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TERATOGENICITY IN PREGNANCY: A REVIEW OF DRUG-INDUCED BIRTH DEFECTS

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ABSTRACT

Birth defects, affecting 3–4% of live births, result from genetic, physical, microbial, or chemical factors. Historic events, such as the rubella outbreak and the thalidomide tragedy, revealed that the placenta does not fully protect the fetus from teratogens. Drugs like ACE inhibitors, antibiotics (e.g., tetracyclines), anti-epileptics, benzodiazepines, NSAIDs, lithium, and chemotherapy agents are linked to severe structural and functional abnormalities in exposed fetuses. Mechanisms of teratogenesis include folate antagonism, oxidative stress, vascular disruption, endocrine imbalance, and receptor- or enzyme-mediated disruptions. For instance, folate antagonism impairs DNA synthesis, leading to neural tube defects, while oxidative stress causes DNA damage, resulting in congenital anomalies. Placental transport proteins, such as P-glycoprotein and BCRP, regulate drug transfer to the fetus, with polymorphisms significantly influencing teratogenic risks. Evaluation of these risks relies on animal studies, cohort and case-control studies, meta-analyses, and registries. Despite advances, challenges persist in risk assessment due to physiological changes during pregnancy, genetic variability in drug metabolism, and limited direct measurements of prenatal drug exposure. Understanding the mechanisms of teratogenesis and fostering effective risk management strategies, including patient education, robust pharmacovigilance, and the promotion of safer therapeutic alternatives, is critical to minimizing drug-induced birth defects. Further research is essential to better elucidate the role of transporter polymorphisms, improve clinical guidelines, and optimize drug safety for pregnant populations.

KEYWORDS: Teratogenesis, Drug-induced birth defects, Placental transport proteins.

INTRODUCTION

Birth malformations have been documented throughout history and are a natural part of the human condition. About 3–4% of liveborn newborns have serious birth abnormalities, which are generally defined as those that are life-threatening, necessitate extensive surgery, or exhibit a significant impairment. As late as 70 years ago, it was thought that the placenta protected the fetus from harmful substances. However, in 1941, it was discovered that a mother's pregnancy rubella infection resulted in a unique pattern of birth abnormalities in exposed infants.[1] The thalidomide tragedy two decades later showed that medications could also be teratogenic. The tragedy of this epidemic was ingrained in the minds of both the public and medical professionals, as thousands of newborns were born with severe limb reductions and other deformities. Other medications, such as accutane and valproic acid, were later found to be teratogenic.[2] Five percent of infants may have congenital malformations, which can include structural, anatomical, metabolic, or functional abnormalities (such as mental retardation). Genetic abnormalities, physical, microbial, or chemical substances that react during pregnancy can be the causes, leading to irreversible health harm that necessitates medical attention. Ten percent of cases have an external component (chemical, physical, or biological) that can directly affect and alter embryo-foetal development, whereas twenty-five percent have genetic variables as the cause. The American Food and Drug Administration (FDA) developed five pharmacological classes in 1979 based on data from both humans and animals: A, B, C, D, and X. Class A medications are safe to use during pregnancy, however class X medications have been shown to cause teratogenicity. In actuality, these classifications are usually not comprehensive and are not always current, which causes patients' concern and doctors' difficulty in interpreting them. As a result, if the classifications are a useful place to start when evaluating pharmacological risk, they must be continuously updated to reflect the most recent information from the literature and meticulous clinical review of individual patients.[3]

EVALUATION OF TERATOGENIC RISK

All teratogenic medications often have a dose-dependent impact and identify a single deformity or particular pattern during a vulnerable stage of pregnancy. Reproductive toxicology studies, which evaluate pregnancy outcomes in comparison to untreated controls at varying doses and gestational periods, are the first method used to investigate teratogenic

potential in animal models. These investigations serve as the foundation for proving a drug's potential teratogenicity, particularly when they are carried out in primates. However, there are significant variances between the animal species and humans, with varying susceptibilities to the same pharmacological agent. Every medication that has been shown to be teratogenic in humans has also shown this property in certain animal species, including thalidomide. Studies on animals have helped us prevent thalidomide-like catastrophes when it comes to retinoid-type medications. Certain medications, like salicylates, can undoubtedly be teratogenic in certain animal species but not in humans because of the high quantities used or their various unique susceptibilities. A single case report or a limited number of deformity cases are often the first indications of teratogenicity in humans. The few instances of congenital abnormalities may indicate a teratogenic effect if the medicine is used by a small percentage of women or causes an uncommon form of deformity. However, the few indicated patients may reflect what is thought to be the "natural" rate of deformity in the general population if it is applied to a large number of patients. Cohort studies and case-controls are now the only trustworthy ways to confirm an existing risk. [4] In order to uncover any teratogenic influence, even tiny collections of cases must be assembled using metaanalysis studies, which constitute another statistical method. Additional information about a drug's safety can be found in special registers that many pharmaceutical companies have developed to collect both historical and prospective data on specific medications. Furthermore, teratology information services have started to operate in a number of nations. These services are able to gather prospective data on drug usage during pregnancy in order to gain a large number of instances with precise and regulated information.[3]

DRUGS KNOWN TO BE TERATOGENIC

Human teratogens can be broadly classified into two groups, according to experience. About 25% of pregnancies exposed to "high-risk" teratogens, such thalidomide and isotretinoin, result in significant abnormalities. More frequently, "moderate-risk" teratogens cause a 5- to 20-fold increase in the incidence of particular birth abnormalities. A medication such as carbamazepine, for instance, may increase the background rate of neural tube abnormalities from 1 in 1000 pregnancies to 10 in 1000. When it comes to how high-risk and moderate-risk teratogens are managed in clinical practice, these distinctions are important.

The management of recognized human teratogens can be divided into three primary strategies. Rarely, a medication may be prohibited or taken off the market if its teratogenic effects are identified, as was the situation with thalidomide in the 1960s.

When a drug poses a serious risk to the fetus but does not offer the women who take it any special or necessary therapeutic benefits, this action is warranted. The majority of teratogens, including valproic acid and phenytoin, are thought to meet significant medical needs despite their moderate hazards. Healthcare professionals educate patients on the teratogenic hazards associated with these medications so that patients can make well-informed treatment decisions. In order to minimize exposure during pregnancy, the third strategy makes use of official risk management programs. These initiatives usually involve informing patients and doctors about the dangers of the medication, restricting access to it, and stressing the significance of preventing pregnancy while undergoing treatment.[5]

Some of the teratogenic drugs include

1. The angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors should not be taken while pregnant, particularly in the second and third trimesters. Administration is linked to delayed intrauterine growth, oligohydramnios, cranial ossification abnormalities, and renal injury. Instead of the drug's direct action, the hypotension it causes may be the mediator of fetal harm.[3] Even the more recently used angiotensin II inhibitors are contraindicated during pregnancy since they have the same side effects as ACE inhibitors.[6] Alpha methyl-dopa is currently the recommended medication for hypertension during pregnancy. Beta-blockers and calcium antagonists would be the second-choice medications.[3]

2. Antibiotics

Aminoglycosides may cause hearing function abnormalities in fetuses. Particularly for streptomycin and kanamycin, this impact has been shown. Due to the potential for changes in normal dentition and deposits in the bone throughout the growth phase, tetracyclines are contraindicated during the second and third trimesters. Depending on the dosage and length of exposure, these medicines can give teeth a yellowish-brown or greyish-brown coloring; in 40% of cases, they can reduce bone formation, primarily in the fibula. Moreover, liver necrosis may result from intravenous tetracycline treatment.[7] Penicillin and its variants are the first-choice antibiotics during pregnancy. Cephalosporins and macrolides can be used as substitutes.[3]

3. Anti-epileptics

First, compared to the general population, women with epilepsy appear to be at a two to three times higher risk of congenital abnormalities. Nonetheless, compared to women who are not receiving treatment, the percentage of deformity appears to be higher among epileptic women receiving treatment. The 1980s saw the discovery of the link between valproic acid and spina bifida, which was later validated by a number of case-control studies and cohorts. It is estimated that between 1 and 1.5% of patients would develop this kind of deformity following valproic acid therapy. Children born to pregnant women who used carbamazepine, particularly in the first trimester, are more likely to have neural tube abnormalities (0.6–1.7%). Five to ten percent of newborns born to women receiving this medication during pregnancy have the diphenylhydantoin syndrome. Hypertelorism, distal-digital and nail hypoplasia, and hypoplasia of the nasal bone structure are also part of this syndrome.[8] Neonates of mothers who took this chemical at the embryonic stage have been shown to have a modest increased risk of neuroblastoma and other neoplasms. From three months before conception until the conclusion of the first trimester, all epileptic women of reproductive age should take a folic acid supplement (5 mg/diem). Given the unique teratogenic effects of anti-epileptic medications, folic acid's use is more than justified because it is known to have a preventive impact against neural tube abnormalities.[3]

4. Benzodiazepines

While benzodiazepines can cause apnea, hypotonia, hypothermia, and neonatal abstinence syndrome with signs and symptoms of neuromuscular excitability, their administration during the first trimester may be linked to a slightly higher risk of labiopalatoschisis. It is better to take benzodiazepines with the shortest half-life, splitting them into two or more daily doses, when the patient's clinical state justifies their usage during pregnancy. Additionally, if at all possible, they should be suspended at least two weeks before birth.[9]

5. Chemotherapy

Anti-neoplastic medications are harmful to the fetus because of their strong effects on cells that are actively proliferating. Congenital abnormalities and miscarriage risk are linked to its use during the first trimester. Folic acid is antagonistic to aminopherine. Central nervous system (CNS), limb, and craniofacial abnormalities are linked to its use during the first trimester. There has also been evidence of an increased risk of miscarriage. An alkylating chemical called busulfan, which is particularly harmful to bone marrow, is used to treat

leukemia and prepare bone marrow transplants. In both people and animals, it has been shown that busulfan can harm embryo cells. In every examined animal species, cyclophosphamide has been demonstrated to be carcinogenic. Also in humans all studies have demonstrated an association with miscarriages, limb and ocular defects and labioschisis. Exposure to this drug during the second trimester of pregnancy can cause facial dysmorphia.[3]

6. Coumarin derivatives

Retarded intrauterine growth, miscarriage, psychomotor deficit, hypotonia, convulsions, nose hypoplasia, faults in calcification of the epiphises (chondrodys plasia punctata), ophthalmic, central nervous system, and hemorrhagic abnormalities have all been linked to the use of oral anticoagulants during pregnancy. Approximately 10% more risk occurs during the first trimester, with the sixth to ninth weeks being a crucial time. Risk is predicted to be between 3 and 5% for administration throughout the second and third trimesters.[3]

7. Ergotamine (high doses)

Ergotamine usage during pregnancy has not been linked to an increased incidence of malformations in offspring, according to a number of studies with large case collections. A number of case reports detailing deformities linked to hypovascularization, including multiple arthrogryposis, intestinal atresia, and brain atrophy, have raised suspicions.[10]

8. Non-steroidal anti-inflammatory drugs (NSADs)

NSAD use in the second and third trimesters is linked to anuria and oligohydramnios, as well as premature closure of Botallo's duct near term, which is followed by necrotizing enterocolitis (NEC), pulmonary hypertension, and cerebral hemorrhage.[94–99] Paracetamol is the preferred medication for its analgesic, anti-inflammatory, and antipyretic properties during pregnancy.[3]

9. Iodides and iodine

Neonatal hypothyroidism and goiter can result from exposure to high levels of iodides during pregnancy, such as from long-term use of topical disinfectants or some expectorants. However, because the thyroid does not absorb iodine before to the tenth week of pregnancy, harm to the fetal thyroid can only happen beyond that point. With an eight-day half-life, iodine-131 is employed in both therapeutic and diagnostic processes. While therapeutic

amounts can raise the risk of leukemia, neoplasms, thyroid damage, mental retardation, miscarriage, and abnormalities, diagnostic doses usually carry little danger.[11]

10. Lithium

Lithium use during pregnancy is linked to a higher incidence of cardiovascular defects, specifically the Ebstein anomaly. Compared to the general population, the risk is 10–20 times higher. In any event, this risk is smaller than what several writers first claimed, with resting values below 1%. Neonatal goiter, diabetes insipidus, cardiac arrhythmia, congestive heart failure, and floppy newborn syndrome are further potential problems.[12]

11. Misoprostol

A synthetic counterpart of prostaglandin E1, misoprostol is used to induce labor or abortion as well as treat peptic ulcers. The majority of research on this medication focuses on women who have had unsuccessful abortion attempts, mostly in South America. According to the studies, there is a substantial correlation between the drug and Moebius syndrome, which is characterized by abnormalities in the CNS and limbs.[3]

12. Isotretinoin

According to published research on humans, exposure at 0.4 1.5 mg/kg/diem during the first trimester of pregnancy causes abnormalities in 18% of cases and miscarriages in 22% of cases.[149–153] The most common deformities affect the heart, hearing, and central nervous system. Additionally, facial dysmorphia is common, and even seemingly healthy newborns might have functional type sequelae such mental retardation, blindness,and deafness a long time after delivery.[13]

13. Thalidomide

Teratogens are modeled after the drug thalidomide. Used to treat insomnia since 1950, the medication was taken off the market right away in the 1960s due to reports of limb deformities in infants exposed to it during the first trimester of pregnancy. An estimated 8,000 kids were born with thalidomide-related abnormalities worldwide, according to calculations. Phocomelia, amelia, heart problems, renal and gastrointestinal malformations, deafness, microtia, anotia, mental retardation, and autism are the main defects brought on by this medication. The risk of teratogenicity reaches 20% between days 34 and 50 of pregnancy.[3] Thalidomide is now being researched as a potential treatment for a number of diseases, including leprosy, AIDS, TB, and Behcet's syndrome. Thalidomide's usage for

cutaneous types of leprosy was authorized by the FDA in 1998. 33 more cases of thalidomide-induced embryopathy were subsequently documented in Brazil. To educate the public about this medication, a program called the System for Thalidomide Education and Prescribing Safety (STEPS) was established.[14]

TERATOGENIC MECHANISMS OF MEDICAL DRUGS

Folate antagonism, disruption of neural crest cells, endocrine disturbance, oxidative stress, vascular disruption, and teratogenesis mediated by certain receptors or enzymes are these pathways. Although several of these pathways may cause birth abnormalities in humans, it should be highlighted that they are currently primarily understood from animal models. Furthermore, several medications may contribute to a variety of birth defect-causing pathways.

1. Folate Antagonism

Dihydrofolate reductase (DHFR) transforms folate into the naturally bioactive form tetrahydrofolate (THF) via two reduction processes. THF is then transformed into 5-methyltetrahydrocfolate (5-MTHF) monoglutamate. 5-MTHF is the primary form of folate that enters cells and circulates in the blood. It is clear that folate-dependent processes are critical for fetal growth and development and that folate requirements rise throughout pregnancy because rapidly proliferating tissues demand the most DNA synthesis. Numerous medications disrupt the metabolism of folate and can cause teratogenic effects by inhibiting the folatecmethylation cycle. Two broad classes of medications function as folate antagonists. The first group of competitive inhibitors of DHFR comprises triamterene, trimethoprim, sulfasalazine, and methotrexate. These inhibitors impede the conversion of folate to THF by binding to the enzyme irreversibly. The second class of medications may enhance folate breakdown, hinder folate absorption, or inhibit other enzymes involved in folate metabolism. This group primarily consists of anti-epileptic drugs, including valproicacid, carbamazepine and phenytoin. According to reports of women who were given nopterin during the first trimester of pregnancy in order to induce abortion, folate antagonists were first thought to be teratogenic in humans. Numerous animal species' experimental investigations have shown that folate deficiency results in intrauterine death, growth retardation, and other congenital malformations.[15]

2. Neural Crest Cell Disruption

The neural crest is a population of pluripotent cells that divides into cranial and truncal groups after originating in the neural folds. These cells migrate during neurulation to generate a variety of structures, including peripheral nervous system components from the truncal crest and bones, cartilage, nerves, and muscles in the craniofacial region. The cardiac outflow tract and pharyngeal arch derivatives such as the thyroid and thymus are derived from the cardiac neural crest, which is a subset of the cranial neural crest. Cardiovascular deformities like as aortic arch anomalies, conotruncal defects, and membranous ventricular septal defects, as well as non-cardiovascular problems such craniofacial malformations and esophageal atresia, are examples of malformations connected to the neural crest.

The development of neural crest cells is regulated by various molecular signals, including fibroblast growth factors, integrins, cadherins, and endothelins. Pax3 plays a key role in cardiac neural crest migration, while retinoic acid, a form of vitamin A, is crucial for proper development. Both excess and deficiency of retinoic acid can cause neural crest-related malformations. Retinoid homeostasis is regulated by retinal dehydrogenases and CYP26 enzymes. Disruptions in these pathways, including the use of certain drugs like bosentan or retinoid inhibitors, may lead to neural crest defects.[15]

3. Endocrine Disruption : Sex Hormones

Since the 1940s, several medications have been created to mimic or block the effects of hormones, such as oral contraceptives, diethylstilbestrol (DES), and hormones used to treat infertility. By altering the release, binding, or metabolism of endogenous hormones, these medications and other endocrine disrupting chemicals (EDCs), like bisphenol A and phthalates, may impair their physiological functions. It's possible that DES can pass through the placenta more easily. Apart from pharmaceuticals that affect endocrine homeostasis as their main mode of action, oral medication coatings like mesalamine and omeprazole may also expose users to EDCs.

Because of its reliance on hormones, male development is more susceptible to endocrine disruption. However, it is difficult to comprehend how endocrine-disrupting chemicals (EDCs) affect people because their mechanisms are intricate and species-specific. A balanced androgen/estrogen ratio is necessary for sexual differentiation in males. Estrogens interfere with Leydig cell development in mice, which lowers testosterone production, and phthalates hinder steroidogenesis in the rat fetal testis, but not in humans. Compromised testosterone

production can lead to conditions like hypospadias. Estrogen exposure may also affect testicular descent through suppression of insulin-like factor 3, though its role in human cryptorchidism remains unclear. Epidemiological studies do not link prenatal estrogen exposure to these disorders.

Alternative mechanisms, such as disruption of androgen signaling, resistance to anti-Müllerian hormone (AMH), or inhibition of sex steroid inactivation enzymes, have been suggested. However, the doses required to induce such effects are typically too high to be considered realistic causes of EDC-induced malformations. Furthermore, no compounds have been identified that affect AMH production or action. Similarly, while some chemicals inhibit enzymes involved in sex steroid metabolism, no pharmacological compounds with this mechanism have been identified.[15]

4. Oxidative Stress

Oxidative stress results in irreversible oxidation of DNA, proteins, and lipids, which in turn causes the inactivation of several enzymes and cell death. It is caused by an imbalance between the formation of reactive oxygen species (ROS) and antioxidant defense mechanisms of a cell or tissue. Apart from causing damage to cellular macromolecules, oxidative stress can hinder the activity of redox-sensitive transcription factors and signal transmission by oxidizing thiols, which can impact gene expression. This may cause birth abnormalities and growth retardation during the prenatal period, and in extreme situations, in-uterine mortality. Although placental enzymes can shield the fetus from oxidative stress, the developing embryo's inadequate antioxidant defense makes it particularly vulnerable to high amounts of ROS, especially in the early stages of organogenesis. A broad range of birth problems, such as skeletal deformities, limb defects, neural tube anomalies (Ishibashi et al., cleft lip/palate), and cardiovascular disorders, are thought to be caused by oxidative stress. A number of medications are known to cause oxidative stress, which is thought to be their primary teratogenic mechanism. These medications include iron supplements, class III antiarrhythmic medications, valproicacid, thalidomide phenytoin, and certain chemotherapy medications.[15]

5. Vascular disruption

Abnormalities are structural birth abnormalities brought on by interference with or extrinsic breakdown of the arteries, veins, and capillaries (vasculature), which were initially developing normally throughout pregnancy. The first three months of a fetus's development

are when a teratogen exerts its influence, according to traditional wisdom. Exposure to substances during pregnancy that can cause vascular disruption can potentially cause damage to typically produced structures later in pregnancy. It may be impossible to tell after birth if a particular structural abnormality, like a limb defect, is the result of a vascular disorder, an intrinsically abnormal developmental process, or, for instance, amniotic banding. Disturbances in blood circulation inside the uterine-placental unit, the placental-fetal unit, or the fetus itself are referred to as vascular disruptions. These disturbances include hyperperfusion, hypoperfusion, hypoxia and obstruction. They may be caused by acute or chronic decreases inuterine bloodflow, vascular infections or an abnormal anatomy in the uterine-placental unit. Failures in the vascular supply in the placental-fetal unit may be caused by factors such placental insufficiency, amnion rupture, and umbilical cord blockage. Vascular disruption in the fetus is caused by blockage with venous endometrial fragmentation, external compression, embolic events, pre-mature regression of embryonic veins, disruption of freshly created vessels, and improper regulation of vessel creation.[15]

6. Specific Receptor-or Enzyme-mediated Teratogenesis

Many medical drugs act on a specific receptor or enzyme in the human body, leading to a particular mechanism of action. Below we describe the possible effects of inhibition or stimulation of some of these specific receptors and enzymes on fetal development.[15]

- Angiotensin-converting enzyme and angiotensin II receptors

Generally speaking, the renin–angiotensin system (Fig. 3) is a humoral system that is crucial for controlling blood pressure and maintaining the equilibrium of extracellular fluid volume. Angiotensin II (ATII), the primary effector hormone of this system, causes vasoconstriction by directly acting on vascular smooth muscle cells, raising blood pressure. The human fetus contains the elements of the renin-angiotensin system. Angiotensin-converting enzyme (ACE) inhibitors and AT II receptor antagonists are two classes of widely prescribed hypertension medications that may interfere with embryonic development by interfering with the renin-angiotensin system. The human malformation syndrome, which is common for ACE inhibitor exposure in the second and third trimesters of pregnancy and is characterized by renal tubular dysgenesis and oligohydramnios, their aftereffects, such as limb contractures and pulmonary hypoplasia, and hypocalvaria, may be exacerbated by the reduction in fetal renal vascular tone.

- Hydroxymethylglutaryl-coenzyme A reductase

The rate-limiting enzyme in the mevalonate pathway, which transforms HMG-CoA into mevalonic acid, is hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, which statins block. Consequently, a variety of abnormalities could result from statins' blockage of this system. However, because statin use among pregnant women is so uncommon, epidemiologic studies with suitable control groups have not yet been conducted to confirm a statin syndrome in humans. Despite this, a pattern of structural flaws has been identified.

- Histone deacetylases (HDACs)

They are found in the majority of species, and their most well-known role is to deacetylate histones. The HDAC1 mutant mice, which die early in development from growth retardation and proliferation abnormalities, demonstrate the importance of HDAC activity for embryonic development. HDAC inhibition's role in the pathophysiology of birth defects in humans has not received much attention, while research on animals suggests that it may cause neural tube anomalies and axial skeletal deformities. Trichohostatin A, salicylates, and valproic acid are medications that block HDACs.

- Cyclooxygenase-1

Because they inhibit cyclooxygenases (COXs), which catalyze the conversion of arachidonic acid to prostaglandins, non-steroidal anti-inflammatory medicines (NSAIDs) have analgesic, antipyretic, and anti-inflammatory properties. COX-1 and COX-2 are the two different isoforms that have been found. In animal research, acetylsalicylic acid (aspirin), the only NSAID that permanently suppresses COX by acetylation, appears to be linked to a higher prevalence of malformations than other NSAIDs. Although first-trimester NSAID exposure did not initially appear to be linked to birth defects in humans, subsequent epidemiologic studies show a higher risk of cardiovascular malformations, particularly cardiac septal defects, and orofacial clefts.

- N-methyl-D-aspartate receptors

N-methyl-D-aspartate (NMDA) receptors seem to be crucial for neuronal migration and synaptic reconnection in the developing brain. In research employing NMDA receptor antagonists or knockout mice, blockade of the NMDA receptor affects neural development, which may lead to defects in the brain's structure and migration of neurons and glial components. Thus, it may be concluded that exposure to NMDA receptor antagonists,

including ketamine, amantadine, and dextromethorphan, may cause mild brain Hydroxytryptamine transporters and receptors.

The monoamine neurotransmitter serotonin (5-hydroxytryptamine, or 5-HT) is taken from the mother's circulation and transferred to the developing embryo. It is engaged in a variety of developmental processes, such as cell proliferation, cranial neural crest migration, and craniofacial structure morphogenesis. Birth abnormalities may therefore result from agonists and antagonists' enhanced activation or repression of 5-HT receptors. Sumatriptan and buspirone are known to be agonists of certain 5-HT receptor subtypes, while quetiapine, granisetro, and risperidone, among others, melantagonize certain 5-HT receptor subtypes. Additionally, the activities of 5-HT are mediated by serotonin transparences, suggesting that prenatal exposure to selective serotonin-reuptake inhibitors (SSRIs) may also result in birth abnormalities. –Aminobutyricacid receptors.

In invertebrates, GABA is the primary inhibitory neurotransmitter, binding to specific transmembrane receptors. Extraneuronal GABA-ergic systems are found in various tissues, including the testis, oviduct, ovary, and pancreas, where GABA is thought to play a role in embryonic development. It may also contribute to palate development, though its exact function in non-neural tissues remains unclear. Drugs like benzodiazepines, which enhance GABA’s effects, are commonly used during pregnancy for conditions like "floppy infant syndrome" and withdrawal syndrome. However, the teratogenicity of benzodiazepines is still debated. Some studies suggest a link to birth defects such as orofacial clefts, cardiovascular malformations, and gastrointestinal atresia, while others find no such association.

- **Carbonic anhydrases**

These are metalloenzymes that catalyze the reversible conversion of CO2 to bicarbonate and protons, playing a role in pH regulation, respiration, biosynthesis, and bone resorption. Various isoenzymes are expressed in developing human and mouse embryos. Carbonic anhydrase inhibitors, like acetazolamide (used to treat epilepsy, altitude sickness, edema, and sleep apnea), have been linked to birth defects, particularly limb deformities. The proposed teratogenic mechanism involves a reduction in intracellular pH, which affects cellular processes like protein synthesis, proliferation, and glycolysis, potentially disrupting development. However, evidence supporting this mechanism in humans is limited.[15]

PATHWAYS, NETWORKS, AND CONGENITAL MALFORMATIONS

For the growth and development of the embryo and fetus, folic acid is an essential substance. A complex network of genes in the cytoplasm and mitochondria regulate its active form, tetrahydrofolate, and several methylated versions. The folate pathway, which supplies one-carbon donors for purine and pyrimidine production as well as DNA methylation, is essential for DNA replication and cell division. The complex relationships between the pathways involved in thymidine synthesis, purine biosynthesis, remethylation, and transsulfuration are becoming more apparent thanks to sophisticated mathematical models, especially in cases of imbalance or genetic variation. Fetal development may be severely impacted by disruptions in this route, whether brought on by insufficient nutrition or medication. Due to inadequate diet and genetic differences in folate, folate insufficiency has been associated with congenital heart malformations, neural tube disorders, and cleft lip and palate, or interactions between genes and environmental factors.

It is well recognized that a number of medications used in medical care might disrupt the metabolism of folate. Some of these folic acid antagonists are teratogenic, while others have suggestive evidence of teratogenic effects, and they can cause folate insufficiency. These medications' teratogenicity is thought to be caused by inhibiting the folate methylation cycle, which interferes with the synthesis of amino acids and DNA. This leads to a lack of precursors for proteins and nucleic acids, which in turn hinders cell division and encourages excessive cell death in the developing embryo. There are two primary types of folic acid antagonists. The first group consists of medications that are competitive inhibitors of dihydrofolate reductase, such as aminopterin, methotrexate, sulfasalazine, pyrimethamine, triamterene, and trimethoprim. Antiepileptic medications including carbamazepine, phenytoin, primidone, and phenobarbital fall within the second category, which interfere with folate function by inhibiting enzyme activity, impairing folate absorption, or increasing folate degradation.[16]

DRUG TRANSPORTERS IN THE PLACENTA

Transport proteins are present on the fetal-facing basal membranes and the maternal-facing brush border of the placental syncytiotrophoblast. These proteins are involved in drug and xenobiotic transport in addition to their primary function of transporting nutrition. Several transporters control the flow of drugs between the maternal and fetal circulations, including MDR1 (P-glycoprotein), MRP1, MRP2, MRP3, and BCRP. Drug exposure, including that of

antiepileptic medications, is impacted by polymorphisms in these transporters, particularly MDR1, MRP2, and BCRP. For example, a study found that if a mother with the ABCB1 3435TT genotype took medicine during the periconceptional phase, her child's risk of having cleft lip/palate increased by 6.2 times. For medications that are P-glycoprotein substrates, this risk was larger. Mice with P-glycoprotein knockout fetuses were 100% vulnerable to avermectin B1a-induced cleft palate, whereas mice with normal P-glycoprotein foetuses were unaffected.[17]

- **P-gp**

The ABCB1 gene encodes P-gp, which is found at the maternal-facing apical membrane of the syncytio trophoblast and is a member of the ATP-binding cassette transporters. Many different compounds with various chemical structures, including many medicinal medications, are transported by P-gp, which functions as an efflux transporter. It may be involved in protecting the fetus from teratogenic medicines during the critical organogenesis phase, as the expression is higher in preterm pregnancy and decreases with gestational age.[18]

- **BCRP**

The syncytiotrophoblast's apical surface and the fetal endothelial cells' luminal membrane in the terminal and intermediate villi both contain the 75 kDa membrane protein known as BCRP. There is conflicting evidence regarding the placenta BCRP expression pattern during pregnancy.[18] Two studies found that mRNA levels remained constant throughout the pregnancy, whereas the latter study also found that BCRP expression increased as gestational age increased. Many antiviral, anticancer, and antibiotic medications exhibit significant overlap in substrate transport selectivity between BCRP and P-gp.[19] The ABCG2 gene, which encodes BCRP, has many polymorphisms that are more prevalent in the Asian population, such as 421C>A, 34G>A, and 376C>T.[18]

- Multidrug resistance-associated proteins (MRPs)

MRPs, which are encoded by ABCC family genes, consist of nine membrane proteins involved in the efflux transport of anion conjugates. The human placenta at full term expresses at least four members of the MRP family: MRP1, MRP2, MRP3, and MRP5. Since MRP2 is the only MRP with known functional polymorphisms in the human placenta, we will focus on this transporter. MRP2 (ABCC2) is located on the apical membrane of the syncytiotrophoblast facing the maternal blood, and its expression increases during pregnancy, indicating its role in fetal protection in late gestation. SNP analysis by Ito and colleagues

identified six nonsynonymous SNPs in 48 healthy Japanese individuals, while Itoda et al. later reported 23 SNPs in the exonic region and four in the promoter region. A notable difference in allele frequency between ethnic groups was found for the 3972C>T SNP, present in about 34-36% of Caucasians, 22% of Japanese, and less than 3% of Southeast Asian populations. Additionally, some SNPs were unique to Asians, while Caucasians and other ethnicities predominantly carried wild-type alleles.[18]

DO TRANSPORTER PROTEIN POLYMORPHISMS PLAY A ROLE IN THE RISK FOR DRUG-INDUCED BIRTH DEFECTS?

It is probable that the fetal exposure to medications ingested by the mother is impacted by transporter protein polymorphisms, which may have an impact on the placental transfer of pharmaceuticals. Few research have examined how trans porter protein polymorphisms affect a newborn's prognosis, and even fewer have concentrated on drug-induced birth abnormalities. The fetal genotype is demonstrated to be crucial in controlling the protection, and previous animal research indicates that the Mdr1a and Mdr1b genes, which encode P-gp in mice, contribute to the fetus's defense against the teratogenic effects of xenobiotics in the mother's circulation. Two clinical trials have documented the contribution of 3435C>T to the risk of drug-induced birth abnormalities. These studies have demonstrated that the maternal genotype is a significant driver of risk for birth abnormalities, in contrast to the prior study that shows a role for the fetal genotype. The maternal 3435TT genotype was found to have decreased P-gp expression in the placenta, which increases the fetus's vulnerability to teratogenicity.[20] The first factor to consider when researching drug-induced birth abnormalities is the kind of medication that mothers take, especially those that are strongly linked to particular birth defects and that are carried by the appropriate placental transporter. The genotype's origin, whether from the mother or the fetus, is the second determinant. Drug pharmacokinetics in the mother's circulation are influenced by her genotype, which also impacts fetal exposure. The fetal genotype impacts transporter expression in the placenta. Therefore, the most accurate assessment involves considering both maternal and fetal genotypes.

There is still much to learn about the function of transporter polymorphisms in assessing the risk of drug-induced birth abnormalities. However, carrying out pharmacogenetic research on this subject presents numerous difficulties. First of all, the pharmacokinetics of the medicine of interest may be changed by the physiological changes that occur in the mother during

pregnancy. The second difficulty is that prenatal drug exposure and transporter protein activity cannot be directly measured. The involvement of metabolic enzymes, which are highly polymorphic, in drug pharmacokinetics presents the next difficulty. The "drug transporter-metabolism alliance" between transporter proteins and metabolic enzymes is well recognized to limit the entry of teratogenic substances into the fetus.

The fetus is protected by the placental barrier, and other protective mechanisms may make up for slight variations in transporter activity. Both the syncytiotrophoblast and the fetal capillary endothelium express some transporters. Since some teratogenic medications are transported by several transporters, it can be difficult to determine which polymorphisms are responsible for an increased risk of drug-induced birth abnormalities. Additionally, changes in transporter performance caused by polymorphisms are frequently contradictory.[18]

CONCLUSION

The complexity of drug-induced birth defects underscores the critical need for vigilance in pharmacological management during pregnancy. Teratogens such as ACE inhibitors, anti-epileptics, NSAIDs, and thalidomide have demonstrated severe impacts on fetal development, ranging from structural malformations to functional impairments. Key mechanisms, including folate antagonism, oxidative stress, and receptor-mediated pathways, provide insights into how these agents disrupt embryogenesis. Moreover, the role of placental transport proteins like P-glycoprotein and their genetic polymorphisms highlights the intricate interplay between maternal and fetal factors in determining teratogenic risks.

Advances in research methodologies, including cohort studies, meta-analyses, and the establishment of registries, have improved the understanding of teratogenic potential. However, significant challenges persist, such as the variability in individual responses due to genetic factors, the limitations of animal models in predicting human outcomes, and the physiological changes during pregnancy that complicate pharmacokinetics. To mitigate risks, healthcare providers must prioritize patient education, informed decision-making, and adherence to updated clinical guidelines. Risk management strategies, such as substituting high-risk medications with safer alternatives and implementing robust monitoring protocols, are essential.

Further research is imperative to unravel the complexities of transporter protein polymorphisms, improve drug safety profiles, and refine therapeutic approaches. A

multidisciplinary effort, integrating pharmacogenetics, toxicology, and clinical care, will be pivotal in minimizing drug-induced birth defects and safeguarding maternal and fetal health.

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