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Review article

Teratogenic Effect of Various Classes of Drugs on Pregnancy

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ABSTRACT:
Congenital abnormalities and their causes are the subject of teratology. The field of toxicology now generally acknowledges that teratogenicity, or the toxicity to reproduction and development, is a crucial component. Prenatal toxicity can cause morphological or functional abnormalities in the developing embryo or foetus, a process known as teratogenesis. Transplacental carcinogenesis, foetal mortality, and stunted foetal growth are also included (in which chemical exposure of the mother initiates cancer development in the embryo or fetus, resulting in cancer in the progeny after birth). Embryonic and foetal alterations, from those with no effect to abnormalities and stillbirths, are induced by intrauterine exposure to a toxicant, especially in the first trimester of pregnancy. Some viruses, spirochetes, and protozoa, as well as ionising radiation, high temperatures, the drug thalidomide, high doses of vitamin A and corticosteroids, certain antiepileptic drugs, antimalarial drugs, antiarrhythmic drugs, and even industrial pollutants like toluene and cadmium can all cause birth defects. Diabetes mellitus, multiple sclerosis, and rheumatoid arthritis are only a few examples of maternal diseases that could contribute to teratogenesis. During the first year after delivery, the incidence of congenital birth abnormalities is between 2 and 5 percent. This research set out to investigate and summarise the most often reported adverse effects of teratogenic medications.

Keywords: Teratogenic effects, antiepileptic drugs, anticancer drugs and antibiotics.

1. INTRODUCTION

Teratology was initially identified in the 1930s as a result of numerous pigs that were pregnant during the tests. As research advanced experiments on animals using congeners of biologically prevalent compounds, most likely the amino acid analogue azaserine, were used to show the effects of xenobiotic agents on embryos. Aminopterin was used to end the pregnancy in the 1950s [1]. The teratogenic risks in human pregnancy are unknown for more than 90% of drug treatments approved in the U.S.A in the past decades. It has been clearly demonstrated that some drugs such as thalidomide and isopretinoin, can cause birth defects [2]. During prenatal care, patients frequently ask about the impact of particular drugs on their pregnancy. Sadly professionals frequently lack knowledge regarding the dangers and benefits of all the medications they recommend. [3]. Pregnant women are frequently exposed to antibiotics due to the prevalence of infections during this time 2% to 7% of all pregnant women experience urinary tract infection, the most prevalent of which are bacteriuria, cystitis, and pyelonephritis [4]. Wilson acknowledged this when he submitted his theories on teratogenisis, stating that not all exposed embryos to teratogens developed congenital abnormalities. The principles say that the embryo's developmental stage, the time of the exposure, and the mother's genotype all affect the embryo's vulnerability to teratogenic agent [5].

Fetal alcohol spectrum disorders (FASDs), which are caused by prenatal alcohol exposure (PAE) and include abnormalities in physical, neurological and behavioural development, can arise from developmental exposure. Growth retardation, central nervous system dysfunction, and craniofci and ysmorphology are just a few example of the negative impacts that can differ from one individual to the next [6]. The precise mechanism by which the medications cause teratogenicity is still unknown. Any injury to a foetus at a certain time during development may result in specific anatomical anomalies, such as those in the cerebellum, eyes, or palate closure, through selective susceptibility [7]. Congenital malformation are more common in children exposed to anti-epileptic drug during foetal life by a factor of 1.8 to 4.0 according to studies but the teratogenic effects of certain medication are not well understand . About 3-6 in every 1000 pregnant women have epilepsy, and the majority of them require medical attention. In case-control studies are susceptible to self-selection bias due to non-responders and recollection bias if drug usage is self-reported [8].

2. DRUGS AND THEIR TERATOGENIC EFFECTS

2.1. Anticonvulsant/Antiepileptic Drugs

Anticonvulsant and mood–stabilizing medication carbamazepine (CBZ) is primarily used to treat trigeminal neuralgia, bipolar disorder, and epilepsy. Pregnant women frequently use this medication since it is extremely effective, well tolerated and in comparison to other antiepileptic medications (AEDs), believed to be quiet safe during pregnancy [9]. Major congenital abnormalities are more common in children of epileptic women (4% to 10%), which is a 2 to 4 fold increase over the estimated prevalence in the general population [10].

The majority of anticonvulsant appears to be potentially teratogenic based on laboratory findings, even if the hydantoin syndrome has not been definitively linked to other anticonvulsants. Wilson has underlined the significance of developmental age, the significance of inherited vulnerability, and the range of effects of drug with many proposed teratogenicity mechanisms. However several researches have suggested that phenobarbital and carbamazepine may be less harmful teratogenic agents than phenytoin for animals [11].

Seizures associated with epilepsy can occasionally result in death. Less is known about the risks that maternal seizures pose to the foetus, however generalized tonic-clonic seizures can lead to hypoxia and lactic acidosis in the foetus, as well as status epilepticus which can result in foetal death [12]. Drug selection for women with epilepsy who are of reproductive age has definitely been influenced by the growing corpus of research on variations in teratogenic potential between AEDs. The Prospective Neuro Development Effects of Antiepileptic Drugs (NEAD trial) which involved early-pregnant women receiving monotherapy with carbamazepine, lamotrigine, phenytoin, and valproate, was the most instructive study [13]. Teratogenic antiepileptic drug exposure is a concern for pregnancies with maternal health conditions other than epilepsy, as many of these drugs are also used to treat psychiatric illnesses, migraine headaches, and neuropathic pain [14].

Several small-scale studies have already evaluated the possibility that exposure to AED during pregnancy can negatively influenced the offspring`s postnatal development. The dosage or choice of an AED is dependent on the patients unique circumstances, including the kind of epilepsy, the frequency of seizures and socioeconomic status, all of which may increase the risk of malformations [15].

2.2. Antibiotic drugs

Antibiotic medication can be both efficient and life saving in the right situation, such as the treatment of asymptomatic bacteriuria to stop ascending infection and pyelonephritis-related adverse pregnancy outcomes. This included tetracycline, kanamycin and streptomycin, which may both result in hearing loss (which can lead to weakening, hypoplasia, and discoloration of long bones and teeth) [16].

Cephalosporin antibiotics are frequently administered parenterally and orally to treat severe bacterial infection. Cephalosporin's, which have been developed over three generations, have a wide range of effects a low apparent level of toxicity. In 1996 Friedmann and Polifka noted that "There are no known epidemiological studies of congenital malformations among offspring of women treated with cephalaxin during Pregnancy," and same observation was made in relation to cefaclor, cefadroxil, and cefuroxime as well [17].

Tetracyclines are prohibited during pregnancy because they are on the list of known human teratogens. The most widely used tetracycline derivative at the moment is doxycycline, which is inexpensive. Sexually transmitted infection (SFI, such as pelvic inflammatory disease, Chlamydia, and syphilis) are also treated with doxycycine. As far as we are aware, there is no proof that using doxycycline while pregnant can cause human teratogenic effects. Unfortunately, the tetracycline were classified as potentially dangerous due to serious side effect , including teratogenicity after doxycycline was created [18,19].

The public understanding of the dangers of drug use during Pregnancy has largely grown since the thalidomide tragedy. In contrast, every participant in a prospective study of pregnant women had used at least two medicines, and 93% of them had taken five or more. Antibiotics accounted for almost 37% of the medicines utilized [20].

The antibiotic ampicillin, which is a member of the aminopenicillin family, was most frequently taken when pregnant. Within 30 minutes, ampicillin can be seen in foetal serum because it quickly crosses the placenta and enters the foetal circulation and amniotic fluid. Thus, it might result in congenital heart and blood vessel abnormalities [21].

2.3. Anticancer drugs

Pregnancy was confirmed in the beginning of 1978. The patient was informed about the possibility of relapse without maintenance and the potential teratogenic effect on the foetus. The only abnormal physical findings were distal limb abnormalities. Both thumbs were missing their distal phalanges, and the remains of the right thumb was extremely hypoplastic [22]. Cancer chemotherapy's mainstays include natural substances and their analogues, such as doxorubicin, daunomycin, paclitaxel, and vinblastine. Anticancer medications have adverse effect because they target targets found in all normal calls, which restricts their use in the treatment of cancers. These teratogens are not harmful to adult women, but they might be harmful to embryos [23]. Over the past three decades, the effectiveness of chemotherapy of chemotherapy for treating human cancer has grown [24]. Sedative and a broad range of immunomodulatory and anticancer effects set thalidomide apart from these chemically similar counter parts. Thalidomide is racemic, meaning it includes equal amounts

of both the left and right-handed optical isomers, due to the asymmetric carbon that gives the molecule optical activity [25]. Arsenic and thalidomide are two notorious teratogens that are currently used as anticancer medications. When treating multiple myeloma, thalidomide is beneficial. Thalidomide was also used to "cure" morning sickness during pregnancy, which is the very illness that thalidomide was designed to prevent [26]. Methotrexate is given to a woman who is already known to be pregnant as part of the treatment for ectopic pregnancy. A continuing pregnancy may be exposed to Methotrexate if an ectopic pregnancy is incorrectly diagnosed in a woman who is already carrying a baby inside her uterus or if she is treated while carrying both an ectopic and an intrauterine pregnancy [27].

2.4. HIV drugs

More than 90%of all human immunodeficiency virus (HIV) infections in newborns and kids are caused through mother-to-child transmission. This study demonstrated that zidovudine (azidodeoxythymidine, AZT), when used as intensive monotherapy during pregnancy and delivery and given orally to infants for six weeks following birth, reduced vertical HIV transmission by two-thirds in the absence of nursing [28]. A sizable pool of possible study participants for several new medications being researched includes women who have HIV infection or AIDS. Women may experience the disease`s natural history differently [29]. Pregnancy-related physiological changes, such as blood volume expansion and gastrointestinal, enzymatic, and hormonal change, may also have an impact on the pharmacokinetics of antiretroviral medications. These changes can result in altered absorption, decreased protein binding, and increased elimination [30]. Trimetrexate should not be used since it has been shown to be teratogenic at low dosages in numerous animal studies, is linked to fetopathy in humans when used with the biochemically related drugs methotrexate and aminopterin, and may have adverse effects on placental and foetal growth [31]. Pregnant women with active OIs who take medications for which there is little evidence available about their usage during pregnancy should undergo extra assessment of foetal growth and wellbeing [32]. A joint pharmaceutical industry initiative, the Antiretroviral Pregnancy Registry was created to prospectively identify any significant teratogenic effect involving any of the ARV medication that pregnant women are exposed [33]. However, due to the potential teratogenic effects of the antiretroviral medicines, the use of antiretroviral therapy during foetal embryo organogenesis, which occurs before 14 weeks, was not advised [34].

Antiretroviral prophylaxis for HIV- positive pregnant women should be made available to stop perinatal HIV transmission. Combination regimens comprising zidovudine (ZDV) and protease inhibitors (PI), with a more pronounced antiviral activity [35].

2.5. Thyroid drugs

One of the most prevalent endocrine conditions that affect pregnant women is hyperthyroidism, which can seriously affect how a pregnancy develops and turns out [36]. Pregnancy related hyperthyroidism is a dangerous illness that increases the risk of negative obstetric outcomes like miscarriage, stillbirth, preterm birth, and intrauterine growth restriction. Since the 1940s, anti-thyroid medication (ATDs) have been in use, and they are the therapy of choice during pregnancy [37]. Pregnant women with hyperthyroidism run the risk of placental abruption or severe pre-eclampsia [38]. About 0.2% of pregnancies result in thyrotoxicosis, which is most commonly brought on by Graves disease (GD). Surgery, radioactive iodine therapy, and medicinal therapy using antithyroid medications (ATDs) are the three available treatments for Graves disease. It is not advised to treat maternal GD with radioactive iodine while you are pregnant. Miscarriage is a danger that comes with surgery. ATDs are therefore the preferred method of treating GD during pregnancy [38-40] As a result, ATDs with the lowest effective doses are the chosen treatment for hyperthyroidism during pregnancy and shown how TSH, thyroid hormones, TRAb, and ATDs are moving from the mother's to the fetus's circulation [41].

2.6. Analgesic drugs

Aspirin is the most traditional and widely used nonsteroidal anti-inflammatory analgesic. Pregnant women who regularly take high dosage of aspirin appear to have much lower birth weights for their new born. It appears that therapeutic standard doses have no impact on the mother`s health or the newborn`s birth weight [42]. According to gestation week; the antenatal care logbook kept by the obstetricians; and the medications consumed throughout pregnancy [43]. Given that some NSAIDs are over-the-counter (OTC) and thus accessible without a prescription, it is difficult to estimate the frequency of NSAID usage during pregnancy. Inflammatory bowel conditions and chronic rheumatic illnesses including rheumatoid arthritis and Spondyloarthritis are indicators for long term NSAIDS use during pregnancy [44]. Risk factors for developing condition that can result in cerebral infarction include maternal medications and illegal drugs, particularly opiates. The opiate codeine, which is frequently found in prescription cough medicines, is converted to morphine in the body and theoretically raises the risk of perinatal arterial stroke [45]. A high rate of embryonic death and resorption was observed when aspirin or other inhibitors of PG synthesis were given to mice in later gestation, in addition to the teratogenic effects of aspirin supplied to animals in early gestation [46]. Mothers who take indomethacin rarely have the side symptoms of nausea, vomiting, and dyspepsia. Indomethacin can aggravate gastritis and peptic ulcer disease, as can any prostaglandin synthetase inhibitor. It also causes some gastric irritation [47].

2.7. Antidiabetic drugs

The majority of medications used during pregnancy pass through the placenta, it has yet to be established whether or not it would have teratogenic effects on the developing fetus. It found that the some of antidiabetic drugs can easily cross the placenta or some drugs do not cross the placenta. The drugs that cross the placenta was may show teratogenic effect during pregnancy. Glyburide was the antidiabeticdrug that not cross the placenta. So, the foetus has not suffered any negative effects from the safe usage of Glyburide during pregnancy. On the other hand, Tolbutamide, glibenclamide and glipizide can cross the placenta easily. Their small doses are given to pregnant woman with diabetes melitius [48-49]

Within ten years of giving birth, type 2 diabetes will strike about 70% of women with GDM. According to several research and among patients from various racial and geographic backgrounds, there are significant differences in the risk of developing type 2 diabetes [50]. Women with type 2 diabetes who were using either sulfonylureas (when specified, glyburide 5-20 mg/day), biguanides (metformin 1.5-3g/day), or both, were the subject found cohort studies in. compared to women taking insulin, only 2 studies found that women taking oral medicines had a higher prevalence of congenital abnormalities [51]. The detrimental effect of the antidiabetic medication metformin (MET) on the Daniorerio embryonic developments were examined in the current study [52].

We hypothesized that lowering hyperinsulinemic insulin resistance with metformin during pregnancy in women with the disorder would lower the rate of early pregnancy loss because metformin has beneficial effects on several risk factors for miscarriage in the polycystic ovary syndrome (namely: hyperandrogenemia, hyperinsulinemic insulin resistance, and obesity) [53].

2.8. Antiarrhythmic drugs

Digoxin: Pregnant women have used digoxin safely and successfully for a very long time. When administered in a suitable dose, digoxin is neither teratogenic nor linked to any other unfavourablefoetal outcomes [54]. Drugs of the class 1 antiarrhythmic class work by obstructing sodium channels. Studies on quinidine, procainamide, and lidocaine revealed that they are often free of pregnancy related adverse effect [55]. Class III Antiarrhythmics, however, have also been known to cause embryonic arrhythmia and brief cardiac arrest, leading to episodes of sever embryonic hypoxia followed by reoxygenation. This is in addition to bradycardia [56].

Class III Antiarrhythmic has also been demonstrated in animals to be proarrhythmogenic. The rabbit has been a useful animals model for assessing new medication ability to induce Torsade de Pointes because the rabbit heart appears to be particularly susceptible to this condition [57].

Prenatal care included the use of nifedipine, carbamazepine, cyclophosphamide, prednisone, atenolol, and ibuprofen. Women exposed to calcium channel blockers considered their teratogenic risk to be significantly higher [58]. Increasingly, amiodarone is utilized to manage ventricular and supraventricular arrhythmias. Amiodarone's use in pregnancy has been constrained due to the medication's high iodine content (75 mg per 200mg), which raises questions about its potential effect on the foetus [59].

2.9. Antimalarial drugs

A category of people for whom the risk-benefit is frequently ambiguous is pregnant women with malaria. As a result, Doctor is reluctant to prescribe during pregnancy. In some countries where chemoprevention of malaria is strongly advised, physicians advise pregnant women not to take chloroquine or any antimalarial medication [60, 61].

Pregnant women that take artemisinin compounds, including a small number in the first trimester, did not show increased risk for miscarriage, stillbirths, or malformation despite the embryotoxicity seen in laboratory animals [62]. Based on research on malaria parasites, several ideas might be developed regarding the causes of DHA toxicity in developing embroys. Pregnancy- related malaria has profound clinical repercussion for both the mother and is a major public health concern [63]. It is complicated how plasmodium falciparum parasites interact with the placenta during pregnancy and the phathophysiology of malaria; practically all of these interactions favour the parasite at the expense of the mother and the foetus [64].

High doses of CQ exposure during pregnancy have been more closely linked to human birth malformation than low doses of CQ exposure, which are typically employed for similar situations. Additionally, Levy et al. (1991) discovered a higher than average rate of foetal loss, but no indication of congenital abnormalities [65].

2.10. Oral contraceptive drugs

There are conflicting findings the teratogenic risk connected to the use of birth control pills just before or during the first few months of pregnancy. Two different forms of birth defect in the heart and congenital limb reduction are the only negative consequences on offspring associated with oral contraceptives [66, 67]. They also impact the blood coagulating system. For instance, the natural anticoagulant protein S levels drop during pregnancy and oral contraceptives use [68]. For investigation of exposure and risk assessments, oral contraceptives are routinely combined. The incomplete state of our knowledge regarding the causes of birth defects at this time [69].

Additionally, oral contraceptives are put on the line. When it comes to a who has diabetes or prediabetes, the danger of dramatically worsening her carbohydrate intolerance pales in comparison to the risk of adopting a less effective method of contraception (if that only other option) and maybe having a potentially fetal pregnancy [70]

3. CONCLUSION

The use of teratogenic drugs should be avoided during pregnancy in less severe (non life-threatening) diseases such

as acne and psoriasis.It are necessary to select non-teratogenic drugs instead of teratogenic drugs during pregnancy if possible and not harmful for pregnant women. The necessary use of teratogenic drugs may have to be continued in severe maternal diseases such as epilepsy and cancer if the discontinuation of treatment causes worsening of the disease and pregnant women agree with it.

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