Neuropsychiatric disturbances in patients under 18 years of age exposed prenatally to opioids: A Literature Review.

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ABSTRACT

Opioid consumption has increased greatly in recent years, creating a public health crisis that affects all types of population. The use of illegal opiates amongst pregnant women has also risen, causing a surge in the frequency in which adverse neonatal outcomes, such as Neonatal Abstinence Syndrome (NAS), are seen in clinical practice. Furthermore, children exposed prenatally to these substances have cognitive, motor and psychiatric adverse outcomes throughout their lifetime. This article's objective is to provide an updated literature review about opioid use during pregnancy and its consequences on children exposed in-utero.

Key words: *Neurodevelopmental Disorders, Prenatal Education, Prenatal Exposure Delayed Effects, Pregnancy.*

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INTRODUCTION

The consumption of illegal and prescription opioids is increasing, and it has become an epidemic crossing socio-economic and demographic barriers. Furthermore, the use of these substances during pregnancy is also on the rise. An American study found that 1 in 5 pregnant women on Medicaid insurance used opioids during pregnancy, 2.5% of which received a prescription for more than 30 days. This increment in the prevalence of opioid consumption during pregnancy has led to a rise in the rate of adverse neonatal results, including neonatal abstinence syndrome (NAS).[1,2]

Following an extensive search in multiple databases (Pubmed, ScienceDirect, and Scielo), we found no literature reviews that encompassed globally and by growth and pediatric developmental stages the different neuropsychiatric disturbances that can present in children exposed prenatally to opioids.

This review aims to fill the literary gap in this area and provide a summary of the motor, psychiatric and neurocognitive disturbances that can appear in children under 18 years of age with a history of prenatal opioid exposure.

Opioid pharmacology

The endogenous opioid system consists of a family of three types of opioid neurotransmitters, known as endorphins, enkephalins, and dynorphins, which derive from the cleavage of different precursor peptides. Endogenous opioids interact with three transmembrane G protein-coupled receptors: MOR, DOR, and KOR. These receptors are distributed throughout the whole nervous system, both central and peripheral, and their functions in the latter include generating inhibitory responses to painful stimuli and regulating gastrointestinal, endocrine, and autonomous functions.[3,4]

Opioid drugs are divided into three groups: natural, synthetic, and semisynthetic. They are widely used in clinical practice for the treatment of postoperative pain and as an analgesic component of anesthesia; however, their use for the treatment of non-oncologic pain has been questioned, given their potential to generate dependence and addiction.[3,6]

Regarding the effect of the exposure to exogenous opioids during fetal development, it has been proven that these drugs cross the placenta and can act on fetal endogenous opioid receptors, which appear during pregnancy for the modulation of pain and pleasure.[4,5]

Overview of neurodevelopment, pregnancy, and childhood

Fetal neurodevelopment is a complex process involving various genetic and environmental factors. Different studies have shown that the activity of the endogenous opioid system has an influence on critical phases of neurodevelopment. For example, the activation of opioid receptor Mu regulates the proliferation of neural progenitor cells, particularly in the dorsal telencephalon.[7,8]

Neuronal proliferation and migration occurs mainly during the first half of pregnancy. In contrast, the second half is characterized by glial proliferation and apoptosis, as well as the sprouting of axons and dendrites and the formation of synapses. The connections between different brain regions as functional networks and their myelination start in the third trimester and continue throughout the first year after birth.[9]

There is a wide variety of environmental factors that can affect neurodevelopment. Some situations that cause maternal stress during pregnancy, like emotional stress, anxiety, depression symptoms, and substance abuse, correlate with specific effects in the offspring's brain function, its hypothalamic-pituitary-adrenal (HPA) axis, autonomous nervous system, immune system, among others.[7,10,11]

Moreover, neurodevelopment continues in postnatal life, which is why environmental factors after pregnancy can affect development at this stage too.[12]

Pathophysiology

The endogenous opioid system is crucial for the regulation of neurogenesis. Its function in the

central nervous system (CNS), specifically in limbic areas, is involved in mood regulation, reward processing, and indirect regulation of the HPA axis, which controls hormones related to stress.[7,9,10]

A study carried out in rodents showed that prenatal exposure to morphine decreased Brain-derived neurotrophic factor (BDNF) levels, which strengthens neuroplasticity. At the same time, a pregnancy in an optimal environment had a positive effect on such levels. Low BDNF levels are associated with the development of Attention-Deficit/Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD), and depression.[11,14,15]

The structures most affected by the excessive consumption of exogenous opioids include white matter, basal ganglia (putamen and globus pallidus), and the inferior lateral ventricle. Certain studies suggest that the most specific alterations to white matter in children exposed to opioids since the embryonic period could be related to induced apoptosis in neurons and the microglia. Investigations carried out with the use of Magnetic Resonance Imaging (MRI) in children aged 9-14 years exposed prenatally to opioids, found differences in white matter in multiple cortical association sites like the superior and inferior longitudinal fasciculus. They also reported smaller regional brain volumes in the amygdala, cortex, thalamus, nucleus accumbens, putamen, globus pallidus, brainstem and cerebellum. Nonetheless, it is worth mentioning the results of other studies which did not find significant differences in neuroanatomic volumes, nor in thickness, area, cortical volume or general neurocognitive performance.[13,16,17]

Another study carried out in pregnant rats concluded that daily administration of low to moderate doses of opioids did not interfere with pregnancy results, but it produced dependent offspring which suffered from NAS and had disturbances in their response to stressful factors in the late neonatal period and adult life, showing that prenatal exposure to opiates can generate changes in stress response and anxiety-like behaviors.[18]

Moreover, opiates interfere with the GABA system, which can influence the balance of excitatory and inhibitory signals, leading to an excessive excitation, which can be a mechanism of cell injury and death. Likewise, they can compromise the expression of proteins in neuronal plasticity in both positive and negative ways. Other findings involve the effect of opioid peptides such as enkephalin, which is associated with depression in fetal DNA synthesis.[19,20]

Furthermore, fetal gender may greatly influence the effects of exposure to illicit substances and alcohol during the late prenatal development period, partly because of prior differentiation of the male body and brain due to testosterone, differences in postnatal metabolism and possible genomic effects.[21]

Effects in children

The effects of prenatal opioid exposure in children under 18 years of age are diverse and depend on the duration of exposure, dose, type of opioid, and the mother's pathologic and toxicologic comorbidities.

For practical purposes this section will be divided by pediatric age ranges.

Neonates: 0-28 days of life

Regarding cognitive development, a systematic review of 26 cohort studies reported lower neurocognitive test scores in neonates with in-utero opioid exposure compared to controls. Motor development is similarly influenced by exposure to opioids and other substances, with infants with simultaneous exposure to opioids and cocaine showing poorer quality of movement, greater hypertonicity and poor quality reflexes.[11,22]

In the physical examination of the newborn it was found that exposed neonates presented smaller head circumference than their peers. This alteration seemed to be influenced by the presence of NAS. In children diagnosed with NAS the effect persisted until school age, while in exposed children that were not diagnosed with NAS it normalized at approximately 6 months of age. For this reason,

timely diagnosis and treatment are essential at this stage, since long-term results depend to a large extent on this. Additionally, a relationship has been found between prenatal opioid exposure and low birth weight, small for gestational age, and preterm delivery.[5,14,19,23,24]

It has also been demonstrated that the autonomic function of exposed neonates, measured by the presence of respiratory sinus arrhythmia and heart rate, is negatively altered in children with concomitant exposure to opioids and cocaine compared to other exposure groups showing higher heart rate and lower respiratory sinus arrhythmia in these neonates, which demonstrates a lower parasympathetic control in relation to the environment. Likewise, several articles have demonstrated a relationship between opioid exposure and changes in the characteristics of crying which suggest alterations in different mechanisms such as CNS reactivity (threshold, latency), respiratory control (energy, dysphonation and vocal expressions) and neural control of the vocal tract (fundamental frequency, hyperphonation). In the "Maternal Lifestyle Study" it was evidenced that in neonates exposed to opioids, there were fewer short vocal expressions and more hyperphonation, and that these effects were maintained even after controlling for other variables; likewise, greater energy and fundamental frequency were observed in children with prenatal co-exposure to cocaine and opioids.[11,25]

Infants: 1-24 months old

The literature has also reported cognitive alterations in children with prenatal opioid exposure up to two years of age. In children exposed to medically assisted therapy (MAT) for opioid-dependent pregnant women, there were some differences found in the sensory profile (sensation seeking behaviors, sensory sensitivity and sensory avoidance) and self-regulation in the still face paradigm experiment, a scale used to measure the infant's positive or negative affect in response to maternal facial expression.[8,9]

In behavioral development, it has been demonstrated that opioid-exposed infants, when compared to unexposed controls, had a tendency to form attachments and an attachment style at an earlier age. However, this has not been shown to influence the type of attachment that may develop. Similarly, it has been found that children prenatally exposed to methadone are more at risk of presenting disorganized behavior, seeking and maintaining less contact and presenting a greater number of avoidant behaviors. On the other hand, a 2014 systematic review and meta-analysis did not find significant alterations in the cognitive, psychomotor, or behavioral domains in infants exposed to heroin or methadone, although a tendency to poorer results in these was evidenced. Likewise, in terms of motor development, a 2019 meta-analysis showed that children with prenatal opioid exposure scored lower on motor tests than controls. This contradicts the results of the Maternal Lifestyle Study, which found that despite evidence of a psychomotor deficit in exposed infants, this was not significant after controlling for existing covariables.[22,26,27,28]

Preschoolers: 2-6 years old

In a systematic review that included children aged 1 to 60 months with at least two months of methadone-assisted therapy during pregnancy, the cognitive scores of the group with and without opioid exposure were compared and lower performances were found in the exposed group, being important to note that this did not necessarily indicate developmental delay. At 36 months of life, those who had had in-utero exposure to methadone or buprenorphine were found to have normal scores on tests of cognition, sensory processing and behavior, but this was not compared with any control group.[29,30]

When language was assessed by the Preschool Language Scale-Third Edition, 60% of the in utero drug-exposed preschool group had lower scores on the expressive language subscale, compared with 33% of the unexposed children, but not on receptive language. When they tested the Bracken Basic Concept Scale-Revised, which assesses school reading, it resulted in significantly higher scores in the unexposed group, while 40% of the in-

utero drug-exposed children scored lower than the controls. Relevant differences in attention found using the Gordon Diagnostic System on the Delay Task Efficiency ER percentile reflect lower impulse control in the exposed group. However, in the evaluation with the Knox Cube Test raw score, the control group had lower visual attention time. Likewise, the use of the Stanford Binet scale did not show a significant difference in general intelligence between the groups exposed and not exposed to opioids in utero, as well as other aspects that do not seem to be significantly reduced in the exposed group, such as visual control, manual dexterity and sustained attention. On the other hand, children exposed to opioids prenatally, during their first 6 years of life were diagnosed in a higher percentage with an emotional or behavioral disturbance and did not show an expected normal physiological development.[7,14]

A 2014 meta-analysis showed no significant disabilities in cognitive, psychomotor, or behavioral outcomes for infants and preschoolers who have been chronically exposed to opioids, but did find a trend toward poorer outcomes in all categories. The results were limited by the few studies analyzed, the heterogeneity of the population, and the few subjects analyzed in the papers. Contrastingly, a 2015 meta-analysis revealed defects in working memory, impulsivity and cognitive flexibility. Following these results, another study described deficits in executive function (cognitive flexibility, strategic planning and decision making), assessed by neuropsychological tests. Those exposed also scored worse in short-term memory and inhibition tasks.[27,30]

Results from longitudinal studies show that children fail to normalize their impairments over time, regardless of having an appropriate environment. Likewise, the effects of exposure could be sex-dependent, with males being more affected than females up to 4 and a half years of age; from this period up to 8 and a half years of age, exposed girls do differ from the control group.[31]

School-age children: 7-12 years old

Davis & Templer explored cognitive function in a group with methadone exposure, and found lower functioning and IQ scores compared to the control group. Furthermore, lower IQ scores were found secondary to exposure to opioids, compared to isolated exposure to cannabis or tobacco. In addition to presenting a higher percentage of ADHD[14], exposed children present more internalized emotional regulation problems, such as anxiety and depression, and externalized aggressive behavior.[30]

Regarding the use of opioid analgesics during pregnancy, a cohort study carried out in Norway evaluated 3-year-old children who had prenatal exposure to this type of medication, and found no differences in language competence or communication skills.[32]

Teenagers: 12-18 years old

Children of women who use substances have been shown to be vulnerable in cognitive, emotional, and social function in adolescence. One study found that adolescents prenatally exposed to opioids had lower average brain and intracranial volumes for their age. However, no significant differences in neurocognitive development were detected.[22,29]

Regarding social risk behaviors, in a US study of a low-income, multiethnic population, the group with in utero exposure to opioids was more likely to use cannabis at younger ages. In another study, behavioral test results also showed significantly elevated levels of hyperactivity, impulsivity, and attention problems on the Brown ADHD Scale and the Strengths and Difficulties Questionnaire, or SDQ. During the study, it was found that some parents and relatives had been diagnosed with ADHD, so this high prevalence could be attributable to hereditary factors.[14,33]

Prevention

Regarding the prevention of neurobehavioral alterations and NAS caused by prenatal exposure to opioids, there are two ideological currents. The first is medically supervised detoxification, which involves gradual weaning from opioids. It has been shown that this therapy exposes mothers to

a higher risk of relapse, which is why its use has been declining. Defenders of this practice argue that lower rates of NAS are achieved with it, however, this has been disputed in more recent studies. This phenomenon could be attributed to changes in the definition of NAS, the application of broader criteria, and the underdiagnosis of this entity in the past. As a second option there is the medication-assisted treatment (MAT). This consists on replacing illegal opiate substances with pharmacological equivalents commonly used in clinical practice, such as methadone (full opioid receptor agonist) and buprenorphine (partial MOR receptor agonist). Traditionally, methadone has been used as standard therapy during pregnancy; however, recent studies have challenged this practice.[17,29,34]

Studies carried out in neonates, such as the "MOTHER trial", have found that the results related to NAS are more optimal in children exposed prenatally to Buprenorphine, showing a shorter duration of treatment, lower doses of morphine, a shorter hospital stay, and in general a lower severity of the syndrome, compared to children exposed to Methadone. Other observed benefits of MAT with Buprenorphine in these newborns were a lower presence of hypertonia, excitability and signs of stress related to withdrawal, as well as better self-regulation when making the same comparison with Methadone. It is believed that these early neurobehavioral differences could have implications for the future development of these patients. Likewise, a retrospective study published in 2015, in addition to having found similar benefits of buprenorphine treatment in the evolution of NAS, found a negative correlation between head circumference at birth and the use of methadone, especially if it was administered at birth. high doses. Additionally, regarding the results of neurodevelopment, no neurocognitive differences were found between the exposure groups when using the Bayley scale, but higher scores on the AIMS scale were found in the children of those who received Buprenorphine.[12,19,35]

CONCLUSIONS

Currently, the consumption of opioids in women of childbearing age has shown an upward trend, which is concerning, since, in the event of pregnancy, it constitutes an increased risk of prenatal exposure and adverse outcomes in the offspring.

The validity of the studies included in this review may have been compromised by recall bias, as parents tend to more accurately recall exposures when an unfavorable outcome occurs. Additionally, studies that use different scales and tests are compared, which could lead to measurement bias. And, finally, a selection bias may occur in which exposed patients with more severe conditions were included or studied the most. Another important limitation of this review is the heterogeneity and, in some cases, the lack of definitions of opioid exposure, making it difficult to properly compare the results of the studies included.

The contradictory results regarding the neurobehavioral effects and psychomotor results between the classic reviews on this subject and the most recent ones, may be due to concomitant exposure to multiple psychoactive substances in children or to the use of different cognitive tests and at variable ages. Additionally, the discrepancies in the results could be explained by confounding variables such as low socioeconomic status, educational level, maternal age and quality of time and maternal care. Most studies that control these variables do not find statistically significant differences between children exposed prenatally to opioids and controls. Therefore, maternal drug use is not necessarily the sole culprit, but family and environmental characteristics also play a fundamental role.

It is concluded that there is no clear association between the development of neuropsychiatric disorders and in-utero exposure to opioids, although it has been directly related to neonatal abstinence syndrome. More studies are needed to determine the association and causation between exposure and outcome in these patients.

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