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DRUG ABUSE IN PREGNANT WOMEN AND FETAL TOXICITY: A META-ANALYSIS

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Abstract: The abuse of illicit drugs during pregnancy is a very worrying issue that must be addressed in our society. Since, the components present in these substances of abuse can cause various maternal and fetal harm during the gestational period and after birth. The objective of this study is to analyze the main results of the pathophysiological, epidemiological and clinical aspects of the use of these illicit drugs during pregnancy. Through an integrative literature review of a descriptive nature with a qualitative approach in the databases, Lilacs, Scielo, Pubmed, Uptodate in the period from 2018 to 2023. The results of this research are expected to provide a greater understanding of this situation, as despite being a important problem, it lacks studies.

Keywords: Pregnancy, Illicit drugs, Primary health care.

INTRODUCTION

The use of illicit drugs, tobacco and alcohol in Brazil is present in young people of reproductive age in the majority, impacting pregnancy and generating impacts on maternal and fetal health (MARANGONI, et al. 2022). Furthermore, it is important to analyze that tracking pregnant drug users in Brazil is very complex, as many do not seek out the primary health care system to carry out prenatal consultations, which are extremely important for analyzing fetal development. for fear of involvement with the police or social coercion (BALESTRA, 2020).

During pregnancy, both physical and psychological changes occur in pregnant women, the psychological changes mostly consist of developing an escape from reality, which often leads to the search for the use of hallucinogenic substances. Therefore, it is possible to observe that illicit/legal drugs are considered a disease by the World Health Organization (WHO) and that they affect

around 5% of the world's population.

Therefore, it is important to analyze the sociodemographic data present in Brazil, so in the period from January 2023, it was possible to observe data related to hospitalizations for congenital malformations in relation to color/race, with the most affected population according to DATASUS, the population mixed race with 3,406 cases of hospital admissions, followed by white with 2,580, black with 235, yellow 77, indigenous 14, and no information 640, totaling 6,952 cases of hospitalization due to these congenital changes.

Therefore, in relation to toxic substances from legal substances, the use of alcohol is evident, as it is a substance that is easily accessible and legally accepted in our society. Therefore, the consumption of these substances can act directly on fetal development, as there is no evidence of safe doses for the mother and the fetus, which can vary according to the gestational trimester, maternal and fetal metabolic capacity, and can cause serious anomalies such as in the case of Fetal Alcohol Syndrome. Tobacco is also a legal substance, easily found for consumption, its use generates systemic changes such as vasoconstriction and increases adrenergic stimulation, causing changes in blood flow to the placenta, which can generate some complications such as placental abruption and even miscarriage. Cigarettes also contain several substances, including nicotine, which causes vasoconstriction, reducing the supply of oxygen to the intrauterine fetus, causing future problems. (Silva et al., 2021).

Among illicit drugs, there is cocaine, the fourth most used substance during the gestational period, this drug can cause changes in both users and babies, which can increase the risk of miscarriage, placental abruption and intrauterine growth restriction, among others. other circumstances (BAYLEY; DIAZ-BARBOSA, 2018).

These substances ingested by the mother have a high capacity to cross the blood-brain and placental barriers, which has effects on both parts, mother and fetus. The dose, time of use and the substance used will affect the impact generated (DUTRA et al. 2021). Thus, newborns who have been subjected to these chemical substances may present some changes at birth, including microcephaly, low birth weight, congenital malformations and constant hospitalizations, and these changes can persist throughout their lives (BAYLEY; DIAZ-BARBOSA, 2018).

Therefore, the objective of this project is to carry out a systematic review to list the main recurrences, risk factors, in addition to maternal-fetal consequences and problems that may occur as a result of the use of illicit substances during the gestational period. Furthermore, it is possible to analyze that this research seeks, in the future, to assist in early screening in primary care and health education for pregnant women, aiming to intervene and avoid this issue present in our society.

DEVELOPMENT

This project will have a meta-analysis review methodology, which will be conducted according to criteria from the Item and Preferred Guidelines for Systematic Reviews and Meta-Analyses (PRISMA) (BRASIL, 2014). To be carried out, scientific articles available in databases such as Pubmed, Lilacs, Scielo and Uptodate will be used, from 2018 to 2023. The descriptors used to select the articles will be: illicit drugs, Maternal and fetal changes, Pregnancy and Primary care the health. Thus, the inclusion criteria will be articles with research on drug abuse during pregnancy and its most recent consequences with a publication limit of 4 years and the exclusion criteria will be research that does not correspond to the theme or is incomplete and has a date of publication over 4 years.

JUSTIFICATION

As stated, it is essential to analyze the use of drugs by pregnant women, their possible maternal-fetal complications, since in Brazil there are few studies that address the research of illicit drugs during the gestational period and their fetal changes, as access is more difficult. of drug users in primary health care, either due to abandonment or noncompliance with prenatal care, or because of a fear of being users.

Therefore, it is important to know the epidemiological profile, clinical and pathophysiological changes of illicit drug consumption during pregnancy to attempt screening, monitoring of the patient's pregnancy and prevent future complications for mother and fetus.

Since, to improve intervention strategies in this population and assist in the early recognition and prevention of future damage to both the mother and the fetus, greater knowledge in this area is necessary to become a more discussed public health problem and thus promote health education in the population in question.

RESULTS AND DISCUSSIONS

ALCOHOL

Alcohol consumption in our society can cause major problems for public health, mainly related to pregnancy, and this prenatal exposure to alcohol use can have serious consequences for fetal development, varying depending on the dose of consumption. and the gestational trimester and these teratogenic substances can have an impact on the individual's entire life, being the main cause of cognitive impairment in developed countries (EASSY, 2019). With this, it is possible to analyze that in addition to these changes we can have an increased risk of miscarriage, premature births and fetal growth restriction. (PAVESI,2023).

Thus, after being ingested, alcohol can pass through the placenta freely reaching the fetus in the same proportions that the pregnant woman ingested after 2 hours, but as it does not yet have the enzymes necessary for the correct metabolism of ethanol, this substance ends up having greater exposure to the embryo. (MARIANI,2018). this way, we will have several harmful effects from this situation, as in the case of chronic fetal hypoxia, due to vasoconstriction of the site that compromises the circulation of amino acids, in addition to the decrease in the distribution of carbohydrates, reducing the supply of oxygen and nutrients causing restriction of fetal growth, in addition to increasing prostaglandins in various tissues and as a consequence increasing oxidative stress through the formation of free radicals and causing cell death.(CHUNG,2021)

With this, we have Fetal Alcohol Spectrum Disorders (FASD), which refer to a group of diseases that can result from fetal exposure to alcohol. These disorders include fetal alcohol syndrome (FAS), partial FAS, alcohol use-related neurodevelopmental disorder, alcohol-related birth defects, and FASD with or without sentinel facial features. (MAYA, 2021) Fetal alcohol syndrome is characterized by severe neurodevelopmental deficiency, which may be associated with prenatal and postpartum growth deficit, specific facial dysmorphia such as small palpebral fissures, absent nasal filter, red border of the lip upper thin and structural abnormalities of the central nervous system. (MARIANI,2018)

The socio-epidemiological profile of these pregnant women has a higher prevalence of alcohol use in the southern region of Brazil and lower in the north and northeast regions, mainly in women with greater social vulnerability aged 12-19 years and who have less education as they have less access to information about the harms of this habit,

non-white skin color without a partner during pregnancy, with a higher rate of previous births, unintended pregnancies, no paid work and late start of prenatal care. Risks such as smoking, alcohol, and inadequate prenatal care are present in the majority of these pregnant women, therefore, the importance of public policies that include actions to prevent alcohol consumption and present its harms is indisputable. (CABRAL,2023)

TOBACCO

Smoking during pregnancy is associated with several sociodemographic variables. Pregnant women who smoke tend to be older, have a lower level of education and have a history of more previous pregnancies and abortions. Furthermore, they are more likely to consume alcohol, illicit drugs and passive exposure to smoke at home. On the other hand, having a planned pregnancy and a better socioeconomic condition are negatively associated with smoking. (FUJITA,2021)

The prevalence of tobacco consumption during pregnancy varies considerably between countries, and in Brazil, estimated rates exceed the world average. In 2012, approximately 9.6% of pregnant women admitted to smoking during the gestational period, these statistics do not include the potentially even greater exposure to tobacco when considering the presence of passive smokers. (PAVESI, 2023)

The habit of smoking in pregnant women's families persists throughout generations, being considered normal in family norms. The scarcity of leisure activities outside the home environment was also observed. (FUJITA,2021). Psychological aspects, such as anxiety, depression, perceived stress and a personality with a high degree of neuroticism, were also more prevalent in pregnant smokers. (SIQUEIRA,2019)

Just like alcohol consumption, tobacco use in society is significant, presenting serious ramifications for public health. These effects intensify considerably during pregnancy, posing a threat to fetal and embryonic development and child health. The damage from these teratogenic agents has the potential to last throughout the individual's life. As a consequence, tobacco has the potential to trigger a series of adverse impacts on the health of both the mother and the fetus. Among these effects, the number of cigarettes is correlated with the restriction of intrauterine growth and reduction in the average birth weight, in addition, placental anomalies, the occurrence of premature births, prenatal mortality and an increase in the probability of the occurrence of death syndrome are seen. sudden. (PAVESI, 2023).

The impact most often associated with smoking during pregnancy is a reduction in the baby's birth weight. The main components of cigarettes, carbon monoxide and nicotine, negatively affect fetal growth by decreasing the availability of oxygen to the fetus. (SILVA,2022) Nicotine, capable of crossing the placenta, influences the cardiovascular system and the central nervous system (CNS) of the fetus, resulting in a neurophysiological and teratogenic impact. Breastfeeding mothers who smoke may present masked symptoms related to the baby, such as colic and crying or, depending on the number of cigarettes consumed, even more serious effects, such as reduced breast milk production, difficulties in gaining weight for the baby and symptoms such as diarrhea, tachycardia and drowsiness. (LOMBARDI,2023)

MARIJUANA

Cannabis sativa, or popularly known as marijuana, is the drug of abuse most consumed by pregnant women. Thus, the socio-epidemiological profile, different from alcohol, is that these women have steady partners, who also use the same drug as the

pregnant woman with an intergenerational pattern of use, and multipregnancies. There was also the consumption of other drugs during pregnancy, mainly tobacco, alcohol and marijuana, making it difficult to understand the specific mechanism of cannabis in the fetus, with the maternal age range being 25 to 35 years old with an income of up to two minimum wages and at least nine years of education. (DIAS,2022)

The drug contains chemical compounds psychoactive, considered medicinal or of the best called cannabinoids. One known is tetrahydrocannabinol ($\Delta 9$ -THC), psychoactive component capable crossing the placental barrier, reaching the developing fetus mainly in the initial stage of proliferative growth. Therefore, it can reach the maternal circulatory system by increasing blood pressure and heart rate, which leads to a decrease in uteroplacental perfusion, intrauterine growth restriction (IUGR) and behavioral disorders in fetuses, in addition to being present in breast milk, which can inhibit prolactin production and consequently milk production. (PASCALE,2019).

Exogenous cannabinoids can cause some disturbances in users' reproductive organs until they reach the fetus. Due to its specific receptors such as CB1 which is present in both the cerebral cortex, hippocampus, basal ganglia, cardiovascular system, reproductive system as well as in the ovary, placenta and uterus, gastrointestinal system and CB2 which is present in peripheral nerve cells and tissues immunological, both are G-protein coupled that inhibit Adenyl cyclase and activate cascades of ampc-dependent protein kinase (pKA) is inhibited. (SILVA,2019)

With this, we can analyze that changes in the prenatal period go beyond the modification of genes linked to neurotransmitters essential for neural development. There is a substantial increase in the incidence of newborns with

low birth weight and size smaller than expected for gestational age, resulting in a greater probability of premature births. This prematurity, in turn, is associated with complications and impacts on child development. (PEREIRA, 2019) Studies indicate that such changes can also contribute to sudden baby death syndrome, emphasizing the complexity of genetic, environmental and maternal health interactions during pregnancy. Understanding these situations is essential not only to identify the challenges faced by newborns, but also to implement preventive and interventional strategies regarding substance abuse, aiming to ensure a healthy and promising start in life from conception. (SILVA,2019)

COCAINE AND CRACK

Cocaine is a main alkaloid of the Erythroxylon plant, while crack is a form of cocaine that is produced by mixing sodium bicarbonate and cocaine paste or powder, thus forming a stone. Both have the same active ingredients, but crack has a greater dissemination in the cortex due to its administration via inhalation. (MOUKBEL,2021)When associated with alcohol, cocaine becomes an aggravating factor, as in addition to increasing its toxicity, it also prolongs the feeling of euphoria. (TACON, 2018).

The epidemiological data on these substances in Brazil are very deficient, but studies have revealed that the majority of users are brown or black, with an average age of 30 years, single and with a low level of education, the majority of users are men but in Compared to the quantity of the drug used, women stand out, in addition, a large proportion of users are homeless. (MOUKBEL,2021) Identifying the use of cocaine and crack by pregnant women is a significant challenge due to frequent denial and the similarity of their effects to

other substances or gestational complications. The use of these drugs among pregnant women is on the rise globally, affecting around 90% of female users of childbearing age. (LOMBARDI, 2023)

The effects of crack cocaine on fetal development result from neurochemical and vasoconstrictor mechanisms, amplified by the drug's low molecular mass and high lipid solubility, allowing it to pass through the placental and blood-brain barriers without metabolization. (TACON,2018)

In the central nervous system, the drug blocks the reuptake of neurotransmitters such as dopamine, norepinephrine and serotonin, intensely stimulating the sympathetic autonomic system and causing hypertension, tachycardia and hyperexcitability. (SOUSA, 2023)

The use of cocaine and crack by the mother during pregnancy reduces her appetite, resulting in poor nutrition for her and, consequently, for the fetus, impairing the supply of essential nutrients for fetal development. This can lead to a series of problems in the newborn, such as low birth weight, delayed neuropsychomotor development, reduced head circumference, malformations, mental retardation, bone changes, seizures and increased risk of sudden death. (LOMBARDI,2023) Prenatal exposure to the drug is also linked to a greater risk of complications such as placental abruption, miscarriage, prematurity and fetal growth restriction. (TACON,2018)

Chemically dependent women often have difficulty developing an emotional bond with their children due to psychological and emotional fragility, leading to unstable interactions marked by hostility, aggressiveness, anxiety and depression. Children of these women are at increased risk of experiencing behavioral, psychological, and academic problems, as well as developing

substance dependence in the future. (LOMBARDI,2023)

After birth, it is possible to observe a set of symptoms that affect the gastrointestinal, neurological and autonomic system, characterizing neonatal abstinence syndrome. Signs and symptoms may appear in the first

hours of life, including incessant crying, irritability and difficulty sucking. However, these manifestations can persist in both the short and long term, varying depending on the amount and duration of exposure to the agent in question. (SOUSA,2023)

SUBSTANCES	MECHANISM OF ACTION	CONSEQUENCES	SOURCES
ALCOHOL	Alcohol freely crosses the placental barrier producing free radicals and hypoxia.	Fetal alcohol spectrum disorders (FASD)	(MARIANI, 2018)
TOBACCO	Substances present in cigarettes, such as nicotine and carbon monoxide, cross the placental barrier, reducing oxygen supply to the fetus and acting on the central nervous system.	Influences on the central nervous and cardiovascular system, intrauterine growth restriction and low birth weight, placental anomalies, premature birth, perinatal mortality.	(SILVA, 2022) (LOMBARDI, 2023)
MARIHUANA	THC crosses the placental barrier, altering the endocannabinoid system, resulting in changes in the selectivity and differentiation of axons	Sudden death syndrome, premature births, cognitive and motor deficits	(SILVA, 2019)
COCAINE AND CRACK	Due to its low molecular mass and solubility, it is capable of crossing the placental and blood-brain barriers without metabolization. It also causes blockage of neurotransmitter receptivity and loss of appetite in the user	poor nutrition, low birth weight, prematurity, placental abruption, miscarriages, increased risk of sudden death, malformations, decreased head circumference, bone changes, seizures, mental retardation.	(LOMBARDI, 2023)

FINAL CONSIDERATIONS

Therefore, with this project we can define the main epidemiological profile, pathophysiology and clinical aspects of drug abuse during the pregnancy process and its possible maternal-fetal consequences. Since, despite being an important problem in public health around the world, there is still a lack of studies focused on this topic, especially in Brazil, which may be due to the low adherence of these pregnant women to prenatal care, therefore, new studies are needed to highlight which are the main drugs of abuse and their target audience to seek new propaedeutics for these pregnant women.

Alcohol, as shown above, can be concluded that it represents a serious threat to fetal health, causing fetal alcohol spectrum disorders (FASD), including fetal alcohol syndrome (FAS). The free passage of alcohol through the placenta results in significant impacts

on fetal development, causing chronic fetal hypoxia and increasing the risk of cognitive impairment. The socio-epidemiological profile of exposed pregnant women highlights a higher prevalence in the southern regions of Brazil and in young, socially vulnerable women. The simultaneous presence of risk factors, such as smoking and inadequate prenatal care, highlights the urgency of public policies for prevention and awareness about the harms of alcohol consumption during pregnancy.

Smoking during pregnancy is influenced by a series of sociodemographic variables, with pregnant smokers generally being older, less educated and having a history of more previous pregnancies and abortions. Furthermore, they are more likely to consume alcohol, illicit drugs and passive exposure to smoke at home. On the other hand, a planned pregnancy and a better socioeconomic status are negatively associated with smoking.

In Brazil, smoking rates during pregnancy are higher than the world average, with approximately 9.6% of pregnant women admitting to smoking. Smoking persists throughout generations in pregnant women's families and is rooted in family norms, often accompanied by a lack of leisure activities outside the home environment. Psychological aspects such as depression, perceived stress and neuroticism are also more prevalent in pregnant smokers. Smoking during pregnancy is associated with a range of adverse impacts on maternal and fetal health, including intrauterine growth restriction, reduced birth weight, placental premature births, anomalies, prenatal mortality and increased likelihood of sudden death syndrome. The main components of cigarettes, carbon monoxide and nicotine, negatively affect fetal growth by decreasing the availability of oxygen, with nicotine also influencing the cardiovascular system and central nervous system of the fetus. Masked baby-related symptoms in nursing mothers who smoke, such as colic and crying, are common, as are more serious effects, such as reduced breast milk production and difficulties in gaining weight for the baby, depending on the number of cigarettes consumed.

Another substance mentioned above was cannabis sativa, popularly known as marijuana, which appears as a drug of abuse most consumed by pregnant women. Unlike alcohol, women who consume it generally have steady partners, sharing the intergenerational pattern of drug use, in addition to being multipregnancies. Concomitant consumption of tobacco and alcohol during pregnancy is common in this group, making it difficult to specifically understand the effects of cannabis on the fetus. Tetrahydrocannabinol $(\Delta 9\text{-THC})$, one of the main psychoactive compounds in marijuana, crosses the placental barrier, impacting the fetus, especially during

the initial stage of proliferative growth. This contributes to intrauterine growth restriction (IUGR), behavioral disorders in fetuses and interferes with prolactin production, affecting lactation.

Cocaine and crack, also mentioned, being alkaloids from the Erythroxylon plant, share active ingredients, although crack diffuses more quickly into the cerebral cortex due to its administration by inhalation. Associated with alcohol, cocaine intensifies its toxicity and prolongs the euphoria. Epidemiological data in Brazil reveal that users are predominantly brown or black, single, with low education, and women stand out in relation to use. Its effects during pregnancy include nutritional complications, malformations, and increased risks of premature birth and perinatal mortality. Furthermore, drug-using mothers often have difficulty developing emotional bonds with their children, increasing the risk of behavioral problems and substance dependence in the future. Newborns may manifest neonatal abstinence syndrome, presenting symptoms such as irritability and difficulty sucking, which may persist in the short or long term, depending on the intensity of prenatal exposure.

In view of the above, the seriousness of the consequences of drug abuse during pregnancy is evident, both for mothers and fetuses. Therefore, it is essential to raise awareness about the harmful effects of drugs during pregnancy and implement strategies to protect maternal-fetal health and promote healthy development for future generations.

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