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REVIEW

The most common teratogens as factors of mutability: A literature review

Los teratógenos más comunes como factores de mutabilidad: Una revisión bibliográfica

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ABSTRACT

Introduction: the teratogenic agents during the embryonic period can result in disorders in organ differentiation. Concerns regarding medication use during pregnancy heightened after the thalidomide case in the 1960s, underscoring the need for a balance between caution and effective treatment, given the lack of clear information on risks. The aim of the research was to understand teratogens as factors that increase mutability and highlight the relevance of preventive strategies to ensure fetal and maternal health.
Methods: literature review using the PubMed database, Scopus and Web of Science was conducted. Forty-four articles, documents, clinical trials, and systematic reviews published in English were included. Teratogens and their effects, as well as preventive strategies for teratogenic congenital defects, were explored.
Results: risks associated with specific substances were examined, highlighting their effects on the fetus and providing epidemiological data. Preventive measures such as vaccination, folic acid supplementation, and control of metabolic diseases were addressed.
Conclusions: during pregnancy, it is crucial to avoid exposure to chemicals, drugs, and medications that may harm the fetus. Caution should be exercised with the use of medications, and alcohol, tobacco, and illicit drugs should be avoided. Preventive strategies such as vaccination and folic acid supplementation reduce the risk of congenital malformations and promote a healthy pregnancy.

Keywords: Congenital Defects; Teratogens; Congenital Malformations; Epidemiology; Prevention; Mutation.

RESUMEN

Introducción: los agentes teratogénicos durante el período embrionario pueden resultar en trastornos en la diferenciación de órganos. Las preocupaciones sobre el uso de medicamentos durante el embarazo aumentaron después del caso de la talidomida en la década de 1960, subrayando la necesidad de equilibrar la precaución y el tratamiento efectivo, dado que no hay información clara sobre los riesgos. El objetivo de la investigación fue comprender los teratógenos como factores que aumentan la mutabilidad y resaltar la relevancia de las estrategias preventivas para asegurar la salud fetal y materna.
Métodos: se realizó una revisión detallada de la literatura utilizando la base de datos PubMed, Scopus y Web of Science. Se incluyeron cuarenta y cuatro artículos, documentos, ensayos clínicos y revisiones sistemáticas publicados en inglés. Se exploraron los teratógenos y sus efectos, así como las estrategias preventivas para los defectos congénitos teratogénicos.
Resultados: se examinaron los riesgos asociados con sustancias específicas, destacando sus efectos en el feto y proporcionando datos epidemiológicos. Se abordaron medidas preventivas como la vacunación, la suplementación con ácido fólico y el control de enfermedades metabólicas.
Conclusiones: durante el embarazo, es crucial evitar la exposición a químicos, fármacos y medicamentos

que puedan dañar al feto. Se debe tener precaución con el uso de medicamentos, y se deben evitar el alcohol, el tabaco y las drogas ilícitas. Las estrategias preventivas, como la vacunación y la suplementación con ácido fólico, reducen el riesgo de malformaciones congénitas y promueven un embarazo saludable.

Palabras clave: Defectos Congénitos; Teratógenos; Malformaciones Congénitas; Epidemiología; Prevención; Mutación.

INTRODUCTION

Embryonic and fetal development is an intricate process influenced by a complex interplay of endogenous and exogenous factors. Among the exogenous elements that can significantly affect this development are teratogens, which range from medications and drugs to infections and radiation.[1] These agents can trigger disorders at critical moments of development, resulting in permanent congenital malformations or even embryo or fetal loss.[1]

The embryonic period, particularly between weeks 3 and 8 post-conception, is especially sensitive to external influences, and exposure to teratogens during this time can lead to disorders in organ differentiation and, consequently, malformations.[2] Understanding the impact of these factors on the organogenesis process is essential as it provides a basis for addressing and preventing potential complications in fetal development.

The use of medication during pregnancy has been a cause for concern since the tragic case of thalidomide in the 1960s. Despite advancements in identifying and labeling teratogenic drugs, the need for a proper balance between caution and effective treatment persists.[3]

The lack of clear information about the actual risks of pharmacological therapy in the early stages of pregnancy has led to difficult decisions and, in some cases, unnecessary abortions.

This review addresses the importance of understanding teratogens as factors that increase mutability, exploring examples of specific congenital defects following exposure to certain teratogens, statistical studies, and some of the current implications for decision-making in pregnancy treatment. Additionally, it highlights the basic rules of prenatal toxicology established by Wilson (1977), which provide a conceptual framework for evaluating and understanding the risks associated with exposure to harmful substances during gestation. Knowledge of these rules is revealed as fundamental for addressing the challenges posed by teratogens and, in turn, contributes to the prevention of congenital malformations and fetal developmental dysfunctions. The article also aims to comprehend teratogens as factors that increase mutability and underscore the relevance of prevention through strategies such as vaccination, supplementation with folic acid, water, and salt iodization, as well as abstinence from alcohol and tobacco during pregnancy, and proper medication control for maternal metabolic diseases, in order to ensure optimal health for both the fetus and the mother.

METHOD

The methodology used in this study on teratogenic congenital defects was based on a systematic literature review. Searches were conducted in the PubMed, Scopus and Web of Science databases using relevant keywords such as “congenital defects,” “teratogens,” “congenital malformations,” “epidemiology,” “prevention,” among others. A total of 44 articles were included, including documents, clinical trials, systematic reviews, meta-analyses, and randomized controlled trials, in English and very few in Spanish.

The diversity of defects induced by teratogenic agents was considered. Additionally, the different causes and underlying mechanisms of congenital defects, as well as prevention strategies, were explored. This methodology allowed for a comprehensive overview of teratogenic congenital defects based on a thorough review of the most recent scientific literature within the past 5 years to ensure the relevance and timeliness of the information.

DEVELOPMENT

Teratogenic congenital malformations or defects are developmental disorders that occur before birth during the embryonic or fetal period. The incidence rate among live-born infants is approximately 3 %. The cause can be genetic, external, or teratogenic. Teratogens are environmental factors that lead to permanent structural or functional malformations or to the death of the embryo or fetus. Teratogens include infections, certain medications, drugs, and radiation.[4]

The epidemiology of congenital malformations, also known as dysmorphias, encompasses a crucial field in medicine. Teratology, the discipline responsible for studying the causes and manifestations of these anomalies, reveals an incidence rate ranging from 4 % to 6 %. This phenomenon affects approximately 2 % to 3 % of all newborns and children under five years old.[5] Alarmingly, malformations constitute the leading cause of infant mortality, accounting for about 21 % of deaths, as well as significant disabilities. It is concerning that only a direct cause is identified in 40 % to 60 % of cases, where genetic factors, teratogens, and a combination of both share responsibility. The incidence of minor anomalies, such as microtia or narrow palpebral fissures, deserves special

attention, as they indicate a serious malformation in 3 % to 20 % of cases or are part of a more complex syndrome.[5]

The classification of congenital malformations is fundamental to understanding their nature and origin. They are divided into primary malformations, which occur during organogenesis between the third and eighth week of pregnancy, characterized by total or partial organ failure and structural defects such as agenesis.[6] On the other hand, secondary malformations arise from the destruction or alteration of organs already in development, such as intestinal atresia or amniotic band syndrome. Additionally, there are double malformations or "conjoined twins", originating from incomplete delimitation of embryoblasts at the blastocyst stage, where two fetuses grow together. These can manifest as symmetrical double malformations, where both fetuses have a complete set of organs, or asymmetrical, where an uneven distribution leads to disparate development of both fetuses.[6]

Teratogens, or factors that can induce mutations and malformations, are classified into four distinct categories. Firstly, we have physical teratogens, which include agents such as radiation and other forms of physical energy that have the potential to affect fetal development. The second category encompasses biological teratogens, comprising agents such as viruses and bacteria capable of causing fetal malformations.[7] The third category includes chemical teratogens, drugs, and medications, which can have adverse effects on fetal development if consumed during pregnancy. Lastly, the fourth category addresses ecological, intrauterine, and maternal teratogens, considering environmental factors, intrauterine conditions, and maternal health that may influence fetal development.[7]

The pathophysiology of congenital malformations reveals a complex interaction between different stages of embryonic and fetal development, known as phase-dependent vulnerability. This process begins with gametopathy, characterized by alterations in maternal or paternal gametes before conception, which can trigger structural or numerical chromosomal defects and, in extreme cases, lead to spontaneous abortions.[7,8]

During blastopathy, spanning from fertilization to the first 14 days of gestation, failures in blastocyst implantation can occur, leading to double malformations or the formation of identical twins.[8]

Embryopathy, which takes place between the second and eighth week of pregnancy, is a phase of high susceptibility to teratogens, with specific manifestations in different organ systems. For example, in the central nervous system (CNS), during the period from the third to the 32nd or 40th day of gestation, there is a risk of developing neural tube defects such as spina bifida and mental retardation. Similarly, in the heart (between the third and 7th-9th day of gestation), malformations such as common arterial trunk, atrial septal defects, and ventricular septal defects may occur. These anomalies extend to other systems, including the limbs, ears, airways, genitourinary system, gastrointestinal tract, face, lips, and palate.[8]

According to the WHO, the term encompasses all exogenous influences on intrauterine development that lead to morphological or biochemical anomalies, as well as behavioral disorders diagnosed immediately after birth or later.[9]

Knowledge of the basic rules of prenatal toxicology established by Wilson (1977) is essential as it provides a solid foundation for evaluating and addressing the effects of teratogens during pregnancy, significantly contributing to the prevention of malformations and congenital dysfunctions.[10] These rules offer a framework for understanding how harmful substances affect the embryo during gestation and can cause severe malformations and dysfunctions in organs and systems.

Similarly, the third rule states that various embryotoxic agents can affect embryo development through specific mechanisms, such as interference with folate balance leading to neural tube defects. This understanding helps us better identify the potential risks associated with prenatal exposure to certain substances and implement more effective preventive strategies.[10]

Additionally, rules 4 and 5 highlight that, following exposure to harmful substances, the embryo may experience different outcomes, and that a substance's ability to cross the placenta depends on its chemical and physical properties.[10]

These points are crucial for assessing and addressing the effects of teratogens on embryonic and fetal development, contributing significantly to the understanding and prevention of congenital malformations and dysfunctions.

Finally, the sixth rule emphasizes that the alteration of embryonic development increases with the dosage of embryotoxic substances, indicating a dose-response relationship where high doses may result in teratogenic, embryolethal, or even toxic effects for the mother.[10]

Teratogens

Physical

- Hyperthermia: There has been ongoing debate regarding the increased risk of spontaneous abortion and malformations, such as neural tube defects, cardiac anomalies, and abdominal wall defects, when the body temperature exceeds 38,5°C during the first 6 weeks of pregnancy. Since then, an association with neural tube defects has been established, as demonstrated by a study conducted.[11]
- Electromagnetic Fields: According to the current available information, electromagnetic fields in the low-frequency range do not seem to pose a significant risk to prenatal development. Therefore,

occupational activities involving computer use or exposure to magnetic resonance imaging are also considered safe during pregnancy.[12]

- Ionizing radiation: After the atomic bombings of Hiroshima and Nagasaki, it was observed that approximately 25 % of intrauterine-exposed children had central nervous system malformations. In Central Europe, natural radiation exposure is around 2 mGy. Conventional radiological diagnosis can result in intrauterine radiation doses of up to 10 mGy, as in the case of a standard abdominal X-ray ranging between 1 and 5 mGy. In the case of computed tomography, radiation doses can be higher depending on the section thickness but still remain well below 50 mGy. It is important to note that radiation exposure below 50 mGy represents a very low risk to the embryo. The critical phase for radiation damage is considered to be between the 8th and 15th weeks of pregnancy. However, it is important to emphasize that diagnostic X-ray use is by no means an indication for abortion, according to the American College of Obstetricians and Gynecologists (ACOG) in 2004.[13]
- Radionuclides: In diagnostic settings, the radioisotope technetium-99m is the most commonly used due to its short half-life of 6 hours. Organ scans such as lungs, brain, bones, kidneys, heart, and thyroid gland using this isotope typically result in radiation doses below 5 mGy, which are not considered a cause for concern. As for radioactive iodine-131, its use for treating maternal thyroid disease is no longer recommended, especially after the tenth week of pregnancy, due to the risk it poses to the fetal thyroid gland, as stated by the American College of Obstetricians and Gynecologists (ACOG) in 2004.[13]

Others teratogens

- Contaminants: Lead has been associated with an increased rate of abortions and may affect the development of the fetus's central nervous system. On the other hand, organic mercury was identified as a teratogenic substance after the incident known as Minamata disease in Japan. Children exposed in utero showed cerebral atrophy, microcephaly, mental retardation, seizures, spasticity, and blindness. It is important to note that these effects are not related to inorganic mercury present in dental amalgam fillings. Overall, for most industrial and environmental chemicals, there is a lack of sufficient data to assess their teratogenic potential. However, based on the information available to date, a potential risk of fetal harm should be considered for the following agents: lead, chlorinated biphenyls, chloromethane, diethylene glycol dimethyl ether, dimethylformamide, 2-ethoxyethanol, 2-ethoxyethyl acetate, carbon disulfide, carbon monoxide, 2-methoxyethanol, 2-methoxyethyl acetate, 2-methoxypropanol, and methoxypropyl acetate.[14]
- Infections: During pregnancy, infections pose a significant risk to both the mother and the fetus. Urinary tract infections, for instance, increase the likelihood of complications such as low birth weight, preterm labor, sepsis, pneumonia, and miscarriages, emphasizing the importance of their prompt detection and treatment. Rubella infection during pregnancy can have serious consequences, including a classic triad of cataracts, deafness, and cardiac abnormalities such as patent ductus arteriosus, along with other complications like glaucoma, microphthalmia, pulmonary artery stenosis, intellectual disability, microcephaly, or hepatomegaly.[15] Sexually transmitted infections also pose a risk during pregnancy, with complications ranging from miscarriages and preterm birth associated with gonorrhea and chlamydia, to conjunctivitis, pneumonia, and sepsis in the newborn due to congenital infections. Syphilis, on the other hand, increases the risk of miscarriage and can result in fetal death. Additionally, congenital syphilis can lead to numbness, skeletal deformities, jaundice, and facial anomalies in the fetus. These examples underscore the importance of prenatal monitoring and proper treatment of infections during pregnancy to ensure optimal health for both the mother and the baby.[15,16]

The use of medications during pregnancy

Requires careful consideration due to significant changes in drug metabolism that occur. These changes include an increase in interstitial fluid volume, alterations in the pattern of serum proteins, and increased activity of maternal hepatic enzymes due to elevated levels of sex steroids. These changes can affect the distribution, protein binding, and metabolism of medications administered during pregnancy.[17] Therefore, it is crucial to regularly monitor plasma levels of drugs, adjust doses as necessary, and exercise special caution in pregnant women with underlying diseases that may interfere with drug metabolism. These measures are fundamental to ensuring safe and effective medication management during pregnancy, thus minimizing any potential risk to both the mother and the fetus.

Medication during pregnancy requires special attention due to its potential effects on fetal development. Some medications are contraindicated during this period due to the possible complications they may cause. Among antibiotics, aminoglycosides may lead to ototoxicity, while tetracyclines are associated with mental illness or deafness in the fetus.[18]

Antihypertensive drugs also present risks, such as angiotensin-converting enzyme inhibitors, which may cause oligohydramnios and renal failure, and angiotensin II receptor antagonists, which are associated with

renal dysplasia.[19]

In the case of anticonvulsants, both phenytoin and valproic acid can lead to facial dysmorphism, neural tube defects, and congenital heart defects in the fetus.[20]

Psychiatric medications also carry risks, such as lithium, which may cause cardiac anomalies, including Ebstein's anomaly.[21] Isotretinoin is associated with facial anomalies, congenital heart defects, and neural tube defects.[22] Additionally, warfarin has been linked to skeletal abnormalities, while thalidomide may cause amelia or meromelia and cardiac diseases.[23]

Another medication, diethylstilbestrol, has been associated with clear cell adenocarcinoma of the vagina in female offspring exposed to it.[24] Finally, steroidal hormones and estrogens also pose risks during pregnancy, such as masculinization of female genitals with steroidal hormones and malformations of both female and male genital organs with estrogens.[25]

Drugs

- Alcohol: Ethanol, as a widely used teratogen, is frequently implicated in the occurrence of congenital malformations. Evaluating the risk of alcohol exposure is complicated due to the unreliability of information provided by affected individuals, as well as frequent combinations with other factors such as smoking, an imbalanced diet, and medication abuse.[26] Chronic alcohol consumption has been associated with various anomalies that comprise fetal alcohol syndrome (FAS), including prenatal and postnatal growth restriction, central nervous system defects leading to intellectual disability and behavioral disorders, as well as craniofacial dysmorphia characterized by microcephaly, narrow palpebral fissures, short and broad nasal bridge, and flat midface with maxillary hypoplasia.[27] Additionally, limb anomalies such as camptodactyly, clinodactyly, and phalangeal hypoplasia have been recorded, along with an increased incidence of cleft lip and palate among those with chronic alcohol abuse.[28] Fetal alcohol syndrome is estimated to affect 30-45 % of pregnant women who consume at least 140 grams of pure ethanol per day, approximately equivalent to 1,5 liters of wine. Long-term studies, conducted over more than 10 years, have revealed a fading of most morphological stigmata, but a persistence of microcephaly and intellectual or psychosocial delay. Even with moderate consumption of 2 drinks per day, a 7-point decrease in IQ has been observed. On the other hand, excessive short-term alcohol consumption, defined as at least 5 drinks, has been shown to produce a delay of 1 to 3 months in reading and arithmetic skills after the first year of school.[29] Finally, it has been observed that with regular consumption of around 15 grams of ethanol per day, the first statistically understandable developmental disorders begin to manifest, including discreet impairment of intrauterine growth and mental development.[30]
- Tobacco smoke: In addition to nicotine, tobacco smoke contains carbon monoxide, tar, and heavy metals. Smoking is considered embryotoxic and fetotoxic, and a weak association with facial clefts and clubfoot in offspring has been established, according to a study.[31] Among smokers, reduced birth weight, increased perinatal mortality, as well as a higher incidence of dysfunction and premature birth, are observed.[31]
- Opiates: Heroin addicts often experience intrauterine growth restriction, premature rupture of membranes, and preterm birth. In this context, substitution with methadone or buprenorphine appears to be a reasonable option, provided that a gradual dose reduction is sought under close medical supervision.[32] It is crucial to avoid acute opioid withdrawal at all costs during pregnancy, as it is associated with obstetric complications such as intrauterine growth retardation and preterm birth. After initial neonatal respiratory depression, withdrawal symptoms can be expected, including respiratory distress syndrome, hyperirritability, tremors, diarrhea, vomiting, and cerebral seizures, typically occurring between 24 and 72 hours after birth. These symptoms may also manifest up to 10 to 36 days after birth. It is essential that pharmacological treatment, such as the use of phenobarbital, be administered under clinical supervision to avoid potential life-threatening complications.[32]
- Cocaine: In the case of sporadic cocaine use, a significant increase in the rate of malformations in the early stages of pregnancy has not been detected. However, if substance abuse continues, complications are more frequent due to vasoconstriction, which reduces blood flow and can result in spontaneous abortions, stillbirths, preterm birth, premature placental abruption, growth restriction, microcephaly, and necrotizing enterocolitis. Additionally, various associated malformations have been described, such as cerebral infarctions, anomalies in the genitourinary and skeletal systems, and intestinal atresia.[33]
- Marijuana: No significant increase in the rate of malformations has been observed following marijuana consumption during pregnancy; however, with continued abuse, an increase in perinatal mortality can be expected. A long-term study conducted after regular intrauterine exposure revealed a significant decline in speech and memory performance at the age of 4, according to research conducted.[34]
- LSD: Although skeletal system and central nervous system (CNS) malformations have been reported in association with the misuse of LSD, a definitive epidemiological correlation has not been clearly established. In the event of a pregnancy detected in the context of LSD abuse, it is crucial to perform a

detailed ultrasound evaluation to rule out possible malformations.[35]

- Amphetamines: Amphetamines, popularly known among young people as ecstasy or speed, have gained great popularity today. Experiments conducted with animals have revealed the occurrence of malformations in the central nervous system, as well as in the lip and palate region, associated with the consumption of various amphetamines. In humans, amphetamine abuse has been associated with a higher incidence of heart defects and clubfoot, according to studies.[36]
- Solvents: Organic solvents, such as toluene, gasoline, and halogenated hydrocarbons, are often misused as inhalation agents. Cases of child damage like fetal alcohol syndrome have been reported as a result of this exposure. However, these effects have not been observed after occupational exposure. Nevertheless, it is recommended to minimize professional contact with these solvents by implementing adequate ventilation or considering workplace changes.[37]

Diseases related to malformations

Epilepsy

The rate of malformations in children of mothers with epilepsy is estimated to be 2 to 3 times higher than in the general population, according to studies. Although a slight increase in the risk of malformations has been observed in parents with epilepsy, it is crucial to highlight those anomalies associated with the antiepileptic syndrome, such as orofacial clefts, facial dysmorphism, and limb defects, cannot be solely attributed to the medication in question.[38]

Diabetes mellitus

Perinatal mortality tends to be lower in patients requiring insulin for diabetes control. However, despite the decline in maternal diabetes mellitus in recent decades, a significant increase in the incidence of congenital malformations has been observed, now ranging between 6 % and 12 %. The risk of malformations or spontaneous abortions has been found to be associated with episodes of maternal hyperglycemia during weeks 5 to 8 of pregnancy, according to the American College of Obstetricians and Gynecologists (ACOG).[39]

An example of a characteristic anomaly associated with maternal diabetes is the caudal regression syndrome, which occurs between 200 and 400 times more frequently compared to the general population. Additionally, central nervous system malformations, including neural tube defects and holoprosencephaly, are up to 10 times more common in these cases.[40] Furthermore, cardiac anomalies, such as ventricular septal defects or transposition of the great vessels, are up to 5 times more frequent in newborns of diabetic mothers.[41]

Thyroid Disorders

Maternal hypothyroidism has been associated with an increased rate of spontaneous abortions, premature births, and fetal anomalies. On the other hand, iodine deficiency poses a risk to the newborn, as it may develop neonatal goiter or cretinism. In the case of untreated hyperthyroidism, an increase in the rate of spontaneous abortions is also expected.[42]

Prevention

The prevention of congenital malformations is crucial to ensure the health of both the fetus and the mother. Several strategies can significantly reduce the incidence of these anomalies, many of which should be implemented before conception to maximize their effectiveness. Among these strategies is maternal vaccination against rubella, which helps prevent serious complications such as heart abnormalities and deafness in the fetus. Supplementation with folic acid before and during pregnancy is crucial, as it has been shown to reduce the incidence of neural tube defects, such as spina bifida.[42]

Water and table salt iodization is another important preventive measure as it prevents thyroid development disorders such as cretinism, which can affect the cognitive and physical development of the fetus. Furthermore, abstaining from alcohol and cigarettes is essential as the consumption of these substances during pregnancy is associated with a higher risk of congenital malformations and neonatal complications.[43]

Finally, good medication control for maternal metabolic diseases is crucial to minimize risks for the fetus. This includes maintaining appropriate dosage of medications for conditions such as diabetes and hypertension, which can have adverse effects on fetal development if not properly controlled. Together, these preventive measures play a crucial role in promoting a healthy pregnancy and reducing congenital malformations.[44]

CONCLUSIONS

Is crucial to take preventive measures during pregnancy to ensure fetal health by minimizing exposure to chemicals, medications, and drugs that may have adverse effects on fetal development. Special caution should be exercised with medication use due to maternal metabolism changes, and avoiding alcohol, tobacco, and illicit drugs is recommended. Additionally, it's important to consider the risks associated with specific maternal diseases.

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Implementing preventive strategies such as vaccination, folic acid supplementation, and iodization of drinking water can help reduce the incidence of congenital malformations and promote a healthy pregnancy.

REFERENCES

1. Cornwall-Scoones J, Zernicka-Goetz M. Unifying synthetic embryology. Dev Biol. 2021;474:1–4. DOI: 10.1016/j.ydbio.2021.03.007

2. Zaninovic N, Rosenwaks Z. Artificial intelligence in human in vitro fertilization and embryology. Fertil Steril. 2020;114(5):914–920. DOI: 10.1016/j.fertnstert.2020.09.157

3. Bonasia S, Smajda S, Ciccio G, Robert T. Stapedial Artery: From Embryology to Different Possible Adult Configurations. AJNR Am J Neuroradiol. 2020;41(10):1768–1776. DOI: 10.3174/ajnr.A6738

4. Mantri SS, Raju B, Jumah F, Rallo MS, Nagaraj A, Khandelwal P, et al. Aortic arch anomalies, embryology and their relevance in neuro-interventional surgery and stroke: A review. Interv Neuroradiol. 2022;28(4):489–498. DOI: doi.org/10.1177/15910199211039924

5. Simopoulou M, Sfakianoudis K, Maziotis E, Rapani A, Giannelou P, Pantou A, et al. Assessing Clinical Embryology Research: A Global Bibliometric Analysis. Medicina (Kaunas). 2020;56(5):210. DOI: 10.3390/medicina56050210

6. Aguilar-Alaniz E, Reyes-Pavón R, Van-der-Ende J, Félix-Orta FJ, Mora ID, Aroca-Peinado Á, et al. Quality of life of children and adults following cardiac surgery for congenital heart disease: A Mexican cohort. Arch Cardiol Mex. 2021;91(1):34–41. DOI: 10.24875/ACM.20000107

7. Draghici CC, Miulescu RG, Petca RC, Petca A, Dumitrașcu MC, Șandru F. Teratogenic effect of isotretinoin in both fertile females and males (Review). Exp Ther Med. 2021;21(5):534. DOI: 10.3892/etm.2021.9966

8. Ahn D, Kim J, Kang J, Kim YH, Kim K. Congenital anomalies and maternal age: A systematic review and meta-analysis of observational studies. Acta Obstet Gynecol Scand. 2022;101(5):484–498. DOI: 10.1111/aogs.14339

9. Hou J, Sha Z, Hartley W, Tan W, Wang M, Xiong J, et al. Enhanced oxidation of arsenite to arsenate using tunable K+ concentration in the OMS-2 tunnel. Environ Pollut. 2018;238:524–531. DOI: 10.1016/j.envpol.2018.03.047

10. Kühne BA, Teixidó E, Ettcheto M, Puig T, Planas M, Feliu L, et al. Application of the adverse outcome pathway to identify molecular changes in prenatal brain programming induced by IUGR: Discoveries after EGCG exposure. Food Chem Toxicol. 2022;170:113506. DOI: 10.1016/j.fct.2022.113506

11. Asatsuma-Okumura T, Ito T, Handa H. Molecular Mechanisms of the Teratogenic Effects of Thalidomide. Pharmaceuticals (Basel). 2020;13(5):95. DOI: 10.3390/ph13050095

12. Abadie RB, Keller CL, Jones NT, Mayeux EL, Klapper RJ, Anderson L, et al. Review of Teratogenic Effects of Leflunomide, Accutane, Thalidomide, Warfarin, Tetracycline, and Angiotensin-Converting Enzyme Inhibitors. Cureus. 2023;15(12):e50465. DOI: 10.7759/cureus.50465

13. Sehnal L, Smutná M, Bláhová L, Babica P, Šplíchalová P, Hilscherová K. The Origin of Teratogenic Retinoids in Cyanobacteria. Toxins (Basel). 2022;14(9):636. DOI: 10.3390/toxins14090636

14. García-Álvarez JM, Escribano-Sánchez G, Osuna E, Molina-Rodríguez A, Díaz-Agea JL, García-Sánchez A. Occupational Exposure to Inhalational Anesthetics and Teratogenic Effects: A Systematic Review. Healthcare (Basel). 2023;11(6):883. DOI: 10.3390/healthcare11060883

15. Gao S, Wang S, Fan R, Hu J. Recent advances in the molecular mechanism of thalidomide teratogenicity. Biomed Pharmacother. 2020;127:110114. DOI: 10.1016/j.biopha.2020.110114

16. Gilbert RK, Petersen LR, Honein MA, Moore CA, Rasmussen SA. Zika virus as a cause of birth defects: Were the teratogenic effects of Zika virus missed for decades? Birth Defects Res. 2023;115(3):265–274. DOI: 10.1002/bdr2.2134

17. Tari RM, Diallo A, Kouame E, Assogba P, Badjabaissi E, Povi LE, et al. Assessment of the Teratogenic Effect of Sulfadoxine-Pyrimethamine on the Chicken Embryo. J Toxicol. 2022;2022:2995492. DOI: 10.1155/2022/2995492

18. Animaw Z, Asres K, Tadesse S, Basha H, Taye S, Abebe A, et al. Teratogenic Evaluation of 80% Ethanol Extract of Embelia schimperi Vatke Fruits on Rat Embryo and Fetuses. J Toxicol. 2022;2022:4310521. DOI: 10.1155/2022/4310521

19. Michaud PA, Diezi M, Guihard L, Jacot-Guillarmod M, Kleist P, Sprumont D, et al. Including adolescents of childbearing potential in clinical trials with possible exposure to teratogenic medication: a challenge for paediatricians and researchers. Swiss Med Wkly. 2020;150:w20333. DOI: 10.4414/smw.2020.20333

20. Chandramouli S, Alvarez C, Englund TR, Silverstein RG, Sheikh SZ. Teratogenic medication use associated with favourable odds of contraception counselling in a cohort of women with systemic lupus erythematosus at a large tertiary academic medical centre. Lupus Sci Med. 2022;9(1):e000823. DOI: 10.1136/lupus-2022-000823

21. Winterstein AG, Wang Y, Smolinski NE, Thai TN, Ewig C, Rasmussen SA. Prenatal Care Initiation and Exposure to Teratogenic Medications. JAMA Netw Open. 2024;7(2):e2354298. DOI: 10.1001/jamanetworkopen.2023.54298

22. Metruccio F, Battistoni M, Di Renzo F, Bacchetta R, Santo N, Menegola E. Teratogenic and neuro-behavioural toxic effects of bisphenol A (BPA) and B (BPB) on Xenopus laevis development. Reprod Toxicol. 2024;123:108496. DOI: 10.1016/j.reprotox.2023.108496

23. Sarayani A, Albogami Y, Thai TN, Smolinski NE, Patel P, Wang Y, et al. Prenatal exposure to teratogenic medications in the era of Risk Evaluation and Mitigation Strategies. Am J Obstet Gynecol. 2022;227(2):263.e1–263.e38. DOI: 10.1016/j.ajog.2022.01.004

24. Abebe M, Asres K, Bekuretsion Y, Woldkidan S, Debebe E, Seyoum G. Teratogenic Effect of High Dose of Syzygium guineense (Myrtaceae) Leaves on Wistar Albino Rat Embryos and Fetuses. Evid Based Complement Alternat Med. 2021;2021:6677395. DOI: 10.1155/2021/6677395

25. Sa S, Seol Y, Lee AW, Heo Y, Kim HJ, Park CJ. Teratogenicity of D-allulose. Toxicol Rep. 2022;9:821–824. DOI: 10.1016/j.toxrep.2022.03.028

26. Liu M, Lu X, Zhang J, Zhao X, Zhang W, Lin X. Teratogenic jervine increases the activity of doxorubicin in MCF-7/ADR cells by inhibiting ABCB1. Biomed Pharmacother. 2019;117:109059. DOI: 10.1016/j.biopha.2019.109059

27. Vieira R, Venâncio C, Félix L. Teratogenic, Oxidative Stress and Behavioural Outcomes of Three Fungicides of Natural Origin (Equisetum arvense, Mimosa tenuiflora, Thymol) on Zebrafish (Danio rerio). Toxics. 2021;9(1):8. DOI: 10.3390/toxics9010008

28. Bilz NC, Willscher E, Binder H, Böhnke J, Stanifer ML, Hübner D, et al. Teratogenic Rubella Virus Alters the Endodermal Differentiation Capacity of Human Induced Pluripotent Stem Cells. Cells. 2019;8(8):870. DOI: 10.3390/cells8080870

29. Kim A, Lee SY, Chung SK. Caffeic acid selectively eliminates teratogenic human-induced pluripotent stem cells via apoptotic cell death. Phytomedicine. 2022;102:154144. DOI: 10.1016/j.phymed.2022.154144

30. Hirose Y, Kitazono T, Sezaki M, Abe M, Sakimura K, Funato H, et al. Hypnotic effect of thalidomide is independent of teratogenic ubiquitin/proteasome pathway. Proc Natl Acad Sci U S A. 2020;117(37):23106–23112. DOI: 10.1073/pnas.1917701117

31. Sambu S, Hemaram U, Murugan R, Alsofi AA. Toxicological and Teratogenic Effect of Various Food Additives: An Updated Review. Biomed Res Int. 2022;2022:6829409. DOI: 10.1155/2022/6829409

32. Kaleelullah RA, Garugula N. Teratogenic Genesis in Fetal Malformations. Cureus. 2021;13(2):e13149. DOI: 10.7759/cureus.13149

33. Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci. 2010 [acceso: 07/02/2024];40(2):99–114. Disponible en: https://pubmed.ncbi.nlm.nih.gov/20421621/

34. Gagnon A, GENETICS COMMITTEE. Evaluation of prenatally diagnosed structural congenital anomalies. J Obstet Gynaecol Can. 2009;31(9):875–881. DOI: 10.1016/S1701-2163(16)34307-9

35. Christian MS, Brent RL. Teratogen update: evaluation of the reproductive and developmental risks of caffeine. Teratology. 2001;64(1):51–78. DOI: 10.1002/tera.1047

36. Brent RL. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. Pediatrics. 2004 [acceso: 04/02/2024];113(4 Suppl):957–968. Disponible en: https://pubmed.ncbi.nlm.nih.gov/15060188/

37. Beckman DA, Mullin JJ, Assadi FK. Developmental toxicity of cysteamine in the rat: effects on embryo-fetal development. Teratology. 1998;58(3-4):96–102. DOI: 10.1002/(SICI)1096-9926(199809/10)58:3/4<96:AID-TERA5>3.0.CO;2-7

38. Opitz JM. Entwicklungsstörungen des Menschen [Developmental abnormalities in humans]. Monatsschr Kinderheilkd. 1991 [acceso: 01/02/2024];139(5):259–272. Disponible en: https://pubmed.ncbi.nlm.nih.gov/1870596/

39. Gagnon A, GENETICS COMMITTEE. Evaluation of prenatally diagnosed structural congenital anomalies. J Obstet Gynaecol Can. 2009;31(9):875–881. DOI: 10.1016/S1701-2163(16)34307-9

40. Leviton A. Caffeine consumption and the risk of reproductive hazards. J Reprod Med. 1988 [acceso: 02/02/2024];33(2):175–178. Disponible en: https://pubmed.ncbi.nlm.nih.gov/3280787/

41. Nehlig A, Debry G. Effets du café et de la caféine sur la fertilité, la reproduction, la lactation et le développement. Revue des données humaines et animales [Effects of coffee and caffeine on fertility, reproduction, lactation, and development. Review of human and animal data]. J Gynecol Obstet Biol Reprod (Paris). 1994 [acceso: 10/02/2024];23(3):241–256. Disponible en: https://pubmed.ncbi.nlm.nih.gov/8051344/

42. Nehlig A, Debry G. Consequences on the newborn of chronic maternal consumption of coffee during gestation and lactation: a review. J Am Coll Nutr. 1994;13(1):6–21. DOI: 10.1080/07315724.1994.10718366

43. Endler M, Li R, Gemzell Danielsson K. Effect of levonorgestrel emergency contraception on implantation and fertility: A review. Contraception. 2022;109:8–18. DOI: 10.1016/j.contraception.2022.01.006

44. Bastos Maia S, Rolland Souza AS, Costa Caminha MF, Lins da Silva S, Callou Cruz RSBLS, Carvalho Dos Santos C, et al. Vitamin A and Pregnancy: A Narrative Review. Nutrients. 2019;11(3):681. DOI: 10.3390/nu11030681

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CONFLICT OF INTEREST

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