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Review Article

A COMPREHENSIVE REVIEW ON DRUG-INDUCED DISEASES AND TERATOGENICITY

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ABSTRACT

The phrase "drug induced disease" refers to an unintentional pharmacological side effect that causes mortality and morbidity and symptoms severe enough to necessitate hospitalization or medical attention. Anticoagulants, anticonvulsant, anti-seizure agents, antiepileptics, and antihistamines are among the drugs whose fetal developmental toxicity has been shown by epidemiological studies. These drugs can cause miscarriage, birth defects, and other adverse pregnancy outcomes. The primary method for diagnosing drug-related disorders in patients is the patient's or their family's history of drug use. The term "teratogenicity" describes the incidence of congenital defects brought on by teratogenic substances. Various pharmacogenetics has been studied in relation with the teratogenic mechanisms including folate antagonism, oxidative stress, inhibition of the angiotensin-converting enzyme (ACE) and angiotensin II receptor. Physical factors like ionizing radiation and toxic metals, chemical exposures, and pharmaceutical treatments including thalidomide, excessive vitamin A, corticosteroids, antiepileptic, anti-seizure, and antihypertensive medications are some of the sources of teratogenic abnormalities. To receive treatment for drug-induced problems, a patient must first notify a physician. During the course of the two-year trial period, 2381 ADR (Adverse drug reaction) events were reported in total, and 926 (38.89%) of them were drug-induced diseases.

KEYWORDS: Drug-induced diseases, iatrogenic diseases, adverse drug reactions, teratogenicity, teratogenic agents

1. Introduction

A drug-induced disease is one that occurs as an inadvertent side effect of a prescription drug and results in mortality or a major illness with symptoms severe enough to require hospitalization or medical intervention [1].

Epidemiological studies have demonstrated the fetal developmental toxicity of several medications, including anticoagulants, antiepileptics, and antihistamines, which can result in miscarriage, birth abnormalities, and other unfavorable pregnancy outcomes [2].

Several drug classes, including antibiotics, synthetic glucocorticoids, antithyroid medications, hypoglycemic agents, non-steroidal anti-inflammatory drugs (NSAIDs), antipsychotics, antipyretic-analgesic medications, traditional Chinese medicine (or its constituents), and more, have been shown to have an impact on hepatic development. Many medications can also affect the development of the hippocampal, skeletal, and gonadal regions. Anesthetics, antipsychotics, and synthetic glucocorticoids have been demonstrated to impact hippocampal development; NSAIDs, antipyretic-analgesic medications, synthetic glucocorticoids, synthetic estrogens, and hypoglycemic agents can impact testicular or ovarian development; and synthetic glucocorticoids, antibiotics, anticancer drugs, antimalarials, antiviral drugs, and synthetic glucocorticoids have been demonstrated to impact bone development and chondrogenesis.

As an example, it has been demonstrated that the use of tenofovir, clindamycin, and phenobarbital during pregnancy, results in decreased bone mineral content, hepatic functional maturity, and bone abnormalities in human offspring, respectively [2].

Azithromycin and its metabolites can be harmful to humans and animals if they drink tainted water. According to epidemiological studies, 20% to 25% of pregnant women were treated with antibiotics. Azithromycin is a pregnancy category B medication that is frequently used in clinical settings in place of tetracyclines and fluoroquinolones. Azithromycin (PAzE) prenatal exposure during pregnancy, however, may result in unfavorable pregnancy outcomes, such as an increased risk of miscarriage and fetal organ deformity, according to a number of recent research. Furthermore, azithromycin has been demonstrated to produce embryo damage at a dosage of 6.25 µg/mL in in vitro investigations employing rat embryo culture. Furthermore, it has been shown that a few other medications that are clinically safe to take while pregnant can be harmful to the developing embryo. These results collectively show that PAzE may cause abnormal fetal organ development during intrauterine stages [3].

Pregnancy and medication are commonly associated with one another. According to clinical research conducted in numerous nations, over 80% of expectant mothers have used medications at some point in their pregnancy, primarily analgesics, antibiotics, and antiemetics. Fetal safety of medication during pregnancy has gained increasing attention since the storm of the 1960s resulting in deformed kids from thalidomide use during pregnancy [3]. Structure or function defects in the developing embryo or fetus are the hallmark of prenatal toxicity, sometimes referred to as teratogenesis. Intrauterine growth retardation, embryo or fetus death, and transplacental carcinogenesis are all included. Teratogenicity is the term used to describe the introduction or production of malformations caused by pathogens. When teratogens come into touch with embryonic or fetal cells, they have the ability to irreversibly alter the structure or function of an organism. Teratogenesis is the process that results in congenital abnormalities in an embryo or fetus [4].

Any environmental element capable of causing an embryo or fetus to die, grow more slowly than expected, or develop a permanent defect in structure or function is a teratogen [22].

Teratology is a branch of medicine that studies the causes and mechanisms of abnormal development caused by specific drugs. Teratogenesis is the process by which a deformed creature develops. Teratogens are substances that physically or chemically interfere with the processes of development and result in congenital abnormalities. The nature of the agent and the stage of development at which the alteration takes place determine the kind and degree of abnormalities that a teratogen will produce [4]. Chemical poisons, mechanical perturbations, and environmental factors are the three primary categories of teratogens that have an impact on wildlife species. When exposed to a teratogen, an embryo, fetus, or larva may grow more slowly, perish, or acquire structural abnormalities or functional issues [4]. This review article will discuss the different drug-induced diseases that affect all of the body's major systems, as well as the mechanisms underlying drug-induced disease and drug-induced teratogenicity [1].

Types:

There are two categories for drug-induced disorders: Type 1 (expected/predictable) and Type 2 (unexpected/ unpredictable). The medication's anticipated or predictable adverse effects are an outgrowth of its typical pharmacological effects. Bleeding is a side effect of blood thinners (anticoagulant and antiplatelet medicines, for example). Insulin and sulfonylureas are two anti-diabetes medications that might result in low blood glucose levels. Conversely, unpredictable outcomes are unrelated to the medication's intended therapeutic effect. For instance, the lungs may be harmed by amiodarone, a medication used to treat abnormal heart beats [1,27].

2. Diseases induced by various drugs

2.1. System based classification

2.1.1. Nervous system

Anti-seizure medications:

Valproate (VPA): Incidence: 0.5-24%; associated with alopecia. A high blood level of VPA is associated with hair loss [1,31].

Carbamazepine (CBZ): can result in alopecia (incidence 0.3-6%).

Phenytoin(PHT): associated with lupus erythematosus and hair loss.

2.1.2. Gastrointestinal system

NSAIDs: cause esophagitis and peptic ulcers by damaging the mucosa.

Metformin: causes stomach discomfort through unidentified process.

Antibiotics: Infections such as *Clostridium difficile* can result from disruption of the gut flora.

2.1.3. Excretory system

Diuretics: possibly leading to functional kidney failure.

Analgesic nephropathy: prolonged interstitial nephritis is caused by phenacetin usage.

Immunological effects: penicillamine is one drug that might cause glomerulonephritis.

2.1.4. Cardiovascular system

Arrhythmias: caused by quinidine and digitalis, which interfere with impulse conduction.

Hypertension: caused by corticosteroids through elevated angiotensin II levels and salt retention.

2.2. Alopecia caused by anti-seizure drugs

2.2.1. Valproate (VPA)

One of the ASMs (Anti-seizure medications) that is most commonly used to treat focal and generalized seizures is VPA. Additionally, it is recommended for the treatment and prevention of bipolar disorder, neuropathic pain treatment, and migraine prevention. VPA is linked to adverse effects on the nervous system and appearance. Alopecia is one of the top 10 side effects of VPA use that people report. The range of 0.5 to 24% is the incidence of alopecia secondary to VPA. The history of hair loss or anomalies after VPA therapy is used to make the diagnosis. Furthermore, pull tests and modified wash tests can be used to verify it. The majority of the time, hair loss happens three to six months

following VPA introduction. It appears that blood levels of VPA and the incidence of hair loss are directly correlated. Alopecia is linked to high blood levels of VPA (80–150 mcg/L) in 28% of VPA users [6].

2.2.2. Carbamazepine (CBZ)

For the treatment of focal seizures, CBZ is widely used. Additionally, trigeminal neuralgia and bipolar illness are treated with it. While VPA is known to cause alopecia more frequently than CBZ, the incidence of alopecia associated with CBZ varies from 0.3% to 6%. Shuper et al. documented the first instance of alopecia brought on by CBZ in 1985. CBZ was used to treat a girl, 8.5 years old, who had multifocal epilepsy and headaches. Following the cessation of CBZ, hair regrowth was seen and hair loss stopped [7].

2.2.3. Lamotrigine (LTG)

LTG is used as a monotherapy or in conjunction with other antiseizure polytherapies to treat epilepsy. For initial generalized tonic-clonic seizures, focal seizures, atypical absence seizures, myoclonic seizures, and atonic seizures, it is the first-line treatment. In addition to being used as an ASM, it can be used to treat depression and mental disorders. LTG is linked to a 0.8% risk of hair loss. Alopecia caused by lipoprotein gradients was initially documented in 2004. LTG and magnesium VPA were started for a female patient with focal epilepsy who was 24 years old. The dosage of LTG was raised to 100 mg/day and the amount of magnesium VPA was lowered to 600 mg/day. A few months later, hair loss was noticed [6].

2.2.4. Levetiracetam (LEV)

It is believed that LEV is a broad-spectrum ASM. The FDA authorized this medication in 1999 for the treatment of epilepsy. LEV has a low chance of medication interactions and advantageous pharmacokinetics. 0.4% of participants in a trial of 1903 persons reported having hair loss as a result of LEV therapy [6]. One uncommon side effect of LEV treatment is hair loss. Zou et al. documented five instances of alopecia brought on by LEV in 2014. The LEV dosages varied from 500 to 1000 mg per day. It was found that between three and eight weeks of LEV therapy, hair loss due to LEV will occur. The authors came to the conclusion that telogen effluvium was the cause of the alopecia linked to LEV [8]. A case series of three patients who had LEV-related hair loss was published by Aghamollaii et al. [9].

2.2.5. Gabapentin (GBP)

About three out of every four patients experience moderate side effects, including ataxia, somnolence, tiredness, and dizziness, which are linked to GBP. It is the initial course of treatment for neuropathic pain. A case of baldness treated with GBP treatment for neuropathic pain was reported by Eker et al. GBP 1800 mg/day was begun for the patient. A week following the start of GBP therapy, hair loss was seen. Alopecia was observed in patches. Hair regrowth was seen after GBP was stopped [10].

2.2.6. Phenytoin (PHT)

Overall, 0.3% of respondents linked PHT to hair loss, and 0.3% said that hair loss made them intolerable. Herranz et al. evaluated the clinical side effects in 392 pediatric patients receiving long-term monotherapy of phenobarbital, primidone, PHT, CBZ, and VPA. Compared to the other medications under investigation, PHT was more frequently linked to cosmetic side effects. PHT was given to the young patient in large dosages, which resulted in drug-induced lupus erythematosus. Therefore, it is important to check for further clinical signs of autoimmune disorders in patients who develop alopecia while receiving PHT medication [11]. Two further examples of alopecia due to PHT-induced lupus erythematosus have been reported in the literature [12,13].

2.2.7. Pregabalin (PGB)

Rarely were cases of isolated alopecia due to PGB reported in the literature. Out of 143 PGB users, Chen et al. reported only one patient who experienced baldness [14]. A different investigation using data from the Netherlands Pharmacovigilance Centre Lareb found that 0.07% of cases of PGB-induced baldness were reported. Notably, there may be a direct correlation between PGB dosage and hair loss [15]. Higher dosages of PGB were more frequently associated with baldness in Wistar rats [6]. A paper by Turgut et al. detailed a female adult with fibromyalgia. PGB 75 mg/day was started, and after a week, the dosage was raised to 150 mg/day. After three weeks of PGB therapy, there was a noticeable loss of hair. PGB was removed from service. Two weeks of PGB discontinuation resulted in full hair regrowth [16].

2.3. Anticonvulsant drugs

One of the most frequent sources of possible injury to the fetus is the medication that pregnant women use to prevent seizures. The anticonvulsant medications carbamazepine, phenytoin, and phenobarbital, which were most commonly used to stop seizures, were discovered to cause significant malformations, microcephaly, stunted growth, and unique small abnormalities of the fingers and face in infants exposed to them during pregnancy in the 1970s and 1980s [17]. The anticonvulsant drugs are categorized in Table 1.

Table 1. Congenital Malformations Associated with Anticonvulsant Drug Exposure

Anticonvulsant drugs	Malformations
Phenytoin	Penile hypopadias caused by an inguinal hernia with ventricular septal defect
Phenobarbital	Fallot tetralogy
	One-sided cleft lip
Phenytoin and carbamazepine	Defect in the ventricle septum

2.4. Drug-induced gastrointestinal system diseases

Medication-induced GI (gastrointestinal) problems include inflammatory bowel diseases and irritable bowel syndrome. Drugs can alter GI physiology (anticholinergic drugs cause constipation, NSAIDs cause ulcers), affect the gut flora (antibiotics can increase risk of *Clostridium difficile* infection), or produce symptoms through unidentified mechanisms (for example, metformin causes diabetes). Various drug induced GIT (gastrointestinal tract) system diseases are illustrated in Table 2 [18].

Table 2. Drug-induced gastrointestinal system-based diseases [18]

Disease	Drug	Mechanism
Oesophagitis	Iron, NSAIDs, bisphosphonate, potassium chloride, and tetracycline	Due to damage to the mucosa
Gastroesophageal reflux	Calcium channel antagonists and nitrates, progesterone, methylxanthine, dopaminergic compounds, and anticholinergic medications	Modification of the pressure of the lower oesophageal sphincter
Dysphagia	Alcohol, antipsychotic medications	Inhibition of the activity of striated muscles
Nausea and vomiting	Dopaminergic agents, opiates, digoxin, and chemotherapeutic agents	Acting through a central nervous system chemoreceptor

2.5. Drug-induced excretory system diseases

The following conditions will be discussed based on their pathophysiological mechanisms: nephrogenic system fibrosis, immune-related toxic effects, analgesic neuropathy, drug-induced glomerular diseases, the direct toxic effects of the drugs, renal hemodynamics-related renal failure, and crystalline neuropathy. Various drug induced excretory system diseases are illustrated in Table 3 [19].

Table 3. Drug-induced excretory system-based diseases [19]

Disease	Drug causing	Mechanism
Functional renal failure	Diuretics, estroprogestins	Aggregation of platelets and thrombotic microangiopathy
Analgesic neuropathy	Phenacetin	Neuropathic pain and persistent interstitial illnesses
Glomerular diseases	Penicillamine, Interferone, Levamisole, Procainamide, and Alpha Methyl Dopa	By influencing the immunological system

2.6. Drug-induced cardiovascular system diseases

A wide range of medications that are harmful is used to treat cardiovascular disease. The most frequent ones include quinidine, procainamide, and phenytoin toxicity and cardiac arrhythmia brought on by digitalis. Oral contraceptive users are susceptible to thromboembolism, for example, and there are other poorly recognized adverse effects on the cardiovascular system from medications not used in cardiac treatment. Various drug induced cardiovascular system diseases are illustrated in Table 4 [20,21].

Table 4. Drug induced cardiovascular system-based diseases

Disease	Drug causing	Mechanism
Arrythmia	Quinidine, digitalis, procainamide, phenytoin	Modification of the creation and conduction of impulses. Quinidine lengthens the Q-T interval while reducing the A-V conduction time. Distinctive intraventricular conduction delay negatively impacts the function of the left ventricle.
Bradycardia	Beta blockers	Beta adrenoreceptor activation is compromised.
Hypertension	Prednisone, oral contraceptive	Modification of the capacity to retain sodium. Increased plasma angiotensin II level.

3.Teratogenicity

3.1. Teratogenic effects

- Defects related to brain injury
- Defects in the spinal cord
- Heart abornamlities
- Defects in the kidney
- GIT flaws
- Problems with anal atresia [6].

3.2. Teratogenic agents

Avoiding known teratogens is also advised. These include the following:

- Valproate
- Alcohol
- Tobacco
- Aminopterin
- Cocaine
- Warfarin
- Thalidomide
- Tetracycline
- Coumarin
- Buprenorphine
- Danazol

There are certain agents that are not easy to avoid. These may be required because of a medical condition and cannot be avoided. For example, phenytoin may be necessary to control seizures if you have epilepsy and are pregnant. Even though phenytoin may have teratogenic effects, it might be preferable to take medication than to risk having uncontrollable seizures while pregnant or nursing a child [4,30].

3.3. Teratogenic Malformations Associated with Drug Exposure

3.3.1. Isotretinoin, etretinate

When a pregnant woman takes isotretinoin, there is a 25% chance of fetal abnormalities. The essential exposure window is between week four and week ten of pregnancy. Hydrocephalus, microcephaly, cerebellar dysgenesis, depressed nasal bridge, microtia or absent external ears, cleft palate, anomalies of the aortic arch, cardiac defects (ventricular septal defect, atrial septal defect, tetralogy of Fallot), and hypoplastic adrenal cortex are among the defects. Additionally, there is a rise in spontaneous abortions. Women who are on isotretinoin and of childbearing age have access to a pregnancy prevention program. Moreover, pregnancy abnormalities have not been linked to the use of topical retinoic acid. Etretinate can result in skeletal, cardiovascular, and central nervous system abnormalities, just like its congener isotretinoin. Etretinate, in contrast to isotretinoin, binds to lipoproteins and stays in the bloodstream for years following treatment [22].

3.3.2. Thalidomide

The critical period was no more than 14 days after conception, and the sensitive period for the development of human thalidomide birth abnormalities was 23 to 28 days postconception. During this period, prenatal exposure caused about 20% of births to result in newborns with anomalies, the most common of which were limb deformities ranging from tetra-amelia or phocomelia of the upper and lower limbs to triphalangeal thumb, occasionally with preaxial polydactyly of six or seven toes per foot [22,29].

3.3.3. Ergotamine

Ergotamine is an ergot alkaloid found naturally that contracts smooth muscle. Ergotamine's constrictive effects on developing fetal blood vessels could be the cause of jejunal atresia and IUGR. Women who took ergotamine for migraine treatment did not experience any unfavorable effects on their pregnancy. According to a report from the Hungarian Case-Control Surveillance of Congenital Anomalies (1980–1986) database, three NTDs (Neural Tube Defects) were present in 9460 infants born to women who were exposed to ergotamine during the first three months of their pregnancies [23]. There haven't been any known controlled research on ergotamine use during pregnancy [22].

3.3.4. Metronidazole

The common treatment for gynecologic infections is metronidazole, an antibiotic and antiprotozoal drug. A few rare cases have been linked to it and birth abnormalities. Prematurity, spontaneous abortions, stillbirths, or abnormalities are not linked to the use of this medication during pregnancy, according to the majority of published reports [22,28].

3.3.5. Trimethadioine, paramethadione

One-fourth of pregnancies ending in spontaneous abortion are caused by maternal usage of these medicines. The majority of liveborn infants have malformations, developmental delays, and prenatal and postnatal growth deficiencies. These malformations include brachycephaly with midfacial hypoplasia, broad nasal bridge, V-shaped eyebrows with or without synophrys, arched or cleft palates, and malpositioned ears with excessive folding of the superior helices or anterior cupping. Common cardiovascular problems include tetralogy of Fallot and septal defects. Other common conditions include kidney malformations, tracheoesophageal anomalies, hernias, and hypospadias. Survivors frequently experience speech difficulties and mild to moderate mental retardation [22].

3.3.6. Warfarin

Women who have had artificial heart valves or thromboembolic disease in the past frequently need long-term anticoagulant therapy. After exposure throughout the eight to fourteen-week gestational period, there is

an approximately 25% chance for impacted newborns. Warfarin reduces the capacity of proteins to bind calcium by preventing the synthesis of carboxyglutamyl from glutamyl residues. Choanal stenosis could happen. Primary locations for calcific stippling are the paravertebral processes, proximal femurs, and tarsals. In around 50% of the affected infants, there has been brachydactyly and tiny nails, with the condition being more severe in the upper extremities. Exposure in the first or second trimester can cause optic atrophy, microphthalmia, and blindness. Microcephaly, optic atrophy, mental retardation, seizures, hypotonia, and visual impairment are examples of brain abnormalities. The stippled calcification, skeletal deformities, and nasal hypoplasia associated with warfarin embryopathy may be explained by proteins inhibiting calcium binding during a critical time of ossification [22].

3.3.7. Acetaminophen

The main component of several painkillers is acetaminophen. When used at or below the authorized dosage, acetaminophen-containing painkillers have been taken by thousands of pregnant women without any evidence of an increased risk of birth abnormalities [22].

3.3.8. Statins

The hypolipidemic medications known as statins are prescribed to patients with or at risk for cardiovascular disease in order to reduce their serum cholesterol levels. The enzyme that catalyzes the rate-limiting step in the cholesterol biosynthesis mevalonate pathway — the creation of mevalonate from HMG-CoA — is 3-hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase, which is inhibited by statins. The growth of the embryo and fetus depends on cholesterol, which is a necessary component of cell membranes. It is also a precursor to steroid hormones and is necessary for hedgehog signaling to be activated and spread, which controls important developmental processes like CNS patterning. These medications have been classified by the FDA as pregnancy category X, which means that women who are pregnant or may become pregnant should not use them. Early pregnancies may unexpectedly be exposed to harmful factors of which there are about 50% in the United States [22].

3.4. Pharmacogenetics of birth abnormalities caused by drugs

We conducted a review of the literature to determine the extent to which pharmacogenetics has been studied in relation to the following putative teratogenic mechanisms: folate antagonism, oxidative stress, inhibition of the angiotensin-converting enzyme (ACE) and angiotensin II receptor, inhibition of cyclooxygenase (COX)-1 and COX-2, and inhibition of 5-hydroxytryptamine (5-HT)-reuptake.

3.4.1. Folate metabolism

Folate, or 5-methyltetrahydrofolate, is a necessary cofactor in a variety of biochemical processes, such as the creation of purines and pyrimidines and DNA methylation. Pregnancy increases the need for folate because folate-dependent processes are essential for fetal growth. When taken during pregnancy, folate antagonists appear to raise the incidence of cardiovascular problems, oral clefts, and urinary tract defects — disorders that are hypothesized to be lessened by folic acid supplementation — in addition to NTDs. It should be noted that valproic acid and phenytoin have effects on the metabolism of folate in addition to being redox-cycling agents that produce reactive oxygen species (ROS), Valproic acid has been implicated in the pathophysiology of birth abnormalities. Findings suggest that genetic factors may increase susceptibility to birth abnormalities following exposure to valproic acid [24].

3.4.2. ACE inhibition & angiotensin II receptor antagonism

Renin-angiotensin system (RAS) homeostasis of extracellular fluid volume and blood pressure regulation are significantly influenced by RAS. The AT1 and AT2 subtypes of angiotensin II (ATII) receptors are the two kinds that exist. Vasodilatation is induced and growth and cell proliferation are inhibited when ATII interacts with the AT2-receptor. The kidney, adrenal gland, heart, liver, and other fetal tissues all have significant concentrations of the AT2-receptor, which shows that the receptor plays a crucial role in fetal development. Given the significance of ATII in embryonic development, there is a possibility that birth abnormalities are associated with medicines that impact ATII, like AT1-receptor antagonists and ACE inhibitors. In fact, it has been reported that using ACE inhibitors during the first trimester increases the risk of cardiovascular and CNS abnormalities [22,24,25].

3.4.3. 5-HT-reuptake inhibition

Serotonin, also referred to as 5 HT, is crucial to a number of activities that occur throughout embryonic development. Therefore, birth abnormalities may result from antagonists and antagonists of the 5 HT-receptors. Mice with cranial malformations have been demonstrated to be exposed to selective serotonin-reuptake inhibitors (SSRIs) [26]. Overall, there doesn't seem to be much of a danger of birth abnormalities in people when using SSRIs. Additionally, fluoxetine intake in the first trimester has been linked to cardiovascular abnormalities. On the other hand, birth abnormalities are not linked to other SSRIs such as fluvoxamine, sertraline, and (es)citalopram [24]. The differences between fluoxetine, paroxetine, and the other SSRIs that are suspected of contributing to birth abnormalities are discussed below in Table 5.

Table 5. The secondary pharmacodynamic characteristics of sertraline, fluoxetine, and paroxetine, three selective serotonin reuptake inhibition

SSRI	Secondary properties
Paroxetine	Paroxetine is the SSRI with the strongest affinity for the non-adrenaline transporter and muscarinic acetylcholine receptor
Fluoxetine	Strong 5-HT receptor inhibitor with strong affinity for D2 receptors
Sertraline	High affinity of the D2 receptor

3.5. Clinical Scenarios

3.5.1. Neural tube defects (NTDs)

Agents: folate antagonists and antiepileptics.

Clinical manifestations: anencephaly and spina bifida.

Mechanism: disruption in folate metabolism.

3.5.2. Cardiovascular anomalies

Agents: ACE Inhibitors - afect the development of the cardiovascular system by preventing angiotensin signaling.

Clinical manifestations: septal defects and hydroplastic left heart syndrome.

Mechanism: inhibition of angiotensin signaling, which is essential for the development of the heart.

3.5.3. Skeletal and limb malformations

Agents: thalidomide and isotretinoin.

Clinical manifestations: causes amelia (limb absence) and phocomelia (limb shortening).

Mechanism: interference with the development of limb buds in the early stages of pregnancy.

3.5.4. Craniofacial Abnormalities

Agent: isotretinoin

Clinical manifestations: micrognathia, cleft palate.

Mechanism: interference with the migration and development of cranial neural crest cells.

3.5.5. Growth retardation and organ malformations

Agents: warfarin, ACE inhibitors.

Clinical manifestations: renal agenesis and intrauterine growth retardation (IUGR).

Mechanism: disruption of prenatal organogenesis and vascular growth.

4.Conclusion

Drug-induced sickness is a worry for patients, healthcare professionals, and administrators of health facilities. It hasn't received the attention it deserves, despite being a significant challenge in clinical practice. The fact that DID (Drug-Induced Diseases) makes health care experts. uneasy, which makes them reluctant to take part in research meant to lessen DID (Drug-Induced Diseases), could be one explanation for this. Although there have been a number of case reports on certain iatrogenic disorders published in India, a comprehensive study on the topic has not yet been released. It is uncertain how frequently or widely DID is present in our nation.

Abbreviations

ASM: Anti-seizure medications

IUGR: Intrauterine Growth retardation

NTD: Neural Tube Defects

DID: Drug-Induced Diseases

PAzE: Prenatal Azithromycin Exposure

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