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HEALTH SCIENCES

Potential developmental effects of licit and illicit substances in humans: An approach to risk-specific dose and incidence

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Abstract: Teratogens encompass any agent capable of causing a birth defect or elevating the incidence of defects within the population. This category includes substances like drugs, both legal and illegal. These substances cause congenital anomalies depending on the stage of development at the time of exposure, the dose, and the exposure time associated with the embryo. The most sensitive period is the embryonic stage, when the three leaflets give rise to tissues and organs. Susceptibility to teratogenesis decreases during the fetal phase but morphological and functional disturbance of the fetus may still occur. Substance use during pregnancy and its adverse effects are a public health problem and the lay population does not have access to this information. Particularly concerning is the period within the first six weeks of pregnancy, often before a woman realizes she is pregnant. Developmental data for many substances are simply not available, which makes the problem more serious. The aim of this study is to reflect on the teratogenic effects of licit and illicit substances in humans, focusing particularly on the dose that can induce malformations and their incidence in humans.

Key words: environmental teratogenesis, congenital malformations, drugs, alcohol, medications.

INTRODUCTION

For a long time, it was believed that the placenta and maternal-fetal membranes are completely impermeable and would protect the human embryo or fetus against developmental changes induced by external factors (Tavella et al. 2020). There is now certainty that the development of the human fetus is very susceptible to changes induced not only by internal (genetic) factors but also by external agents. When an external factor results in fetal death, it constitutes developmental toxicity. Conversely, these changes can also lead to birth defects, which is when we refer to them as teratogens. Teratogens encompass any agent capable of causing a birth defect (congenital anomaly) or elevating the incidence of defects within the population (Moore et al. 2016). This category encompasses a wide range of influences, including environmental factors like certain infections, physical agents such as radiation, and various substances, including drugs, that can have harmful effects on fetal formation and development. In this study, we will address the issue of environmental teratogenesis, focusing on the use of licit and illicit substances during pregnancy.

The human embryo is constantly exposed to teratogenic agents ranging from components of pollution to which we are exposed to very simple agents such as medications, with the risk of alterations in embryo development being plausible and real. In addition, many social behaviors also increase the potential risk of

embryonic malformations. Legal and socially accepted drugs such as alcoholic beverages and tobacco are potentially harmful. There are also illicit drugs such as cocaine, which is very common in our society; although illegal, it is widely consumed in many populations. Furthermore, there is a period when the embryo is more susceptible to developmental changes, a fact that aggravates the teratogenic risk (Schüler-Faccini et al. 2011, Silva et al. 2021). Particularly concerning is the period within the first six weeks of pregnancy, often before a woman realizes she is pregnant, during which harmful substances can unknowingly impact fetal development.

Therefore, the aim of this study is to address the harmful effects of licit and illicit substances on fetal formation and development, focusing particularly on the critical dose that can induce malformations and their incidence in humans. Information on environmental teratogenicity can be found in the specialized technical literature. However, the data reported here are not easy to find and are much less accessible to the general public because of the technical language that is difficult for lay readers to understand. Furthermore, developmental data for many substances are simply not available, which makes the problem more serious and complex. Within this context, in addition to reviewing and updating the topic, we aimed to retrieve this information and systematize it on a social media platform with a broad audience. Our aim is to create a social media page addressing the main questions related to the topic in an easy-to-understand language for the general population, which could serve as a guide for the prevention of drug-induced malformations.

MATERIALS AND METHODS

We conducted a bibliographic survey in the PubMed, LILACS, Scopus, Web of Science, and SciELO databases. The following Health Sciences Descriptors (DeCS) were used: teratogenesis, congenital malformations, congenital defects, drugs, alcohol, marijuana, cocaine, antidepressants, and sensitivity (keywords in Portuguese and English). Boolean operators (AND, OR, and NOT) were also applied. As a criterion, we mainly selected articles that reported the dose at which a teratogen was considered to be of risk for a given congenital malformation, as well as articles that reported the incidence of malformations or susceptibility to the substance investigated. After analysis of the texts, among articles that met the objective, publications from at least the last 10 years were evaluated; the main idea of each article was extracted and the studies were grouped based on the similarity of the information.

RESULTS AND DISCUSSION

Susceptibility to teratogenesis basically depends on three factors: the genotype of the embryo, the dose and exposure time, and the critical period of embryonic development. The most sensitive period for the induction of congenital defects is between the third and eighth week of gestation, the period of embryogenesis characterized by maximum cell division, differentiation, and morphogenesis (Moore et al. 2016, Schüler-Faccini et al. 2011, Silva et al. 2021). Substance use during pregnancy is a public health problem that poses risks to maternal and fetal health. The effects resulting from exposure to these substances can cause extremely serious problems during development, with a permanent impact on affected individuals (Gupta et al. 2016).

Teratogenic effects of social (licit) substances

Alcohol and alcoholism

Alcohol has been present in many societies around the world for centuries and is consumed during events ranging from religious settings to celebrations. Fetal exposure to alcohol is a matter of concern because of the easy access and low cost of alcohol and its social acceptance, with its consumption being encouraged especially among the female population. In pregnant women, variables such as genetic factors, nutritional status, and the presence of other diseases must be considered (Moore et al. 2016, Denny et al. 2017).

The teratogenic effects of alcohol are due to intrauterine exposure since alcohol is able to cross the placental membrane (Gupta et al. 2016). The prevalence of alcohol-related congenital malformations ranges from 0.5 to 3 per 1,000 exposed neonates. Due to the metabolism and slow elimination of alcohol, the amniotic fluid becomes saturated with ethanol and acetaldehyde, compounds that can cause damage during organogenesis (Gupta et al. 2016, Mattson et al. 2001). Alcohol elimination by the fetus depends on the metabolic capacity of the pregnant woman. This factor is one of the explanations for the variation in the fetal phenotypes found (Segre 2017). Exposure to concentrations of alcohol similar to that found in maternal blood renders the environment inhospitable to the fetus and favors the development of fetal alcohol syndrome (FAS) (Mattson et al. 2001, Gupta et al. 2016). This most severe subtype within the spectrum of fetal alcohol disorders is characterized by growth deficiency, microcephaly, central nervous system disorders, deficits in the acquisition of verbal/nonverbal and cognitive information, and a distinct pattern of facial abnormalities (Mattson et al. 2001). Even in the absence of the FAS, a significant reduction in fetal growth may occur, without the fetus exhibiting other symptoms (Gupta et al. 2016).

Postnatal exposure to alcohol is also an important issue since it has consequences for the child, especially during breastfeeding. Alcohol is passed into breast milk at a rate of 2% and can cause changes in sleep and neuromotor development, as well as learning deficits in the child (Denny et al. 2017). Among all drugs of abuse addressed in this review, alcohol produces the most severe neurobehavioral effects on the fetus and is also the most common teratogenic agent (Segre 2017). At present, fetal problems related to alcoholism during pregnancy are the main preventable cause of fetal alcohol spectrum disorders (Denny et al. 2017). FAS, the most severe form of this disorder, affects 33% of children born to pregnant women who consumed more than 150 g of ethanol per day. The manifestations of FAS vary depending on the amount of alcohol consumed and the gestational period, among other factors (Silva et al. 2021). Physical characteristics are sufficient for the diagnosis of FAS, even when prenatal exposure is not confirmed (Segre 2017). However, not all characteristics are already present in the newborn and infant and may appear at other stages in life, for example neurological and cognitive changes, which are more evident in adolescence (Denny et al. 2017).

An interesting study evaluated fetal brain function in response to maternal alcohol consumption. The authors measured alcohol consumption in units, where one unit (U) corresponds to 10 ml of neat ethanol, which is equivalent to 50 ml of wine, 500 ml of beer, or 25 ml of spirit (Hepper et al. 2012). The consumption of less than 24 g per day (considering that one standardized drink is equivalent to 12 g) and 5-10 U per week was classified as moderate drinking. Mothers consuming more than 24 g per

day and more than 20 U per week were classified as heavy drinkers (Hepper et al. 2012).

The limit of alcohol in pregnancy that does pose negligible risk to fetal formation and development is in the moderate range, between 30 and 60 g per day. Above these levels, alcohol can cause cognitive impairment and behavioral problems in the fetus. The rate of alcohol absorption is 15 mg/100 ml over a period of 1 hour and is influenced by weight, height, sex, and drinking pattern. Absorption is faster if alcohol is consumed with carbonated drinks or on an empty stomach. Women are metabolically less tolerant to alcohol than men (Oliveira et al. 2012, Moore et al. 2016). This information is given in Table I.

There is no treatment for fetal alcohol spectrum disorders or FAS. The only way to avoid complications is to completely abstain from alcohol throughout pregnancy (Segre 2017) and to implement alcohol prevention programs that include specific strategies for each group of women, alerting to the hazards of alcohol in pregnancy (Denny et al. 2017).

Smoking

According to the World Health Organization (WHO), smoking is the leading cause of preventable death in the world. In 2019, the estimated number of smokers worldwide was 1.14 billion and smoking accounted for 7.69 million deaths. Globally, the percentage of smokers is lower among women (6.62%) compared to men (32.7%). However, this percentage is considerably higher among women in high-income countries, with 17.6% of women compared to 26.9% of men (Tarasi et al. 2022). In Brazil, the prevalence of smoking has decreased over the last few years but is still 14.7% among pregnant women (Fujita et al. 2021). The global prevalence of smoking during pregnancy is estimated at 1.7%; this percentage is higher in high-income countries, reaching 7.2% in the United States and 8.1% in Europe. However, these numbers should be interpreted with caution since up to 25% of pregnant women who smoked before pregnancy incorrectly reported that they had stopped smoking during pregnancy (Tarasi et al. 2022). Data obtained for women from more than 100 countries showed that 52.9% of them smoked daily and continued to smoke during pregnancy (Fujita et al. 2021).

Studies show that women are equally or even more susceptible to the hazards of smoking than men and that factors such as race, ethnicity, and age influence the smoking habit (Tacon et al. 2018). Analysis of the profile of Brazilian women suggests that smoking during pregnancy is associated with a set of sociodemographic variables, including older age, a lower educational level, and a larger number of previous pregnancies and miscarriages. In addition, Brazilian women were more likely to consume alcohol, to use illicit drugs, and to be exposed to secondhand cigarette smoke at home (Fujita et al. 2021).

Exposure of the fetus to tobacco leads to an increase in the number of nicotinic receptors and may favor the early initiation of smoking in adolescence (Tacon et al. 2018). In addition to the external factors cited above, genetic polymorphisms are also responsible for the degree of dependence and the ability to stop smoking (Tacon et al. 2018).

Approximately 4,000 chemicals are produced in cigarette smoke as a result of the chemical processes that occur when a cigarette is burned (Szparaga et al. 2021). Among these substances we have polyaromatic hydrocarbons, which have a multitude of toxicological consequences, and CO. At this point, we will focus our analysis on CO. After inhalation, CO diffuses through the alveolar-capillary membrane and binds to hemoglobin, forming

Table I. Relationship between teratogens, dose and effects on human fetuses.

Substance	"Safe" dose	Dose associated with alterations	Absorbed dose	Exposure time	Incidence	Most common symptom at birth	References
Alcohol	Less than 30 to 60 g/day	From 30 to 60 g/day	15 mg : 100 ml	Within one hour	0.1 to 0.2% of exposed neonates	Fetal alcohol syndrome: IUGR, intellectual disability, microcephaly, ocular and joint abnormalities, small ocular fissures, and behavioral problems	Hepper et al. (2012) Moore et al. (2016) Oliveira et al. (2012)
Nicotine	Less than 0.04 mg/ml	From 0.04 mg/ml	0.03 mg/kg every 20 cigarettes	Within one day	5.01% of exposed neonates	Developmental and maturational delays demonstrated by measures of pinna detachment, fur appearance, incisor eruption, eye opening, and righting reflex	Morales-Suárez-Varela et al. (2006) Schneider et al. (2010)
Caffeine	Less than 300 mg per day	From 300 mg per day	Approximately 300 mg of the maximum dose	Per day	3.71% of exposed neonates	Fetal reabsorption, skeletal alterations, behavioral and nociceptive changes. The association with other substances can cause birth weight reduction when co-administered with cigarettes and intrauterine growth retardation when co-administered with paracetamol	Brent et al. (2011) Burdan (2003) Furuhashi et al. (1985) Souza et al. (2016)
Cocaine	Less than 10 mg/kg/day	From 10 mg/kg/day	2 to 3 mg	Within one day	20.45% of exposed neonates	Linked to low birth weight and height, skull defects, smaller head circumference, and a trend towards prematurity, in addition to neonatal complications and high perinatal mortality	Bingol et al. (1987) Coe et al. (2018) Cunha (2007) Ross et al. (2015) Smith et al. (1989)
Thalidomide	Less than 50 mg (single dose)	From 50 mg	40 to 50 mg of the maximum dose	Single dose	50% of pregnancies	Phocomelia, malformations in the head, bladder, genital organs and especially the heart, with congenital heart disease being the main cause of death among newborns	Rehman et al. (2011) Vargesson (2015) Vianna et al. (2017)
Paracetamol	Less than 75 mg/kg/day	From 75 mg/kg/day	47.5 to 66.75 mg of the maximum dose	Per day	62.16% of exposed neonates	Affecting the liver of both the pregnant woman and the fetus and maternal problems such as hemolytic anemia	Da Conceição Moura et al. (2022) Fernandes (2017) Quintilio et al. (2022) Wanderley & Artigalás (2011)

Table I. Continuation.

Aspirin	Less than 60 to 150 mg/ day	From 150 mg/ kg	60 to 75 mg per 150 mg	Within one day	12.79% of exposed neonates	Fetal hypocoagulability, with an increased incidence of hemorrhagic phenomena, gastroschisis in the first trimester, and inhibition of function and ductus arteriosus closure in the third trimester	Aragão & Tobias (2019) Tagashira et al. (1981) Tanaka et al. (1973) Wanderley & Artigalás (2011)
Ibuprofen	Less than 3 g per day	From 3 g per day	2.4 g of the maximum dose	Per day	4.76% of exposed neonates	Gastroschisis, implantation disorders, ductus arteriosus constriction, prolonged labor, and glomerular defects that can lead to renal failure	Bushra & Aslam (2010) Dathe et al. (2018) Pereira et al. (2020) Wanderley & Artigalás (2011)
Dipyrone	Less than 2 to 3 g per day	From 2 to 3 g per day	1.78 to 2.67 g of the maximum dose, respectively	Per day	6.05% of exposed neonates	Use associated with the risk of Wilms tumor and leukemia in children under two years of age, in addition to the risk of aplastic anemia and agranulocytosis	Aragão & Tobias (2019) Bánhidy et al. (2007) Da Conceição Moura et al. (2022) Quintilio et al. (2022) Wanderley & Artigalás (2011)
Diclofenac	Less than 200 mg per day	From 200 mg per day	100 mg of the maximum dose	Per day	1,81% of exposed neonates	Congenital septal heart defects, double kidney, cerebral atrophy with secondary macrocephaly and microcephaly	Cassina et al. (2010) Ertekin et al. (2019) Padberg et al. (2018)
Methotrexate	11 to 17 weeks: < 100 mg, 17 to 23 weeks:< 200 mg	11 to 17 weeks: > 100 mg, 17 to 23 weeks: > 200 mg	70 mg per 100 mg of the dose administered	Fortnightly	17.24% of exposed neonates	Skeletal and intracranial abnormalities, lack of frontal bone, hypertelorism, jaw hypoplasia, and heart defects	Moore et al. (2016) Schünemann Jr. et al. (2007)

carboxyhemoglobin. When carbon dioxide binds to hemoglobin, carbaminohemoglobin is formed. On the other hand, hemoglobin has a 200 times greater affinity for CO than for oxygen; this bond is stable and slowly reversible, with carboxyhemoglobin spreading to all tissues and binding to other hemoproteins, thereby reducing fetal growth. However, these events also seem to be influenced by the genotype (Peterson & Hecht 2017). In pregnant women, smoking directly affects pregnancy, causing placental hypoperfusion (Silva et al. 2021), which results in chronic hypoxemia in the fetus (Machado & Lopes 2009). Furthermore, smoking can delay intrauterine growth and cause premature rupture of the placenta and ovular membranes (Silva et al. 2021).

The incidence of nicotine-related congenital malformations is 1,034 per 20,603 exposed neonates (Morales-Suárez-Varela et al. 2006). Fetal exposure to nicotine occurs through the activation of nicotinic acetylcholine receptors, affecting neurotransmitter release, gene expression, neuronal growth, cell survival, and the formation and maturation of synapses, which can lead to disorders related

to neurological development and increase the risk of psychiatric problems. Moreover, effects such as developmental and maturational delays demonstrated by measures of pinna detachment, fur appearance, incisor eruption, eye opening, and righting reflex may start to be observed in the fetus (Schneider et al. 2010). The child might be born premature and with low weight (Silva et al. 2021).

The maximum concentration of nicotine tolerated before the occurrence of strong teratogenic effects is 0.04 mg/ml. A standard smoker who smokes 20 cigarettes per day absorbs 0.3 mg/kg of nicotine, resulting in plasma concentrations of 10 to 50 ng/ml. This parameter varies depending on the daily number of cigarettes smoked (Schneider et al. 2010) (Table I). In the case of smoking cessation, nicotine is replaced via patches, gum, spray, and medication or even by replacing conventional cigarettes with electronic cigarettes. Evidence suggests that electronic cigarettes are safe in pregnant women but the effects on the fetus are still unknown (Cavalsan 2017).

Caffeine

A very common substance in daily life and the most commonly used drug (Burdan 2003), caffeine is a psychotropic drug of the group of central nervous system stimulants. Caffeine is found in coffee, tea, chocolate, and cola-like soft drinks. It is also present in analgesics, anti-inflammatory drugs, appetite suppressants, and cold and allergy medicines, whose caffeine content varies depending on the brand and type of product (Rohweder et al. 2023). A cup of caffeinated and brewed coffee (150 ml) contains about 90 mg of caffeine (Nehlig & Debry 1994), which is rapidly absorbed by the body.

The prevalence of caffeine intake during pregnancy is high, with 95% of women occasionally consuming some product containing this substance during pregnancy; of these, 72% continue to regularly consume caffeine during pregnancy and breastfeeding (Souza et al. 2016, Rohweder et al. 2023). Animal tests conducted in the 1970s highlighted the relationship between caffeine and teratogenesis (Rohweder et al. 2023). The incidence of congenital malformations associated with caffeine intake during pregnancy is 174 per 4,689 neonates (Furuhashi et al. 1985). These anomalies include intrauterine growth retardation, reduced birth weight, fetal reabsorption, and skeletal changes (Souza et al. 2016, Rohweder et al. 2023). Exposure of the fetus to caffeine during early neural development can cause behavioral and nociceptive changes that can persist into adulthood (Souza et al. 2016). These changes occur because caffeine can cross the placental membrane; since the liver enzyme system of the fetus is still immature, it is unable to metabolize this substance (Souza et al. 2016), indicating that pregnant women must avoid or reduce caffeine intake during pregnancy (Rohweder et al. 2023).

Brent et al. (2011) showed that the birth weight of newborns is related to caffeine consumption by pregnant women. Newborns of pregnant women who consumed caffeine doses higher than 300 mg per day had a birth weight that was 128 g lower than that of infants born to women who consumed lower doses. Thus, prenatal tolerability is good when this substance is administered at doses less than 300 mg per day. However, the effects on the fetus are intensified when caffeine is administered with other substances (Burdan 2003). For example, the co-administration of caffeine and cigarette smoking led to a reduction of 263 g in the newborn's birth weight (Brent et al. 2011) (Table I). The co-administration of caffeine with paracetamol can cause dose-dependent intrauterine growth retardation. However, there are no reports of an increase in the incidence of

malformations when these substances are co-administered (Burdan 2003).

Teratogenic effects of illicit drugs

Cocaine

Cocaine, which is extracted from the leaves of plants of the genus *Erythroxylum*, is a benzoylmethylecgonine and the first local anesthetic identified. It can relieve pain during different procedures and is used by Peruvian mountain communities to avoid hunger and to relieve fatigue (Silva et al. 2009). Cocaine affects the central and peripheral nervous systems in the pregnant woman and the fetus, inhibiting the reuptake of neurotransmitters at presynaptic terminals, promoting changes in the levels of noradrenaline, dopamine (Barbosa-Méndez & Salazar-Juárez 2020) and serotonin, increasing neurotransmitter concentrations, and inducing vasoconstriction. Cocaine has been reported to cause neurobehavioral disorders in the newborn (Rosa et al. 2014).

The most dangerous form of cocaine is crack, cocaine hydrochloride, because of its high addictive potential and because it is easily accessible given its low price and wide availability. When inhaled, crack smoke is composed of 6.5% cocaine vapor and 93.5% small cocaine particles. Since crack is an addictive drug, dependent pregnant women generally continue to use it throughout their pregnancy (Souza-Silva et al. 2020). Pregnant women who use crack generally combine it with other neuroteratogens such as alcohol, marijuana and tobacco, which can lead to the production of neurotoxic metabolites (Mayes 2002).

The incidence of congenital malformations associated with cocaine is 9 per 44 exposed neonates (Cunha 2007), which corresponds to 3.4% of the population sample. Cocaine is the second stimulant most used by pregnant women (Smid et al. 2020). In the state of São Paulo, it was estimated that 6% of women used cocaine during pregnancy (Cunha 2007).

Cocaine harms the conceptus because it can cross the placental membrane (Smid et al. 2020) and enter the fetal circulatory system (Ross et al. 2015). The metabolites of cocaine can alter the pattern of differentiation and morphogenesis of tissues, in addition to reducing blood flow to the uterus, placenta and fetus (Smid et al. 2020), causing teratogenicity since the fetus is constantly exposed to the drug (Ross et al. 2015). Cocaine can induce the involution of structures, generally in the third trimester when fetal vessels are more susceptible to contraction, which is particularly related to nervous system problems (Spritzer et al. 2011). Furthermore, this substance can cause spontaneous abortion (Smid et al. 2020), prematurity, intrauterine growth restriction (Tavella et al. 2020), and birth complications, posing significant risks to maternal health and severely compromising neonatal, child, and adult health of these conceptuses (Smid et al. 2020).

During pregnancy, damage to the neonate is due to the powerful vasoconstrictive capacity of cocaine (Bingol et al. 1987), which can cause fetal hypoxia (Smid et al. 2020). The main consequence include low birth weight and height, skull defects, a smaller head circumference (Bingol et al. 1987), and a trend towards prematurity. Maternal cocaine use is also strongly associated with neonatal complications, high perinatal mortality (Ross et al. 2015), placental abruption, and preterm labor (Smid et al. 2020). The lower the dose and frequency, and in the absence of association with other drugs, the risks to the fetus are less severe (Bingol et al. 1987). A maternal dose of 10 mg cocaine/kg per day can result in significant behavioral changes in the offspring (Smith et al. 1989), with the absorbed dose being equivalent to 20 to 30% (2 to 3 mg).

In the case of crack, ingestion occurs through the lung and the absorbed dose is equivalent to 6 to 32% of the dose (0.6 to 3.2 mg). Other routes of administration lead to different percentages of the compound; the most severe route of administration is injection, in which the body absorbs 100% of the dose (Coe et al. 2018) (Table I).

A meta-analysis on the fetal effects of cocaine found that many of the adverse effects attributed to the drug might be due to confounding factors of the mother who uses cocaine. Only the risk of placental abruption and premature rupture of fetal membranes appear to be significantly associated with cocaine use (Addis et al. 2001). Another review with meta-analysis provided evidence that maternal or prenatal exposure to crack is clearly linked to low birth weight, preterm birth, placental abruption, and a smaller head circumference (Dos Santos et al. 2018).

Marijuana

In Brazil, marijuana is considered an illicit drug and it is probably the most commonly used by pregnant women (Borges 2014), but there are many countries or communities where it is legally accepted. The prevalence of marijuana use in the city of São Paulo is 4%, while the prevalence of the concomitant use of marijuana and cocaine is 6% (Benevenuto et al. 2017). The composition of marijuana comprises about 480 chemical compounds; of these, 70 are cannabinoids, including tetrahydrocannabinol (THC), the main psychoactive substance (Benevenuto et al. 2017). Few studies have investigated the composition of marijuana smoke; however, it is known to contain harmful substances that are emitted when *Cannabis* is burned (Graves 2020), such as carbon monoxide and hydrocarbons (Benevenuto et al. 2017). The latter are classified as Group 1 carcinogens (Graves 2020) and are therefore toxic, especially for pregnant women. These substances cause an increase in maternal blood pressure and heart rate, which results in uterine vasoconstriction and thus reduces placental perfusion (Silva et al. 2019). Factors such as lifestyle, socioeconomic condition, nutritional status, age, and tobacco use interfere with the definition of the problems that are caused exclusively by the use of *Cannabis* in pregnant women, a fact that contributes to the lack of information in studies investigating how marijuana alone affects pregnancy and fetal development (Benevenuto et al. 2017).

The incidence of congenital malformations associated with the use of *Cannabis* is 1,659 per 42,754 exposed neonates (Reece & Hulse 2020). Exposure to marijuana during early pregnancy is associated with increased fetal resorption and pregnancy loss, while exposure during mid-gestation is associated with fetal growth retardation. Pregnant women exposed during the third trimester or throughout pregnancy were found to be the most affected. Even at low doses, marijuana can increase implantation failures and compromise fetal development, affecting the psychomotor capacity, muscle strength, emotionality, and memory of exposed neonates (Benevenuto et al. 2017) and causing congenital anomalies, preterm birth, and perinatal death (Silva et al. 2019). Marijuana use during pregnancy is also associated with a higher prevalence of dysfunctional and sudden labor and meconium-stained amniotic fluid (Benevenuto et al. 2017). The use of marijuana during breastfeeding may still be harmful to the child since toxic compounds can be present in breast milk (Silva et al. 2019).

Daily exposure of mice to marijuana for 5 minutes, even at a low dose of 50 mg/kg corresponding to 2 mg THC/kg, caused changes in the fetus such as reduced birth weight and a larger number of male pups per litter,

although litter size was unchanged. We did not find the equivalent risk dose in humans. One way to mitigate the effects of marijuana on the embryo during pregnancy is the consumption of a protein-rich diet by the pregnant woman, suggesting a certain degree of tolerance to the effects of the drug (Benevenuto et al. 2017) (see Table I).

Teratogenic effects of medications

Thalidomide

Thalidomide was initially used as a sedative and hypnotic and was later indicated for the treatment of different diseases such as hyperthyroidism, tuberculosis, febrile infectious diseases (Vianna et al. 2017), and even nausea during pregnancy. The drug was sold worldwide since it was considered to be completely non-toxic (Vianna et al. 2017). By the end of the 1950s, studies started to demonstrate a relationship between the birth of children with congenital anomalies and the use of thalidomide (Vargesson 2015, Vianna et al. 2017). This relationship was described in several animal models, which showed that the placenta allows the passage of maternal, environmental and medicinal factors to the conceptus, leaving it vulnerable. These factors were associated with the origin of congenital defects. The period sensitive to teratogenesis ranged from days 34 and 50 after the end of menstruation and from days 20 to 36 after fertilization (Vargesson 2015, Vianna et al. 2017). This discovery was so revolutionary that it led to the founding of the Teratology Society and the scientific area of teratology.

The main findings associated with the use of thalidomide include phocomelia characterized by the generally bilateral and asymmetric malformation of the long bones of the upper and lower limbs, which causes the limbs to resemble the flippers of a seal, hence the name (Vianna et al. 2017). Anomalies can also occur in other organs, such as malformations of the head, bladder, genital organs and especially the heart, with congenital heart disease being the main cause of death among newborns (Vargesson 2015). It is important to highlight that, although thalidomide caused abnormalities of the head region, it did not affect the brain since not all organs were affected by the drug (Vargesson 2015). Thalidomide affected about 12,000 newborns worldwide, including in Brazil, and approximately 40% of them died in the first year of life. For this reason, thalidomide was withdrawn from the European market in 1960. In Brazil, the drug was still sold until 1962 (Vargesson 2015, Vianna et al. 2017).

Animal studies have shown diverse responses to the teratogenicity of thalidomide. While rabbit and primate embryos were more susceptible, with the teratogenic changes observed resembling those seen in humans, no teratogenic effects were detected in rats or hamsters. This finding can be attributed to the low solubility of thalidomide in the plasma of the latter, reducing the supply of the drug to fetal tissues (Vargesson 2015, Vianna et al. 2017). Since drug toxicity tests using different animal species were not mandatory at the time when thalidomide was commercialized, the drug easily entered the market in 1957 and was sold without the need for a prescription (Vianna et al. 2017). Studies indicate that a single thalidomide dose of 50 mg during the most sensitive period of pregnancy can cause birth defects in up to 50% of pregnancies (Vargesson 2015). Regarding the absorption of thalidomide, 80 to 100% of the oral dose is absorbed, corresponding to 40 to 50 mg of a 50-mg dose (Rehman et al. 2011) (see Table I). Nowadays, the sale of thalidomide is controlled since the drug continues to produce teratogenic effects and pregnant women should therefore avoid its use.

Analgesics and anti-inflammatory drugs

Some classes of medications that should be mentioned are anti-inflammatory and analgesic drugs since they are one of the most widely consumed medications that do not require a prescription. The most common are paracetamol, acetylsalicylic acid, and nonsteroidal anti-inflammatory drugs (NSAIDs) (Schüler-Faccini et al. 2011, Wanderley & Artigalás 2011), such as ibuprofen, dipyrone and diclofenac. These drugs are generally considered to be safe; however, they have teratogenic potential during pregnancy and pregnant women must be informed about their possible risks (Schüler-Faccini et al. 2011).

Analgesics include opioids and non-opioids. The sale of the former is restricted since these drugs can cause dependence; however, they are important for treating severe pain. The latter are NSAIDs, which are sold without a medical prescription. NSAIDs act by inhibiting the enzyme cyclooxygenase and the production of prostaglandins, thereby producing different analgesic, antipyretic, and anti-inflammatory effects, which vary depending on the medication used. NSAIDs are not teratogenic in the first two trimesters of gestation but their use is contraindicated in the third trimester since they have been associated with miscarriage and female infertility, with the exception of some drugs. The effects caused by a decrease in prostaglandin include primary pulmonary hypertension in the newborn and reduced renal blood flow, decreasing the production of amniotic fluid. Opioid analgesics are associated with different fetal adverse effects. Their chronic use can restrict uterine growth and cause low birth weight, in addition to neonatal withdrawal syndrome. The last is caused by any opioid but is more common with methadone and heroin since the use of opioid analogs such as morphine is controlled. This syndrome can occur from birth to 2 weeks of age and is characterized by hyperirritability, gastrointestinal dysfunction, respiratory distress, and central nervous system alterations.

Paracetamol is an analgesic and antipyretic that, although it can cross the placental membrane, does not exert teratogenic effects at therapeutic doses. It is therefore considered to be safe and can be prescribed throughout pregnancy (Schüler-Faccini et al. 2011, Wanderley & Artigalás 2011). The exception of paracetamol use is the administration of toxic doses, which can affect the liver of both the pregnant woman and the fetus and can cause maternal problems such as hemolytic anemia (Schüler-Faccini et al. 2011, Wanderley & Artigalás 2011). The incidence of congenital malformations associated with paracetamol use during pregnancy reported in a study on rats is 23 per 37 exposed fetuses (Fernandes 2017). The maximum dose of this drug is 75 mg/kg per day for a healthy adult and any dose above this limit might be toxic (Quintilio et al. 2022). The oral bioavailability of paracetamol ranges from 63 to 89% (Da Conceição Moura et al. 2022), which corresponds to 47.5 to 66.75 mg of the maximum absorbed dose.

Acetylsalicylic acid, when administered during pregnancy, can cause anemia, hemorrhage, and prolonged labor (Schüler-Faccini et al. 2011, Wanderley & Artigalás 2011). Regarding the incidence of congenital malformations associated with acetylsalicylic acid, a study on rats that received an oral dose of 150 mg aspirin/kg showed that 22 of the 172 fetuses examined were born with external fetal anomalies (Tanaka et al. 1973). The anomalies documented for doses of 300 mg/kg include fetal hypocoagulability, an increased incidence of hemorrhagic phenomena such as intracranial hemorrhage, gastroschisis in the first trimester, and closure of the ductus arteriosus in the third trimester (Tanaka et al. 1973, Tagashira et al. 1981). However, the last effect occurs after

exposure to this concentration for 3 days or more (Tagashira et al. 1981). On the other hand, the administration of low doses of this drug (60 to 150 mg/day), corresponding to 60 to 75 mg per 150-mg dose absorbed, does not pose a risk during pregnancy (Aragão & Tobias 2019). These aspirin doses even have positive effects on reproduction (Aragão & Tobias 2019) and may also contribute to reducing miscarriages in pregnant women with systemic lupus erythematosus and antiphospholipid antibody syndrome and to preventing pre-eclampsia and intrauterine growth restriction (Schüler-Faccini et al. 2011).

Ibuprofen is an analgesic and anti-inflammatory drug that, in experimental studies, exhibited teratogenic effects in humans but not in animals. The incidence of congenital malformations in pregnancies in which the woman used ibuprofen was 47 per 988 exposed neonates (Dathe et al. 2018). The main effects observed were gastroschisis, implantation disturbances, ductus arteriosus constriction, and prolonged labor (Schüler-Faccini et al. 2011). The maximum dose of ibuprofen is 3,200 mg per day (Bushra & Aslam 2010). Oral bioavailability is about 80% (Pereira et al., 2020), which corresponds to about 2,500 mg of the maximum absorbed dose.

Dipyrone exerts an action similar to that of paracetamol but with greater anti-inflammatory activity (Schüler-Faccini et al. 2011, Wanderley & Artigalás 2011). The incidence of cases of congenital malformations associated with the use of oral dipyrone is 1,382 per 22,843 exposed neonates (Bánhidy et al. 2007). Although pregnant women who use this drug do not show a significant increase in malformations or miscarriage rates, dipyrone use during pregnancy is associated with the risk of Wilms tumor and leukemia in children under two years of age (Aragão & Tobias 2019), in addition to the risk of aplastic anemia and agranulocytosis (Aragão & Tobias 2019, Schüler-Faccini et al. 2011, Wanderley & Artigalás, 2011). Despite these risks, dipyrone is not directly associated with fetal malformations, as long as it is administered at low doses and for a short period of time (Aragão & Tobias 2019). Ingestion of 2 to 3 g of the drug per dose can lead to dipyrone toxicity (Quintilio et al. 2022). Considering that the oral bioavailability of 750 mg dipyrone is 89% (Da Conceição Moura et al. 2022), the absorbed dose of the drug ranges from 1.78 to 2.67 g per 2- to 3-g dose, respectively.

Diclofenac is indeed used cautiously during early pregnancy for moderate occasional pain. The incidence of serious fetal malformations associated with diclofenac administration during the first trimester is concerning, with 4 per 220 live births affected. These malformations can include congenital septal heart defects, double kidney, cerebral atrophy with secondary macrocephaly and microcephaly (Padberg et al. 2018). In humans, the recommended limiting dosage of diclofenac is up to 200 mg per day (Ertekin et al. 2019). However, it's crucial to be aware of individual differences and factors such as gestational age, maternal health, and potential drug interactions. The bioavailability of diclofenac after oral administration is approximately 50%, meaning that about half of the administered dose reaches systemic circulation (Cassina et al. 2010).

Antidepressants

Antidepressants belong to the group of psychotropic drugs. They are synthetic or natural medicines that affect brain activity and that can have an excitatory, depressant or disruptive effect on the central nervous system. These drugs cannot be withdrawn abruptly because of the adverse effects that discontinuation causes. The most prescribed antidepressants

are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) since they are safer and cause fewer adverse effects (Azevedo Jr. et al. 2023). In women, the period of highest frequency of antidepressant use is the first trimester of gestation and the first postpartum month since these periods are characterized by frequent mood swings and fluctuations (Amorim et al. 2020). In these cases, the most recommended medications are those of the SSRI and TCA classes, respectively (Amorim et al. 2020, Azevedo Jr. et al. 2023).

The teratogenic effect of these types of medication varies depending on the drug used. Among SSRIs, sertraline proved to be the safest, with fewer adverse effects, and is also the preferred medication during breastfeeding (Amorim et al. 2020). Fluoxetine, despite its low risk of causing any adverse maternal or fetal effects during pregnancy (Azevedo Jr. et al. 2023), is not recommended during breastfeeding since therapeutic levels are distributed into breast milk. In the case of TCAs, although there are no reports of an association between these drugs and congenital malformations, they should be avoided during the first trimester. During the period of breastfeeding, with the exception of maprotiline and doxepin, all antidepressants are safe and are not detected at high doses in serum of infants born to mothers who used these medications (Amorim et al. 2020).

In summary, since the safety of antidepressants in general during pregnancy and breastfeeding has not yet been fully established, their use should be avoided. It is recommended to use drugs that have been proven to be less teratogenic and safer for the mother and the fetus. Furthermore, the severity of the maternal mental disease must be assessed and treatment, at low doses, should only be initiated if the maternal health benefits justify the risk for the fetus or neonate (Amorim et al. 2020, Azevedo Jr. et al. 2023).

Chemotherapeutic agents

Chemotherapeutic agents are considered to be teratogenic since they inhibit cell division and can cross the placental membrane, affecting fetal tissues. These drugs can also interfere with essential metabolic pathways, destroying macromolecules both in tumor tissue and in other tissues, resulting in systemic effects (Peres et al. 2001, Peres & Sordi 2011).

In cases in which the pregnant woman has cancer and needs to use cytostatics, the treatment involves maternal and fetal risks. In the fetus, the immediate effects include miscarriage, mutagenesis and teratogenesis, with damage to one or multiple organs and late effects such as growth retardation and gonadal dysfunction. Maternal effects are linked to complications during labor. Thus, the use of these drugs should be discontinued about one month before labor. The risks associated with chemotherapy depend on the stage of pregnancy, the type of chemotherapeutic agent, the duration of use and dose of the drug, the use of mono- or polychemotherapy (Schünemann Jr. et al. 2007), and the characteristics of the placental membrane (Peres et al. 2001). There are three phases that are sensitive to cytostatics: 1) the pre-implantation and implantation phase of the egg (up to 2 weeks): abortion due to irreversible damage is common; 2) the phase of organogenesis (2 to 12 weeks): the period most sensitive to teratogenesis; 3) the growth phase (2nd and 3rd trimesters): the most common damage during this phase are intrauterine growth restriction, an increase in prematurity rate, and perinatal mortality, as well as structural and functional damage to gonadal tissues and the central nervous system because they are not fully formed (Peres et al.

2001, Schünemann Jr. et al. 2007, Peres & Sordi 2011). Chemotherapeutic agents can also pass into breast milk, with serious consequences for the neonate (Schünemann Jr. et al. 2007).

Methotrexate is the main example of a chemotherapy drug with great teratogenic potential, a drug whose oral bioavailability is, on average, 70% (Herman et al. 1989). The main malformations are reported in the first trimester, with a frequency of 17% (10 of 58 exposures) (Schünemann Jr. et al. 2007, Moore et al. 2016, Selig et al. 2012). These malformations can be skeletal and intracranial abnormalities, absence of frontal bone, hypertelorism, jaw hypoplasia and heart defects (Schünemann Jr. et al. 2007, Moore et al. 2016). Selig et al. (2012) presents a case in which a child was exposed every two weeks to methotrexate from weeks 11 to 17 of pregnancy at a dose of 100 mg, with an absorption of 70 mg, and from 17 to 23 to 200 mg, with an absorption of 140 mg, doses that led to the presentation of mild symptoms of methotrexate fetal syndrome in the child.

Contraceptives

The currently most used contraceptives, combined oral contraceptives (COCs) which combine a progestin and an estrogen, are based on synthetic sex hormones (Prahalada & Hendrickx 1983, Rocha 2021). Over the years, contraceptives have undergone structural and dosage modifications, which resulted in the most recent fourth-generation contraceptives (Rocha 2021). However, there are studies indicating an association between the use of oral contraceptives and congenital anomalies (Charlton et al. 2016, Simpson & Phillips 1990) since both estrogens and progestin have been identified to be teratogenic and mutagenic by some authors (Simpson & Phillips 1990). An incidence of congenital malformations of 22,013 per 880,694 neonates exposed up to the first year of life has been reported (Charlton et al. 2016). Anomalies observed in neonates include hypoplastic left heart syndrome, limb reduction defects (Charlton et al. 2016, Simpson & Phillips 1990), urinary tract anomalies, gastroschisis, and hypospadias (Simpson & Phillips 1990). If synthetic estrogen, ethinyl estradiol or mestranol, was administered as monotherapy, no teratogenic effects were observed in dogs, rats, or rabbits (Prahalada & Hendrickx 1983). However, a study on rats showed that maternal exposure to diethylstilbestrol, a synthetic estrogen, resulted in congenital malformations observed only in adulthood, cancer in the offspring including clear cell adenocarcinoma of the vagina and cervix, genital tract anomalies, and vaginal adenosis in exposed offspring. In the case of lineage, there was no increase in the incidence of cancer but genital tract anomalies and the possibility of changes in social behaviors were observed (Mittendorf 1995). On the other hand, progestin, when administered alone, was found to be teratogenic in rats, rabbits and rhesus monkeys, and norethindrone was teratogenic in rats, rhesus monkeys, and dogs. The effects of this hormone in rhesus monkeys included an increase in the number of stillbirths, virilization of female fetuses, and cryptorchidism in male fetuses. In contrast, the administration of norethindrone combined with ethinyl estradiol at therapeutic doses was not teratogenic in rats or rabbits (Prahalada & Hendrickx 1983).

Ahn et al. (2008) showed that the relationship between the use of COCs during the perinatal period and newborn outcomes varies according to the medication administered. In the case of administration of one tablet containing 0.075 mg gestodene and 0.03 mg ethinyl estradiol, among the 54 fetuses exposed for 4 weeks, there were two cases with low birth weight (weight < 2.5 kg), four were large for gestational age (weight > 4 kg),

and birth defects included facial dysmorphia in one case and meconium peritonitis in another case. On the other hand, in the case of maternal exposure in four different pregnancies to tablets containing 0.05 mg levonorgestrel and 0.03 mg ethinyl estradiol for a period of 3.3 weeks, there were no adverse effects related to the use of this COC in three neonates, resulting in good pregnancy outcomes. The oral bioavailability is 99% for progestin, about 45% for ethinyl estradiol, and almost 100% for levonorgestrel (Baptista et al. 2007), corresponding to approximately 0.075, 0.015 and 0.05 mg, respectively.

Although studies have demonstrated a relationship between malformations in human neonates and the use of COCs, especially those containing high doses of progestin, these drugs do not significantly increase the incidence of cases when compared to the incidence of anomalies in regular pregnancies and should therefore not be considered human teratogens (Ahn et al. 2008). A review on the topic showed that exposure to oral contraceptives immediately before or during pregnancy does not appear to be associated with an increased risk of serious birth defects (Charlton et al. 2016).

Systematization of the results

The present results are summarized in Table I. This table lists the teratogens investigated, the dose considered to be safe, the dose associated with alterations in the embryo, absorbed dose (when known), the exposure time that represents a risk to the embryo, and the incidence in humans. In the case of COCs, we did not find concrete evidence of teratogenic effects in the studies analyzed. Regarding antidepressants, since the safest and most recommended classes for use by the general population are SSRIs and TCAs, this type of medication was not included in Table I. As intended, a social media page with a broad audience was created (see link: https://www.instagram.com/agentes_teratogenicos/). We were careful not to use real photos of children with deformities. Thus, the most striking characteristics of the effects of teratogenic agents were presented in simple but eye-catching figures. The aim is not to shock the audience but to inform them. The images were then released for public access. Although launched only a few weeks ago, the site already has hundreds of followers. This shows that people search for this type of information, which is of great interest to the public. We intend to continue this dissemination and interaction with society.

CONCLUSIONS

In summary, it is important that pregnant women abstain from the use of illicit and licit substances throughout pregnancy, so that embryonic/fetal development is not compromised. Furthermore, in the case of unrestricted, socially accepted and widely consumed substances, their use should be avoided, especially during organogenesis. If this is not possible, pregnant women must use them only when strictly necessary and under medical supervision. To raise awareness among the general public regarding the negative impact of substances used during pregnancy on embryonic/fetal development, the information was systematized and written in easy-to-understand language to be displayed on a social media platform with broad audience, serving as a guide for the prevention of malformations induced by teratogenic agents.

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