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Review Article

An Overview Of Teratogenicity, Encompassing An Investigation Of Birth Abnormalities Resulting From Teratogenic Medications

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ABSTRACT

The implementation of this article is to deliver a fast and easy summary of an overview of what we know right now about the human origins and risk factors teratogenic organizational anomalies. Despite the fact that several recent studies looked at supplementary unfavorable conclusions such as birth weight insufficient, fetal mortality, and efficient issues, the structural birth will be the topic of our discussion of abnormalities in this Commentary. According to FDA, we discussed the various classes of teratogenic drugs. The exceedingly challenging issue of delivering optimum therapeutic advantage for the mother while protecting the protection of the fetus must be labeled when administering Anticancer drugs, Antiepileptic drugs, Antibiotics drugs, Anti-thyroid drugs, Anticoagulant drugs, Anti-tubercular drugs during pregnancy. The time of exposure to the medication, the dose, and the drug's placental translocation are all considered to have adverse consequences on the fetus. We explored different teratogenic medication assessment metrics in this article.

INTRODUCTION

Several medical teratology experts have suggested a grade of well-known teratogens in humans in recent years (e.g., Brent, 2004; Holmes, 2011; Balken et al., 2011). Those of us working in the meadow has also seen a considerable increase in informational resources and systematic examinations into the congenital structural defects in humans: causes and risk factors. Teratology information services (see www.mothertobaby.org) and multicenter research studies, such as the National Birth Defect Prevention Study, European Surveillance of Congenital Anomalies, Slone Epidemiology Center Birth Defects Study, International Clearinghouse for Birth Defects Surveillance and Research, and the Spanish Collaborative Study of Congenital Malformations, to name a few, are among these resources. The

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advancements in clinical teratology knowledge make it important and appropriate to consider where we are in our efforts to understand the causes of structural malformations and where we should go next.[1] Prescription of the sedative thalidomide triggered a worldwide pandemic of numerous birth defects fifty years ago. Leprosy and multiple myeloma are currently both treated with the medication. However, because of its high teratogenic effect, its usage is restricted. The chemical mechanism by which thalidomide produces limb deformities and other developmental problems has long been a mystery, and several theories have been proposed to explain it.[2] The efficiency with which the mother metabolizes the agent, placental transfer, the sensitivity of fetal tissues, and the capacity of the fetus to metabolize and destroy the agent all contribute to a medicine's teratogenicity.[3][4][5] Only about 30 commonly prescribed drugs have been proven to be teratogenic in humans when administered at clinically effective levels, and even fewer are now in use.[6] The goal of this article is to give a quick and easy overview of the present level of knowledge about the general consideration of teratogenic drugs according to pharmacological classification such as Anticancer drugs, Antiepileptic drugs, Antibiotics drugs, Antithyroid drugs, Anticoagulant drugs, Anti-tubercular drugs, and along with evaluation of teratogenicity, in addition with recent advances in teratogen research and computer-based approaches for detecting the teratogenicity.[7]

GENERAL CONSIDERATION OF TERATOGENIC DRUG

Only at precise moments during development are drugs teratogenic. Teratogenicity is defined as any pharmacological or chemical agent that causes aberrations or anomalies in the embryo's development. To avoid such issues, it is essential to understand which medications should be taken during pregnancy. In 1979, the FDA created an A, B, C, D, X system to categorize the possible teratogenic risk of drugs. According to the FDA, the category 'A' is the safest, while 'X' is strictly prohibited during pregnancy. According to research published in 2001, there was insufficient information on the danger or safety of more than 90% of FDA-approved drugs taken during pregnancy between 1980 and 2000. The effects of a medication on a fetus are determined by the fetus's stage of development, as well as the drug's potency and dose. During pregnancy, a woman's plasma volume increases by 30 to 50%, and her cardiac output and glomerular filtration rate rise in a corresponding proportion.

1. **Category A:**

No evidence of harm to the fetus in the first trimester has been found in controlled studies in women. Vitamins and levothyroxine are examples of drugs in this category.

2. **Category B:**

Medications in this category are usually thought to be safe. Animal studies have shown a danger to the fetus that has not been substantiated in controlled research in pregnant women in the first trimester, and there is no indication of risk in the second and third trimesters. Acetaminophen and amoxicillin are two examples of drugs in this category.

3. **Category C:**

Pregnant women may be administered drugs from this class if the benefit to the mother outweighs the danger to the fetus. There are no controlled studies on women, and there is no research in women and animals that have shown a harmful effect on the fetus. Diltiazem and spironolactone are two examples of drugs in this category.

4. **Category D:**

If the advantages to the mother outweigh the danger to the fetus, this class of drugs can be administered during pregnancy. Although there is evidence of human fetal danger, the advantages to the mother may outweigh the risk to the fetus. Phenytoin and valproic acid are two examples of drugs in this category.

5. Category X:

Pregnancy is contraindicated for drugs in this category. Any possible advantage to the mother is outweighed by the risk to the fetus. Teratogenic effects have been documented in animal and human studies. Thalidomide and warfarin are two examples of drugs in this category. Thalidomide: It is a category X drug that is highly teratogenic therefore it is contraindicated in pregnancy after thalidomide crisis. In the 1960's pregnant ladies ingested thalidomide with phocomelia.[8]

Anemia, constipation, gastroesophageal reflux, gestational diabetes, nausea and vomiting, and hypertension are all common pregnancy concerns.

PHARMACOLOGICAL CLASSIFICATION ACCORDING TO TERATOGENIC EFFECT

A. TERATOGENIC ANTICANCER DRUG

The exceedingly challenging issue of delivering optimum therapeutic benefit to the mother while protecting the safety of the fetus must be addressed when administering chemotherapy during pregnancy. The time of exposure to the medication, the dose, and the drug's placental translocation are all considered to have adverse consequences on the fetus. Drugs that have a high lipid solubility, a low molecular weight, and a low plasma protein binding rate have a greater placental transfer rate.[9] Because doing research on the placental transfer of anticancer medications in human individuals is fraught with ethical issues, most data has been obtained through animal investigations.[10]

CYTOTOXIC AGENT

The risk of congenital deformity in fetuses in mothers who underwent chemotherapy during pregnancy is around 5%. The majority of cases, however, received chemotherapy during the first trimester; the rate of these malformations occurring in those receiving chemotherapy after the second trimester is 3%, which is the same as the percentage of fetuses observed to have congenital morphological abnormalities in normal pregnancies. Furthermore, data show that about 15% of chemotherapy patients had spontaneous abortions. Oligohydramnios and IUGR are common side effects of chemotherapy during pregnancy, although preeclampsia and PROM can also develop.[11][12] Stillbirths are also on the rise, according to studies. Furthermore, there have been reports of bone marrow suppression throughout the perinatal period, which is likely to be induced by chemotherapy. After a few weeks, though, this naturally improves.[13]

1. TAXANE

Taxanes have less information than anthracyclines. Weekly paclitaxel has therefore been approved for use from the second trimester onwards when clinical treatment of breast cancer is necessary.[14] Taxanes, which are useful for the chemotherapeutic therapy of breast and gynecological cancers, are known to be transferred to the placenta at a low rate of 1–2%. Despite the low amounts, long-term exposure is possible due to the drug's ability to stay in fetal tissues.[15] The medications were discovered in fetal tissues 72 hours after taxanes were given to the dams, according to animal tests, which was considered to be related to taxanes' strong liposolubility and tissue affinity. Compared to paclitaxel, docetaxel has a greater tissue affinity[16] Furthermore, embryonic livers do not exhibit CYP3A4, one of the enzymes involved in taxanes metabolism.[17-18]As a result, embryotoxicity and fetotoxicity are

elevated, implying a higher risk of intrauterine fetal death (IUFD) and a reduction in body weight. Despite the use of taxanes during pregnancy, no increased fetal or maternal problems were found in a cohort study undertaken in clinical practice as compared to conventional chemotherapy.[19] Furthermore, when combined with platinum-based medications, taxanes are considered the leading choice in the field of obstetrics and gynecology, even while treating pregnant patients.[20-21]

2. VINCA ALKALOID

The plasma protein binding rate of vinca alkaloid formulations is rather high, suggesting that they may have minor impacts on the embryo.[9][22] However, when used in conjunction with other medicines or even as monotherapy, there have been some cases of significant abnormalities; consequently, care is advised. Moreover, during animal trials on baboons, the placental transfer rate of vinblastine was determined to be 15%.[22] Treatments for malignant lymphoma include vincristine and vinblastine. Vinblastine is used in the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) treatment regimen for Hodgkin's lymphoma, while vincristine is used in the CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) treatment regimen for non-lymphoma. Hodgkin's Even during pregnancy, these therapies have been proven to be helpful [23] Despite concerns of fetal harm, these regimens are suggested beginning in the second trimester.[20]

PREGNANCY DURING CHEMOTHERAPY

Contraception should be strongly advocated throughout chemotherapy treatment[20] Additionally, contraception is suggested for the first 3–6 months following the completion of treatment. If the woman is pregnant while getting chemotherapy, she should consider terminating the pregnancy since there is a higher chance of drug-induced fetal abnormalities.[20] Patients with breast cancer who are susceptible to premenopausal hormones may lose out on becoming pregnant due to the long-term use of tamoxifen after surgery[24]. However, if medication is stopped too soon, the chance of recurrence rises, putting patients who want to have children and their doctors in a difficult situation. At the moment, the date of tamoxifen withdrawal is decided on a case-by-case basis after a thorough discussion with the patient. Meanwhile, the POSITIVE trial is still proceeding.(NCT02308085) investigates the impact of stopping tamoxifen for up to 2 years on the incidence of pregnancy.[25]

TERATOGENIC ANTIEPILEPTIC DRUG

The exceedingly challenging issue of delivering optimum therapeutic benefit to the mother while protecting the safety of the fetus must be addressed when administering chemotherapy during pregnancy. The time of exposure to the medication, the dose, and the drug's placental translocation are all considered to have adverse consequences on the fetus. Although some studies have hypothesized that mothers' epilepsy plays a role in causing fetal abnormalities, recent findings suggest that AEDs therapy is the primary cause of malformations, and a large number of studies have assessed the rate of major congenital malformations and long-term effects associated with in utero AEDs exposure.[26-28]

1. PHENYTOIN

Following the 1940s, phenytoin was the most often used AED for the treatment of convulsive seizures, and it has been well researched. The possibility of FM due to phenytoin was initially suggested by Speidel and Meadow, but subsequent research failed to show that phenytoin in monotherapy was a significant teratogen.[29] Although a fetal hydantoin syndrome with facial alterations and terminal digit modifications has been documented,

they are not considered severe defects. There hasn't been any information on a specific pattern. Phenytoin's importance as a key teratogen is still debated.[30]

2. PHENOBARBITONE

FM has been linked to phenobarbitone since 1963, according to a number of publications. A case-control study of the pro-drug methyl-phenobarbitone, which has been associated with mouth clefts and heart abnormalities, revealed a further relationship. A malformation rate of 1.5–5.35 percent was observed in five investigations with a total of 2200 individuals. Untreated WWE served as controls in two of these experiments.[31][32] Holmes et al. published a noteworthy study that found a statistically significant increase in FM when phenobarbital was used.[33]

3. VALPROATE

VPA was first launched in Europe in 1962 and seemed to be well accepted. The dose was probably larger than necessary when used to manage most generalized seizures as well as all other signs of primary generalized epilepsy. A plethora of research has indicated that doses more than 700 mg per day are unacceptably teratogenic.[34][35] In France, there have been several cases of significant major abnormalities, namely spina bifida. The use of VPA in monotherapy and polytherapy was associated with a nearly 20% FM rate, according to a Lancet Editorial.[36]

BENZODIAZEPINES

Clonazepam and diazepam are not thought to be significant teratogens. Wide et al. reported on 48 pregnancies that resulted in three fetuses with FM following clonazepam exposure, while the OR for FM was not statistically substantially enhanced in a case-control analysis of diazepam exposure.[37]

4. ZONISAMIDE

This medicine was first tested in the late 1980s, however, it was removed owing to concerns of renal stones. This was not a concern in Japan or the United States, where it was widely utilized. Kondo et al. reported two FM in 26 pregnancies but none with zonisamide alone.[38]

NEW ANTI-EPILEPTIC DRUG WHICH SHOWS TERATOGENICITY

Initially, all new AEDs were developed to treat partial epilepsy. Unfortunately, effective and targeted medications for the treatment of hereditary generalized epilepsy are limited. Over time, authorization for lamotrigine (LTG), topiramate (TPM), and levetiracetam were expanded to encompass hereditary generalized epilepsy. Data on usage in monotherapy are less solid for these pharmaceuticals than for traditional drugs since they were utilized as add-on therapies in many countries. First-trimester exposure to LTG, oxcarbazepine, TPM, gabapentin, or levetiracetam, compared to no medication exposure, was not related to an elevated incidence of significant birth abnormalities among live-born children in Denmark.[39]

A. OXCARBAZEPINE

In Scandinavia and North America, this medication has grown very popular. Retrospective reports of deformities have been linked to this medicine when used alone. According to Artama et al., FM incidence in kids of women who were not subjected to oxcarbazepine was 11.1 percent, compared to 0.8 percent in offspring of women who were not exposed to oxcarbazepine.[39] The joint NEAD research is a significant milestone endeavor, revealing prospective results and detailed examinations of children exposed to AED during pregnancy.[40] This effort has resulted in a number of good reports. Its major findings are significant because they imply that neurodevelopmental impairment may be much

more severe than many of the physical abnormalities caused by AED exposure in utero. The study's conclusions are concerning and are mentioned often. The mean IQ for children aged 3 who were exposed to LTG was 101, 99 for those exposed to phenytoin, 98 for those exposed to CBZ, and 92 for those exposed to VPA after adjusting for maternal intelligence quotient (IQ), maternal age, AED dose, gestational age at birth, and maternal preconception use of folate. There was a dose-dependent relationship between VPA consumption and IQ. Future research should explore the issue of dosage, as VPA is obviously a neurodevelopmental teratogen at large doses.[41]

B. TERATOGENIC ANTIBIOTICS DRUGS

Untreated sexually transmitted or urinary tract infections during pregnancy are linked to severe morbidity, including low birth weight, premature birth, and spontaneous abortion. Approximately one in every four pregnant women will be administered an antibiotic, accounting for almost 80% of all prescription drugs in pregnant women. Antibiotic exposure during pregnancy has been linked to both short-term (e.g., congenital malformations) and long-term consequences in the baby (e.g., alterations in gut microbiota, asthma, atopic dermatitis). However, it is believed that only 10% of drugs have enough evidence to be used safely and effectively during pregnancy. In general, antibiotics such as beta-lactams, vancomycin, nitrofurantoin, metronidazole, clindamycin, and fosfomycin are regarded as safe and effective during pregnancy. Fluoroquinolones and tetracyclines should be avoided during pregnancy. Pregnancy-related physiological changes increase glomerular filtration rate, total body volume, and cardiac output. These modifications may cause pharmacokinetic changes in antibiotics, necessitating dosage adjustments or careful monitoring and assessment.[42]

Different Class of Antibiotic Drug use are as follows;

I. AMINOGLYCOSIDES

The most regularly given aminoglycosides are amikacin, gentamicin, streptomycin, and tobramycin. The serum half-life of aminoglycosides is shortened during pregnancy, and clearance is accelerated. Since of this, and because pregnant women have a higher volume of distribution, aminoglycosides may have a lower serum peak concentration compared to non-pregnant women. Aminoglycosides pass the placenta and can be hazardous, especially if given during the first trimester of pregnancy.[43] Case reports of irreversible bilateral congenital deafness associated with maternal streptomycin usage in the first trimester have been recorded, prompting a boxed warning and FDA Pregnancy Category D for the class in the United States.[44]

II. BETA-LACTAMS AND RELATED ANTIBIOTICS

a. FLUOROQUINOLONES

Despite being classed as Pregnancy Category C, fluoroquinolones are typically contraindicated during pregnancy. They are extensively dispersed throughout the body, with different routes of elimination for each drug. Protein binding percentages range from 20% to 50%.[45] Fluoroquinolones may be safe during the first trimester, but they are not advised since they have been linked to fetal damage in earlier animal studies.[46] There is a possible link between fluoroquinolones and fetal kidney toxicity, heart abnormalities, and central nervous system damage.[47] Animal studies have shown that the fetus suffers from bone and cartilage degeneration. Data are inconclusive, and further research is needed to validate these connections. Because of

weak study designs, small sample sizes, and confounding variables in published human studies, authors of a recent literature review concluded that fluoroquinolones may not pose the same risks to humans as they do to animals; however, the data are still insufficient to support their routine use in pregnancy.[48] Fluoroquinolones should only be used during pregnancy if there are no other options, according to the available data.[49]

II. ANTHRACYCLINE ANTIBIOTICS

During animal experiments, epirubicin and doxorubicin showed a modest incidence of placental transfer of about 1–10%. Idarubicin, on the other hand, is very liposoluble and has a lengthy half-life. As a result, this medicine might have a high incidence of placental translocation. The anthracycline antibiotic doxorubicin is the most commonly utilized. A few participants in a prospective breast cancer research were given 5-FU, doxorubicin, and cyclophosphamide (FAC) treatment from the second trimester onwards, according to one report. There were no reports of an increase in short-term adverse effects (such as congenital defects), thus it was thought that it may be used safely

III. TETRACYCLINE

Tetracyclines classified as Pregnancy Category D, have been shown to be teratogenic in humans. They are connected to birth abnormalities, and high dosages have been linked to maternal liver damage. Tetracyclines, in general, enter into tissues and bodily fluids, with the degree of penetration proportional to lipid solubility (minocycline > doxycycline > tetracycline). Elimination routes varied per agent, and protein binding varies greatly by the agent. Tetracyclines cross the placenta and, if taken beyond the second trimester, can bind to calcium in the developing baby, causing irreversible bone and tooth discoloration. They are not recommended beyond the fifth week of pregnancy. Tetracyclines should be used with extreme caution, if at all, during pregnancy, and only when there is a demonstrated benefit. Doxycycline may be explored in pregnant women who suffer life-threatening tick-borne infections in rare situations.[42]

VI. STREPTOMYCIN

A substantial amount of information on the teratology of this pharmaceutical drug has been acquired. Externally administered SM prevents normal embryonic development in Rana pipiens in a direct proportion to the drug's dose and exposure time. In guinea pigs, doses similar to human dosages failed to cause functional or histopathological problems. Higher dosages, on the other hand, caused vestibular impairment. Even huge doses failed to create harmed progeny in mice, whereas modest but clear damage was shown in rats. SM passes the placental barrier in a variety of ways, with fetal amounts reaching up to 50% of maternal blood concentrations. Defects in maternal excretion or detoxification, as well as increased permeability of the placenta owing to structural defects and other disorders, might affect this level.[43][44]

A. TERATOGENIC ANTITHYROID DRUG

Because of the suspected link between methimazole and congenital abnormalities (also known as methimazole embryopathy), which include aplasia cutis, esophageal atresia, choanal atresia, facial abnormalities, and developmental delay, propylthiouracil is the drug of choice for hyperthyroidism during pregnancy in North America. Since epidemiological research linked methimazole to aplasia cutis.[50] There have been reports of aplasia cutis or other abnormalities in newborns exposed to methimazole while still in the womb. However, in a prospective cohort analysis involving 241 women who used methimazole and 1089 women who used

nonteratogenic medicines, the overall incidence of significant congenital abnormalities in methimazole-treated newborns was not greater than in nonteratogenic drug-treated infants.[51] Furthermore, two retrospective investigations found no increase in congenital defects in babies exposed to methimazole while in the womb. Another rationale for the preference for propylthiouracil over methimazole is that propylthiouracil has a lower transplacental transit rate than methimazole, according to small research. A later investigation contradicted this conclusion.[52]

Antithyroid drugs during lactation

Propylthiouracil is frequently advised as the antithyroid of choice during breastfeeding since it appears to pass less to a nursing newborn via breast milk than methimazole. Neither propylthiouracil nor methimazole, on the other hand, appear to represent a major risk to breastfeeding babies. Thyroid function and neurodevelopment of nursing infants were not affected in research including 139 lactating moms on methimazole and their nursing infants. In breastfeeding neonates, dosages of up to 20 mg/d of methimazole did not produce hypothyroidism. The thyroid function of nursing infants should be monitored until further studies are available if the mother obtains a high dosage of methimazole during breastfeeding.[53]

Which drug: PTU or MMI?

Transplacental passage: Nine pregnant women consumed PTU and MMI in the only in vivo human investigation to formally evaluate the possibility of placental transmission.[54] 2 hours before the elective termination of pregnancies ranging in gestational age from 8 to 20 weeks, 5S-labeled substances were administered. Only seven of the nine ladies had all of their information. The ratio of fetal serum or cord blood MMI levels to maternal drug levels varied from 0.72 to 1, showing a significant rate of drug transfer in the case of MMI or carbimazole. The ratio for PTU was 0.27 to 0.35, showing a significantly lower transfer rate. These researchers also got drug transfer data from pregnant rats, which corroborated their findings. The recognized variations in drug binding to albumin (PTU..MMI) and lipid solubility, as well as putative changes in maternal/fetal volumes of distribution, excretion, and metabolism of each substance, were linked to the variances in placental transit.[55] Recent research employing isolated perfused human placentae demonstrated no difference between PTU and MMI in the rate or amount of transplacental transit. Despite the fact that PTU is heavily protein-bound [49] percent to human serum albumin], transfer rates through the placenta were unaffected by the perfusate protein content, suggesting that unbound medication is extracted very efficiently. The failure to attain a steady state with a single dosage of medication was suggested as a possible reason for the discrepancies between this study and the previous findings. Although it is unknown whether this in vitro model is completely representative of in vivo events, the lack of a difference in PTU and MMI placental transfer is consistent with clinical observations of similar fetal outcomes with both drugs in terms of thyroid function and congenital anomalies, as well as data showing that cord blood PTU levels were similar to or higher than simultaneously obtained maternal serum PTU levels.[55]

B. TERATOGENIC ANTICOAGULANT DRUG

Pregnant women with artificial heart valves have a number of problems in their care. Heart failure, thrombo-embolic problems, arrhythmia, infectious endocarditis, and maternal mortality are all risks for pregnant women. The hypercoagulable condition of pregnancy increases the risk of

thromboembolism, hence selecting an anticoagulant is very crucial during pregnancy. There is presently no consensus on which anticoagulant technique is the safest and most effective during pregnancy.

1. WARFARIN

For the mother, warfarin is considered the safest therapeutic choice. Warfarin, unfortunately, crosses the placenta and is linked to an increased risk of fetal loss. 1 If used during the first trimester, warfarin is linked to teratogenic lesions, whereas using it later in pregnancy increases the risk of fetal hemorrhagic problems and maternal hemorrhage during labor. Long-term usage of unfractionated heparin is safe for the fetus, although it is linked to osteoporosis and thrombocytopenia in the mother. Recent consensus recommendations have incorporated low molecular weight heparins (LMWHs) as treatment alternatives, and findings from case series with LMWH medication in pregnancy imply a risk of valve thrombosis ranging from 10% to 22%. In pregnancy, no randomized controlled studies comparing various anticoagulant treatment regimens have been reported.[56]

C. TERATOGENIC ANTI-TUBERCULOSIS DRUGS

Most authorities advise against giving any medicine to a pregnant woman due to the risk of fetal harm. Antituberculosis (anti-TB) medications are one type of drug that must be tested for teratogenic effects as a result of this issue. Pregnancy may occur while undergoing TB treatment, in which case the danger to the developing baby must be taken into account while counseling the expecting woman and her obstetrician.[57]

1. KANAMYCIN

The teratogenic effects of KNM in animal models and humans are still partially understood. When fed to pregnant guinea pigs at a dosage of 200 mg/kg per day, KNM caused detrimental isomorphic consequences in the fetus, particularly in the Corti organ. The ability of KNM to penetrate across the placental barrier has been established. The antibiotic was quickly transferred from the mother to the fetus after injection of 500 mg into 27 gravidas with simple pregnancies before delivery, with a delayed buildup in the amniotic fluid. KNM usage during pregnancy has only been studied in a few cases. Jones described one example of a pregnant woman who got KNM and experienced a gradual hearing loss that progressed to absolute deafness over the course of a few weeks. Despite the fact that the patient's hearing was never restored, her 3-year-old child passed the assessment with flying colors.[58]

EVALUATION STUDY OF TERATOGENICITY

This preclinical study of a drug's long-term safety necessitates high throughput tests for potential cytotoxic, mutagenic, embryotoxic, and teratogenic effects. Because of the rising number of new compounds released into the environment each year, as well as the increasing amount of chemicals brought into the environment, there is a strong demand for a quick, reliable, and cost-effective approach for detecting developmental toxicity.

A. EVALUATION BASED ON ANIMAL

Traditionally, huge numbers of animals have been used in preclinical drug screening to anticipate potential medication adverse effects. Pregnant laboratory animals, often mammals such as mice, rats, rabbits, and nonhuman primates, are subjected to a variety of animal-based test methods developed for screening possible teratogenic activity. As a result, the test substance is given to the fetus on a daily basis during the organogenesis

stage. The fetus is evaluated for skeletal, visceral, and external defects at this stage of development.

To make matters more complicated, various other factors like the dam's nutritional status, variations in embryo developmental age from litter to litter or within the same litter, and placental functions must be considered when interpreting data. Pregnant animal research alone is not equipped to forecast the teratogenic potential of novel drugs, it might be asserted. Furthermore, due to opposition to tests on real animals, there is a growing political and public pressure to minimise the use of laboratory animals.[59]

B. EVALUATION OF ENTIRE EMBRYO

The valuation of a relative index of teratogenicity of the test substance is possible by cultivating entire embryos at an early stage of organogenesis and exposing them to a probable teratogen. Teratogen screening uses mammalian embryos, such as those from the rat or mouse (rodent embryo culture) and embryos from the South African clawed frog Xenopus laevis (frog embryo teratogenesis assay-Xenopus, FETAX).[60]

In a complete embryo culture test, there are several criteria that might indicate the teratogenic activity of a substance.

I. Changes in the creation of macromolecules like DNA,
II. RNA, and proteins Inhibition of mitosis,
III. Odds of entering the cell cycle Cytotoxicity is a term used to describe a condition when cells are damaged Cell-to-cell aggregation
IV. Cell adhesion and motility are examples of changes in cell behavior.
V. Cell differentiation is being stifled.
VI. Changes in organ morphology or cell form, for example.
VII. embryos with abnormalities.[61]

C. EVALUATION OF TERATOGENIC MICROMASS

The micromass teratogen test is an in vitro technique for detecting chemicals that interfere with some of the normal cell differentiation processes seen in developing embryos. The test is based on midbrain or limb cells from chick, mouse, and rat embryos that were exposed to test substances for varying amounts of time and concentration. In vitro cultivation of embryo limb or rather central neural cells in small volumes at high density causes the cells to differentiate into chondrocytes or neurons, starting with a large number of small aggregates or foci of cells. As a result, cell adhesion, motility, communication, division, and differentiation, as well as the novel creation of tissue-specific enzymes and structural proteins, may all be detected in micromass cultures. The approach is suitable for producing large numbers of homogeneously responsive cultures from tiny quantities of embryo tissue (96-well microtiter plate performance). Ex vivo experiments involve a phase of in vivo embryo exposure that will function as a control for the effects of drug metabolism and pharmacokinetics by exposing the cells to the test substance either directly in culture or transplacentally prior to culture.[62] Furthermore, the micro mass test may be used to replicate the in vivo susceptibility of specific embryonic tissues or species to teratogenic chemicals by employing cells from various organs and species. According to studies comparing chemicals from various classes, the percentage of teratogens detected can range from 60 to 90%, and the percentage of non-teratogens detected can range from 89 to 100%, depending on the test configuration chosen, the compounds used, and the length of exposure to the test agent.

D. RECENT ADVANCES IN TERATOGEN RESEARCH AND ASSAY

In fact, the focus is on gene expression alterations in cells cultivated in vitro with known or prospective teratogens. The connection of the transcriptome with traditional toxicological endpoints may discover biological targets and biomarkers of developmental toxicity that have previously been unknown. Furthermore, identifying the dose-response correlations between environmental exposures and the disruption of certain processes important during early embryonic development is expected to be useful in determining the mechanisms that underpin teratogenicity. Microarray analysis and quantitative real-time reverse transcription PCR are the two most often used methodologies for measuring relative mRNA expression levels. Both methods can be used to find genes that are prone to teratogen-induced dysregulation. Histone deacetylase inhibition, G1 phase cell cycle arrest, and induction of apoptosis have all been identified as gene expression responses linked to in vivo impacts of teratogenic chemicals thus far. Thus, examining toxicogenomic responses to short-term (6 hours) in vitro exposures of a teratogenic chemical might be a relevant component in mechanistic research and developmental toxicity screening tests. Additional computer-based approaches for predicting a compound's teratogenic potential have been developed, including computer simulations of normal and aberrant cell and tissue development, as well as analyses of structure-activity connections and chemical hydrogen-bond formation. Nudge++TM is a powerful computer modeling framework for studying multicellular organisms' morphogenesis. The model's details have been published elsewhere. In a nutshell, model cells carry out pre-programmed activities in response to internal and external signals. The model evaluates cellular circumstances and generates cellular activity as it iterates over the cell population. Tissues and organs are made up of groups of these interconnected cells.[63]

In the field of maternal-fetal medicine, machine learning is being used :

The intrinsic inconsistency between the restricted target rationale for teratogenesis and the level of uncertainty that informs prescription behavior for gravid individuals highlights the need for more robust small-molecule teratogenicity predictions. Furthermore, because phase I trials are unethical for expecting populations and animal models are intrinsically restricted for researching human health, computer modeling using healthcare data is the most reliable technique of predicting medication safety in pregnant women.[64] Machine learning (ML) classifiers may play a key role in systematically identifying correlations between maternal medication history and bad fetal outcomes since they are tuned to find similarities across linked data sets (such as binding affinity and phenotypic data for a cytotoxic target). While these models are not meant to replace existing physician expertise of responsible prescriptive practice, they do provide an appealing possibility to identify significant correlations within existing biological data that might lead to relevant POC conclusions.[65-66]

DISCUSSION

In this review, we discussed various types of drugs that are teratogenic in nature. Nowadays there are recent advances in teratogen research and assay, in that we discussed the microassay analysis, additional computer-based approaches in that Nudge++TM is a powerful computer modeling framework and also we added in our review machine learning (ML) classifiers may play a key role in systematically identifying the correlation between maternal medication history and bad fetal outcomes.

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