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Neurodevelopmental Abnormalities in Children Associated with Maternal Use of Psychoactive Medication

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Abstracts

Background: Due to its negative effects on the unborn child and the mother as a consumer, pregnant women's intake of psychoactive substances has become a public health concern. Additionally, consuming these chemicals has been linked to several neurological development changes in children, including behavioral issues (such as attention deficit hyperactivity disorder and autism spectrum disorder), cognitive issues, and sensory and motor function changes.

Objectives: To perform a thorough, comprehensive study of the neurodevelopmental problems in children linked to maternal drug use.

Method: A search of the scientific literature on studies about neurodevelopmental abnormalities linked to maternal use of psychoactive medications during pregnancy and published in the previous ten years up to June 2022 was conducted from PubMed, Google Scholar, and Directory open access Journals.

Results: The initial screening identified 380 articles. We excluded 50 unaccessible articles and 160 articles due to publication dates and study types; after that, 62 articles were also discarded because they were duplicates, and 68 were excluded because the information was irrelevant or systemic reviews, so we finally obtained 40 articles for full-text reading distributed as follows: 18 from PubMed, 12 from Directory Open Access Journal, and 10 from Google scholar

Keywords: Child Development, Attention Deficit Disorder, Autism Spectrum Disorder, Neurodevelop-

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mental Disorders

Introduction

The use of psychoactive substances during pregnancy is a risk factor for both the mother and the child. Although their use is likely underestimated, their combined use is becoming more frequent [1].

The prevalence of psychoactive substance use is increasing, which is why it has become a public health problem that requires priority attention. Colombia is no stranger to this situation, and in the reports of the 2019 National Survey on the Use of Psychoactive Substances, it was found that 84% of those surveyed were alcohol consumers; 33.3% from tobacco; 1.8% from tranquilizing drugs; 8.3% marijuana; 2.1% from cocaine, and 1.6% from inhalable substances [2].

The consumption of psychoactive substances is a public health problem because it impacts economic and social development and increases healthcare costs because it can lead to more than 60 infectious and chronic diseases [3,4]. Likewise, this situation in the case of pregnant women can have significant effects on the cognitive development of the fetus, with a delay rate that can double during the first two years of life [5], in addition to producing growth alterations and abnormalities in behavior [6]. This is because these substances cause a teratogenic effect that influences fetal development and the responses of the fetus in the uterus, with medium and long-term consequences. These substances include alcohol, tobacco, and drugs, which can influence fetal behavior and cause the development of various pathologies [7].

In the specific case of maternal alcohol consumption during pregnancy, it has been detected that children exposed to it have deficits in the hippocampus, frontal lobe, corpus callosum, and basal ganglia, sometimes manifesting with mental disability; learning, memory, and problem-solving difficulties; attention deficit hyperactivity disorder (ADHD), among others, which are part of syndromes associated with neurodevelopmental disorders [8].

Neurodevelopment is a dynamic interaction process between the child and the environment that favors the maturation of the nervous system and the development of brain functions [9]. This type of development, which is complex, begins very early in life and continues for several years after birth; it has critical periods such as intrauterine life and the first year of life and goes through different stages that are not consecutive but rather overlap and are influenced by the external or internal environment [10]. This environment is considered harmful if the mother consumes psychoactive substances during pregnancy [11].

In this way, the consumption of psychoactive substances is considered a critical risk factor for neurodevelopment. It, therefore, has consequences such as congenital damage, motor, cognitive, and language deficits, and social and

emotional problems [12]. In this regard, Tillman *et al*. [13] suggest that inappropriate habits and practices during pregnancy, such as the consumption of psychoactive substances, have consequences for anatomical and physiological alterations of the fetus. Other authors affirm that substances such as cocaine usually have secondary effects on neurodevelopment, such as malformations at the brain level and changes in intrauterine growth and development. However, this is also accentuated because users often combine it with alcohol or other illegal substances [14,15].

Cannabis (marijuana) is another frequently used and controversial psychoactive substance due to its medicinal use [16]. Although a linear association between its consumption and the effects on maternal and fetal health has not been established, some systematic reviews and meta-analyses find an association with neonatal disorders, such as low birth weight, and neurodevelopmental disorders, such as conditions visual, memory, reasoning, expression, and verbal comprehension, as well as some related to impulsivity and hyperactivity [17].

This article results from a systematic qualitative review that sought to answer the PICO question: What neurodevelopmental disorders are most frequently related to exposure to psychoactive substances during the fetal period?

Methods

This systematic review was carried out using articles indexed in Google scholar, PubMed, and Directory Open Access Journal, databases; we excluded old or duplicated articles. The information search was carried out by three researchers who worked independently; when there were differences between them, they were resolved by consensus. In addition, an evaluation of the methodological quality of the studies was carried out using the STROBE guide for observational studies.

The MeSH terms used in the search were "drugs used in pregnant," "Central Nervous System, "psychoactive substance in pregnancy "," "Substance-Related Disorders," "Motor Skills Disorders," "Drug use disorders," and "Growth and Development." "disorder," which was combined with the boolean operators "AND" and "OR"; also, filters were applied.

Cohort, longitudinal and observational studies published in English were included and carried out in children and adolescents between 2 and 18 years of age who presented neurodevelopmental disorders such as psychomotor disorders, perceptual-motor skills disorders, language disorders, memory and behavioral disorders, and whose mothers had used psychoactive substances (alcohol, cannabis, cocaine, among others) during pregnancy.

We excluded; duplicated or unreliable articles, Systematic reviews, studies in children with congenital disorders not associated with maternal

use of psychoactive substances, studies without a control group, and those whose response to the PICO question did not contribute to this study's objective.

Data analysis

After collecting and reviewing the information independently, three researchers did the respective reading. They evaluated the methodological quality of the full texts of the pre-selected articles according to the Prime guide.

Results

Description of the studies

Search Results: The first search of the databases identified 380 articles (180 in PubMed, 150 in Directory Open Access Journal, and 50 in Google scholar), of which we excluded 50 unaccessible articles then 160 articles were also excluded due to publication dates and study types; Of the 170 that obtained, 62 were discarded because they were duplicates and 38 also excluded because the information is not relevant Of these, 30 were excluded because they were systematic reviews, did not have a control group, and had outcomes different from those required by the PICO question, so we finally obtained 40 articles for full-text reading distributed as follows: 18 from PubMed, 12 from Directory Open Access Journal, and 10 from Google scholar as shown in figure 1.

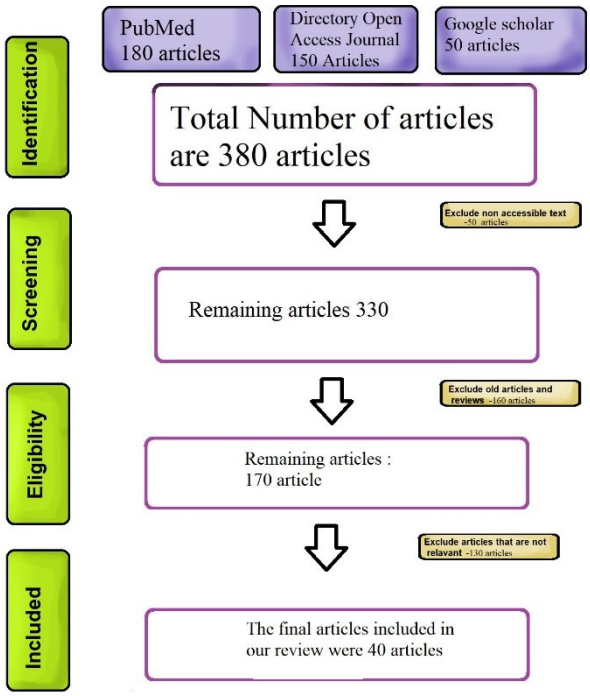

Figure 1 illustrates the included and excluded articles selection

The selected articles presented the research results in Australia, Canada, the United States, the United Kingdom, and Sweden. They included 2,314,505 children/adolescents between 2 and 18 years of age.

Methodologically, it was found that three studies were cohort studies, one was a longitudinal study, and three were retrospective cohort studies designed to analyze the presence and relationship between exposure to psychoactive substance use during pregnancy (alcohol, cannabis, cocaine, opioids, and tranquilizing drugs) and alterations in the neurodevelopment of the exposed population. The outcomes in all the studies refer to developmental disorders manifested in

changes in behavior, psychomotor skills, language, and perceptual-motor skills.

Evaluation of quality and risk of bias: it is highlighted that after the review with the STROBE guide (used because it is about observational cohort studies), some weaknesses were evidenced, such as that the retrospective cohort studies were subject to the data provided by the entities in charge of protecting the information; in others, the diversity of the population observed and its origin could also constitute a weakness. However, the authors clarify this point later in the study's limitations, giving pertinent recommendations for future work.

Heterogeneity analysis found that the studied protocols differed in population selection, the instruments used for measurement, and the substance(s) to which the study population had been exposed. Regarding the outcome, one study measured performance, four established an association between the variables analyzed, and two established the prevalence and incidence of neurodevelopmental disorders in exposed subjects, all agreeing that the abuse of psychoactive substances in the prenatal period constitutes a risk factor for normal child development.

Exposure substances: the exposure substances in the fetal period identified in the study were alcohol, cannabis, cocaine, and general and serotonergic antidepressants, which caused consequences in the formation of the brain and generated short and medium-term manifestations in the affected [17].

Outcome: the use of antidepressants was related to the presence of autism spectrum disorder (ASD); in this regard, Skogheim *et al* . [18] established the association between the use of antidepressants during the first trimester of pregnancy, on the one hand, and birth complications and neurological development disorders of the product, on the other. For their part, Doney *et al*. [19,20], a retrospective cohort study conducted with 35,906 single births, found that 2,837 mothers (7.9%) used antidepressants and that 2.0% (95% CI: 1.6 -2.6) of the children of these women were diagnosed with ASD. Thus, the authors found that the incidence of ASD was 4.51 cases per 1,000 person-years among children exposed to antidepressants versus 2.03 cases per 1,000 person-years among unexposed children.

Regarding alcohol use and fetal alcohol spectrum disorder (FASD), Doney *et al* . [20] found an association between this disorder and poor performance on the Beery-Buktenica Test of Visual-Motor Integration Development (VMI): mean VMI scores were "below average" (M=87.8±9.6) and visual perception scores were "average" (M=97.6±12.5), with no differences between groups. The researchers also found that few children had severe VMI impairment (1.9%). Still, rates of moderate impairment were high (47.2%), and children with FASD had significantly lower acceptable motor coordination scores and higher

rates of mild impairment (M=87.9±12.5, 66.7%) than children without learning disabilities (M=95.1±10.7, 23.3%) and with learning disabilities (M=96.1±10.9; 15.4%), but without FASD. Other authors, such as Mukherjee *et al*.[21], a study involving 99 people with FASD found that 74% had ADHD (p=0.924), while 68% had ASD (p=0.742).

Other substances such as cocaine, cannabis, and opioids were also identified in this review as having a risk for fetal neurodevelopment. Cocaine, for example, according to the findings of Bennett *et al*.[22], can affect language development, specifically syntax and phonological understanding; These authors also found that exposure to this alkaloid harmed the results of the applied tests since the mean performance scores in phonological awareness were affected (t=2.38; p=0.02), in elision (t=2.51; p=0.01) and the blending words subtests (t=1.98; p=0.05).

Opioids are other substances whose consumption during pregnancy constitutes a risk factor. In the study by Azuine *et al* . [23] , For example, it was found that exposure to this type of medication was associated with higher risks of fetal growth restriction (OR: 1.87; 95% CI: 1.41-2.47) and preterm birth (OR: 1 .49, 95% CI: 1.19-1.86). These authors also found an association between a said variable and a higher risk of lack of expected physiological development (OR: 1.80; 95% CI: 1.17-2.79) and behavioral disorder/emotional disturbance (OR: 2.13;95% CI: 1.20-3.77). In school-age children, opioid exposure was associated with an increased risk of ADHD (OR: 2.55; 95% CI: 1.42-4.57).

Lastly, regarding prenatal exposure to cannabis, Corsi *et al* . [24,25] found an incidence of ASD of 4 cases per 1,000 people per year in exposed children, compared to 2.42 cases per 1,000 people in unexposed children. The adjusted risk was 1.51 (95% CI: 1.17-1.96).

Discussion

The consumption of psychoactive substances during pregnancy is a public health problem that not only impacts the pregnant consumer and health services due to the costs it generates but also compromises the child's development from intrauterine life to adolescence, which is considered to cause short, and medium, and long-term affectation.

This study identified that pregnant women's most frequently used substances were alcohol, cocaine, cannabis, and tranquilizers. Still, it was also found that some pregnant women used them in combination. In this regard, Qato [26] stated that the consumption of alcohol cannabinoids persists during pregnancy, and this will cause several dangerous effects on the fetus, as also described by Faherty *et al*.[27], and suffering from neonatal abstinence syndrome, which is characterized by a set of symptoms and signs of hyperexcitability that occur as a consequence of

the cessation of the supply of addictive substances, according to Al-hussainy *et al*.[28].

The development of behavioral disorders such as ASD and ADHD are the main findings in studies on children exposed to substances such as cocaine during pregnancy. Carlier *et al* . [29] considered that these pregnancies have a high risk for both the mother and the fetus, firstly because they generate a higher risk of spontaneous abortion and secondly because they have consequences for child development, such as growth and cognitive disorders (problems of attention, memory and motor skills). These authors also established that combining psychoactive substances and potentiating the risk makes it difficult to measure the consequences of each of the implications on child development.

Studies such as the one by Bayrampour *et al* . [30] confirmed that cannabis use has consequences on neurological development, which can occur from intrauterine to the first years of life. Likewise, El Marroun [31] considers that further research should be carried out in this regard, as they state that the evidence shows the association between the consumption of this substance and the development of neurological problems in children, expressed in ADHD, poor cognitive function, and TORCH.

Some antidepressants were associated with disorders in child development in the present work. In this regard, Young-Wolff *et al.* [32] affirms that depression before, during, and after pregnancy, by itself, constitutes a risk for the development, in children, of cognitive and behavioral disorders such as ADHD. Therefore, it should be taken into account—special care with antidepressants is used for its management due to the possible consequences on child development. Likewise, Morales *et al.* [33], A systematic review of observational studies also found an association between exposure to antidepressants and the appearance of ASD and ADHD. Therefore, it should be considered a risk factor for the development, as has been done in multiple investigations [34-36].

FASD has been widely studied for its short, medium, and long-term impact on those who suffer from it. For example, May *et al.* [37] stated that in the West, the prevalence of this pathology is greater than previously thought. Other studies have established that in addition to behavioral and learning disorders [37], FASD has been associated with sensory-motor alterations and changes in fine and gross motor skills in children exposed to alcohol during pregnancy [38-40].

One of the limitations of this research is related to the design of the different studies, which included multiple measurement instruments and had a great diversity of variables to study.

Conclusions

The different studies included for analysis in this study establish a relationship between the usage of psychoactive medications in pregnant and the

presence of alterations in the development of children as a result of said pregnancies that must be taken into consideration and that indicate that it is necessary to continue advancing. In this type of research, the existing ones are primary studies with different designs and systematic reviews. Likewise, since this is a public health problem that affects the development of children, work must continue on programs to promote and prevent the use of psychoactive substances, with a particular interest in pregnant women.

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