidance, proper information, and follow-up by Medical and Nursing staff, thereby avoiding the risk of relapse and hospitalization, maternal non-compliance with medication, and the risk of self-destructive or hetero-destructive (mainly towards the newborn) behavior. However, we do not believe that the data are sufficient to

draw final conclusions regarding a causal relationship between antipsychotic exposure and adverse outcomes.

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