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TERATOGENIC EFFECT OF DRUGS AT DIFFERENT STAGES OF PREGNANCY

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ABSTRACT: Objective: Teratogens play a crucial role in the 4-5% of infants who are born with physical or functional abnormalities in this world. Teratogens are recognized for their capacity to harm fetuses or neonates. **Observations:** Pregnancy-related exposure to certain substances may result in birth abnormalities or malformations of the fetus, such as behavioral or emotional problems, low IQ, physical deformities, *etc*. Because teratogens are more likely to cause harm between 15 to 60 days during organogenesis, major abnormalities are more prevalent in early embryos than in newborns. There are many different kinds of medications, and some of those that are often used during pregnancy can have teratogenic effects during various trimesters. Pregnancy is often separated into three trimesters. According to several studies, 70% of pregnant women consume at least two or three medications, including prescription pharmaceuticals and over-the-counter medicines, throughout pregnancy or the first trimester of organogenesis. **Conclusion:** The current study focuses on how pregnancy and physiology during that time influences the pharmacokinetics of drugs that may reach and harm the fetus depending on the stage of pregnancy, as well as various factors affecting teratogenicity and concrete steps to address them.

INTRODUCTION: Chemicals that are used in the drugs as active agents are often called as ‘teratogens’ that has the capacity to cause birth defects or anomalies in the fetus during pregnancy and study of these anomalies' occurrence, progression, and origin is known as teratology. The duration of exposure, the quantity of the teratogenic material, and the developmental stage of the embryo or fetus at the time of exposure are only a few examples of the variables that might have teratogenic effects on the embryo or fetus [1].

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As such, teratogens are of the types, physical agents, metabolic conditions caused by such agents, infection related and drugs and chemicals related. Given that pregnancy is a unique physiological situation that are only experienced by women only after attaining a certain physical age and conditions, this may have an impact on a drug's pharmacokinetics. As a consequence, may lead to teratogenicity medicines, depending on the trimester.

This can cause changes in the structure or function of the fetus inside the mother’s womb that can extending to including physical deformities, problems with the child's emotional or behavioural growth, and a lower intelligence quotient (IQ) if given to the mother while she is pregnant. Typically, pregnancy is divided into three subdivisions, namely, First trimester (week 1 to

week 12), Second trimester (week 12 to week 26), third trimester (week 27 to end) [2].

FDA Rating System: Category A, B, C, D, and X are named by FDA based on the quantity and quality of research done on the medicine (not on its safety during pregnancy or usage), was published in 1979 as a result of the thalidomide catastrophe, which included over 10,000 children. There wer modifications made by FDA later and now, all previous classification are removed from all drug labeling for medications in market for the next three to four years for any medicines introduced after June 2015 [1].

According to their subsections, '*Pregnancy* 'includes individuals with labour unto delivery. This sect comprises of pregnancy exposure registry, risk summary, clinical considerations and data. Additionally, it offers essential facts on pregnancy testing or birth control before, during, or after drug therapy, as well as a medication's influence on fertility or pregnancy loss as delineated in **Table 1**. These details pertain to medicines that should not be taken while breastfeeding owing to recognized clinical effects on the newborn [1].

Drug Interactions: A combination of drugs when given separately or simultaneously, two teratogens may have different consequences, if either of the drug(s) have such teratogenic effects. Folic acid, for instance, inhibits cortisol-induced teratogenesis in mice, possibly by activating enzyme systems that break down the teratogen or compete with it for binding sites [1]. There are evidences that demonstrates that the teratogenicity of aspirin in rats is increased by the food preservative benzoic acid, possibly through the inhibition of enzymes, the destruction of cells, and the saturation of binding sites on carrier proteins, which, if present, would lower levels of the unbound active teratogen. Here, they work synergistically. A single teratogen can influence many organs within a species, subject to its time of administration, as represented in **Fig. 1**. Thalidomide administration between days 35 and 37 can causes ear abnormalities, whereas administration between days 41 and 44 may lead tophocomelia [1].

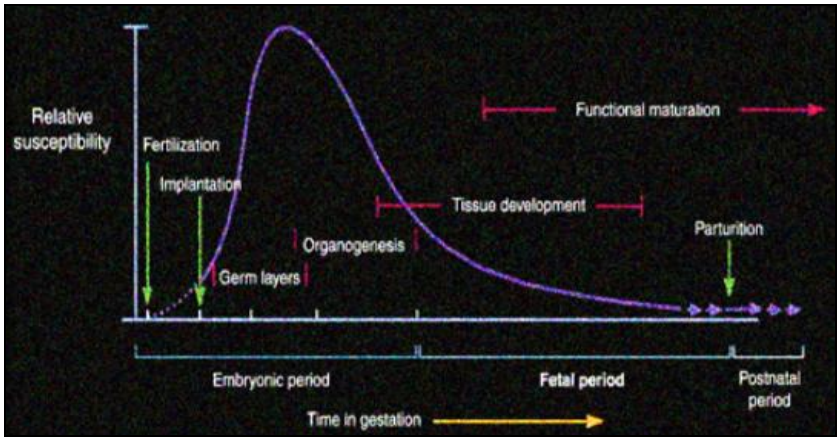

FIG. 1: ASSOCIATION BETWEEN THE RELATIVE TERATOGENIC SENSITIVITY OF EMBRYOS AND INCREASING GESTATIONAL AGE. (SOURCE: DEVELOPMENTAL TOXICOLOGY; J.M. DE SESSO, IN COMPREHENSIVE TOXICOLOGY, 2010)

TABLE 1: FDA PREGNANCY CATEGORIES

Category A	Category B	Category C	Category D	Category X	Category N
Failed to demonstrate a risk to the fetus in the first trimester of pregnancy No evidence of risk in later trimesters	Failed to demonstrate a risk to the fetus No adequate and well controlled studies in pregnant women.	Shown an adverse effect on the fetus No adequate and well-controlled studies in humans	Positive evidence of human foetal risk based on adverse reaction data Potential benefits may warrant use of drug in pregnant women despite	Demonstrates foetal abnormalities Positive evidence of human foetal risk based on adverse reaction data	FDA has not classified the drug

Example - levothyroxine, folic acid, liothyronine.	Example - Metformin, amoxicillin	Potential benefits may warrant the use of drugs despite		The risks involved in use of the drug in pregnant
		Example: Gabapentin, amlodipine	Example - Losartan	Example- Atorvastatin, finasteride

Dosage: Recognized teratogens are more unsafe in large dosages than at low levels for would be mothers. An embryo might respond to a teratogen in any of the three ways, low dose- no effect, intermediate dose- organ specific malformations, high dose, wherein the embryo may be killed. The latter can be termed as teratogenic action unrecognized. Following the thalidomide catastrophe, there are numerous records based on the method of drug administration, dosage, phenomena of drug absorption, and duration of treatment that reveal that the effect of a teratogenic drug can change. Additionally, small doses given over a period of days may have a different impact than an equivalent total quantity given all at once.

Contrarily, a medication that is taken in a sequential manner may destroy the cells that catabolize it, leading to greater adverse effects than would otherwise be expected. A deep understanding of this can be had from **Fig. 2** that represents embryonic periods with varying susceptibility to a teratogen. If an embryo somehow survives the lethal effect of teratogen during the first week of development, not necessarily it will interfere with growth or cause malformations but after the maximum susceptibility period few secondary effects such as vascular occlusion can occur that may lead to anomalies [1].

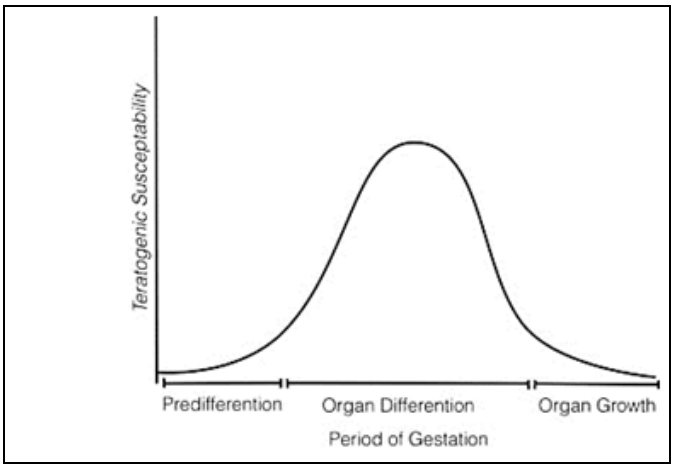

FIG. 2: EMBRYONIC PERIODS OF DIFFERENTIAL SUSCEPTIBILITY TO A TERATOGEN

Stages of Embryonic Development: For treating an expecting mother, if a potential teratogen is administered which eventually gets introduced to the fetus during development, there are three distinct periods of susceptibility with different timings for each organ system that can be agreed by the stages as indicated hereafter.

Before organogenesis, the embryo is at a lower risk of being harmed by the teratogen, ideally two weeks after conception, as the embryonic cells have not yet permanently differentiated, even though a strong influence might kill them. If one cell is destroyed, another cell might be able to take over. And the embryo can live in this manner without displaying any organ-specific abnormalities. During organogenesis, teratogen susceptibility is at its peak, which mostly takes place in humans between embryonic weeks3 and 8 (menstrual weeks 5–10).

During this period, when a teratogenic drug is taken by the mother, damage to the fetus takes place, not only in the form of deformity but also there can be specific spectrum of defects as teratogens operate in an organ-specific way, affecting one organ system at one stage of development and another at another stage. After organogenesis, for the majority of human organ systems, this phase typically starts at 8-10 embryonic weeks (primarily categorized by increasing organ size). At this stage, there is little expectation of apparent deformities, although a teratogen may affect the embryo's development or the size of an organ [1], like giving androgens to a pregnant woman after the 12th week may cause the female fetus' clitoral to expand, but not the urethral opening to be displaced or the labioscrotal folds to fuse. On the other hand, the genotypes of the mother and fetus have an impact on a teratogen's potency. For instance, genotype predicts the occurrence of cleft palate in inbred strains of mice whose mothers receive cortisol during pregnancy [2].

Mechanisms Associated with Teratogenic Drugs: Three predictable mechanisms are applicable to identify the most significant teratogenic pathways associated with the use of pharmaceuticals. A single medication may have several mechanisms at work to induce birth abnormalities, but only six have been identified so far as being employed by teratogenic medicines, as discussed. The folate-metabolizing enzymes are affected here, and the metabolism of lipids and neurotransmitters, as well as the detoxification of foreign substances, both depend on methylation. Folic acid supplementation appears to have a protective impact on the occurrence of several birth abnormalities, although this is not yet clearly evident or consistent enough. Anomalies of the urinary system, heart, limb reduction defects, anal atresia, and orofacial clefts are all thought to have a connection to problems in the metabolism of folate.

Folate Antagonism: Folate, or folic acid, is a water-soluble vitamin B with a high level of polyglutamate, abundant in natural food like green vegetables, eggs, beets, and legumes. Any depletion in the folate methylation cycle can affect the growing baby with higher risk of neural tube defects [1]. In order to combat this, it is advised that women who are pregnant consume at least 400 micrograms of folic acid daily before conception and continue for 3 months. There are certain drugs in the class, competitive DHFR (Di-hydro-folate reductase) inhibitors; work by forming an irreversible bond with the enzyme inhibiting the conversion of folate to THF (tetra-hydro-folate). Another category of drugs alters folate breakdown by interfering with the enzymes involved in folate metabolism, as seen in **Fig. 3.**

Neural Crest Cell Disruption: Primarily two types of neural crest cells are found in embryonic development, namely, cranial neural crest cells (helps in building variety of cell types and structures in the craniofacial region, including intramembranous bone, cartilage, nerves, and muscles) and truncal neural crest cells (contribute to the formation of a plethora of different tissues and organs). For neural crest cells to migrate, differentiate, and proliferate, endothelia's and their receptors are necessary.

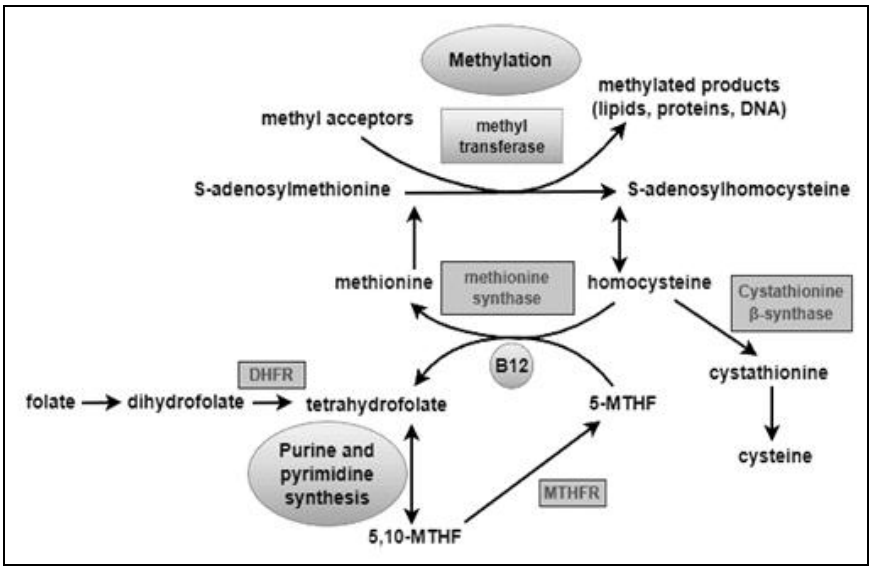

FIG. 3: FOLATE HOMOCYSTEINE METHIONINE METABOLISM. B12, VITAMIN B12; DHFR, DIHYDROFOLATE REDUCTASE; MTHF, METHYL TETRAHYDROFOLATE; MTHFR, METHYL TETRAHYDROFOLATE REDUCTASE

This molecular pathway is disrupted by medications like Bosentan, used to treat pulmonary hypertension and prevent the growth of new digital ulcers connected to systemic sclerosis [1]. Teratogenic effects of retinoids may be mediated through nuclear ligand-inducible retinoic acid receptors (RARs) in addition to retinoid X receptors (RXRs) [1]. They affect other downstream genes that are essential for development owing to it being one of the transcription factors. For animals lacking RARs and RXRs displayed developmental abnormalities, including deformities linked to the

neural crest that are comparable to those caused by vitamin A deprivation, lends support to this theory.

Oxidative Stress: Drugs that are used to treat cancer, cardiac arrhythmias, and epilepsy usually deliver single electron reduction activities and create radical species called ROS (reactive oxygen species). These agents can cause damage by attaching covalently to biological macromolecules. Additionally, both internal and external factors, like phagocytes, cytochrome P450 monooxygenase (CYP), radiation, and exogenous substances, can result in the formation of ROS [1] as evident from **Fig. 4**. Eventually, ROS can result in inactivation of numerous enzymes, cell death by irreversible oxidation of DNA, proteins, and lipids, birth defects, growth retardation, and in extreme circumstances, in-utero mortality (prenatal period) [2].

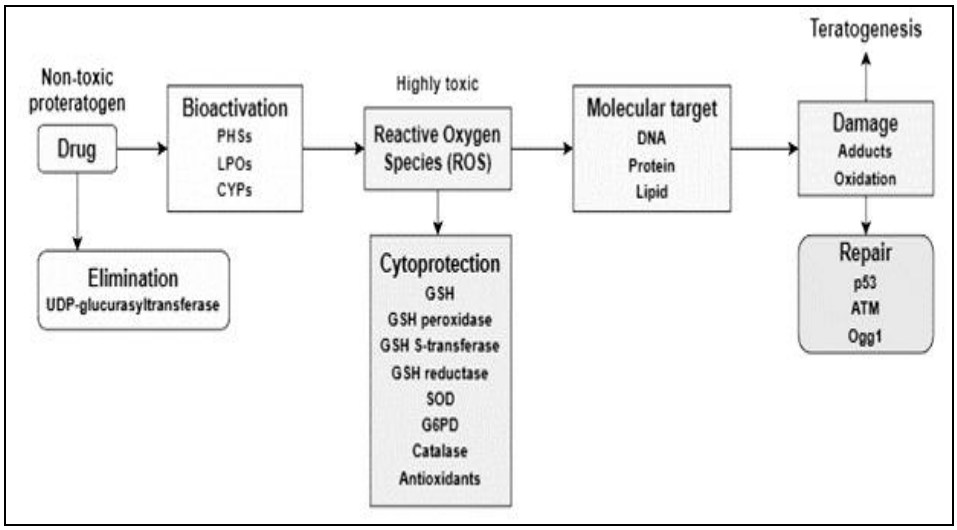

FIG. 4: OXIDATIVE STRESS TERATOGENESIS' MOLECULAR AND BIOLOGICAL CAUSES. G6PD, GLUCOSE-6-PHOSPHATE DEHYDROGENASE; GSH, GLUTATHIONE; LPO, LIPOXYGENASE; OGG1, OXO-GUANINE GLYCOSYLASE 1; PHS, PROSTAGLANDIN H SYNTHASE; SOD, SUPEROXIDE DISMUTASE; UDP, URIDINE DIPHOSPHATE. ATM, ATAXIA TELANGIECTASIA MUTANT. SOURCE: WINN AND WELLS (1995) WITH WILEY-GRACIOUS BLACKWELL'S PERMISSION.

Additionally, maternally generated chemicals that change the factors that determine embryonic oxidative stress or obstruct developing ROS-mediated oxidative stress signaling may have an impact on the likelihood of teratogenicity as well.

Vascular Disruption: Changes like hyper perfusion, hypoperfusion, hypoxia, and blockage in blood flow to the uterine-placental unit, the placenta-foetal unit, or the fetus itself are clubbed together under vascular disruption. Most significant reasons regulating vascular disruptions are vascular infections, sudden or gradual declines in uterine blood flow, abnormalities in the structure of the uterine-placental unit, faulty control of artery formationin fetus, external compression, embolic events, early regression of embryonic vasculature, and blockage with venous engorgement [1]. Case reports of assumed vascular events, includes occlusions, emboli, amnion rupture, and twin placental vessel anastomoses, that provide strong evidence for the whole range of vascular disruption-related birth defects [1].

Teratogenic Drugs in First Trimester of Pregnancy:

Anticonvulsants: Pregnant women getting epileptic attacks and undergoing treatment with anticonvulsant drugs are twice as likely to have abnormal offspring's [1]. Epileptic mother have 5% chances of delivering babies with significant abnormalities in contrast to the overall risk of 2-3% [1]. This risk is escalated for congenital heart disease and cleft lip and palate. Neural tube malformations [1]. Few medications, such as valproic acid and carbamazepine during pregnancy causes genetic susceptibility unlike deficient states created by low folate levels [1]. Fetal Hydantion Syndrome on the other hand can cause crania facial malformation, cleft lip and palate, broad nasal bridge, ocular hypertelorism, abnormal ears, congenital heart

disease, limb malformation in addition to mental and growth retardation.

Anticoagulants: Warfarin is prescribed to mother with acute risk of thromboembolism. Knowing that this drug might cause maternal or foetal haemorrhage [1], warfarin use has been linked to several ophthalmologic and genetic problems other than *Chondrodysplasia punctata*, nasal hypoplasia, bone stippling visible on radiologic examination, bilateral optic atrophy, and mental retardation problems [1]. However, heparin is the drug of choice since the other drugs are unable to cross the placenta owing to its size and significant negative charge [1].

TABLE 2: SIDE EFFECTS OF TERATOGENS

Direct Toxic action	Indirect Toxic action
Fetus: Direct toxicity, Metabolites, Indirect action, e.g., anti-metabolites, anti-vitamin, Pharmacodynamic action e.g., on cardiovascular system, Endocrine balance altered	Malformations: Interfering with fetal metabolism
Fetoplacental unit: Umbilical cord e.g., spasm, Amniotic fluid volume change, Fetal or maternal placental blood flow	Drugs: Folic acid antagonists, Antiepileptic drugs
Mother: Nutritional changes, e.g., vitamin or mineral deficiencies, Biochemical changes with secondary effects on the fetus, e.g., hyperglycemia, Endocrine balance	
Father: Sperm changes	

Antidepressant: Antidepressants are yet another class of drugs that needs attention before prescribing to would be mothers knowing that women at this stage might require due to obvious reasons [1]. Although antidepressants have effects leading to neurobehavioral problems, it is challenging to determine the source of these abnormalities to the fetus [1, 2]. Nulman and team evaluated 228 children between the ages of 16 and 86 months for the neurobehavioral effects of long-term fluoxetine exposure for mothers during pregnancy as an antidepressant [1]. Therefore, it becomes crucial in choosing antidepressants particularly during the first trimester.

Antithyroid: Antithyroid drugs and its prodrugs, are used to treat hyperthyroidism in pregnant patients as well. However, it is difficult to treat foetal hypothyroidism with antithyroid drugs because triiodothyronine (T3) and thyroxine (T4) do not cross the placenta [1]. Antithyroid medications frequently cause congenital deformities, including orofacial clefts, neural tube defects, and limb deficits [1].

Vitamin A (Retinoic Acid): During development, retinoids, are essential for cellular differentiation and tissue specificity [1]. There is 35% probability that mothers who take isotretinoin from 15th day of conception may have isotretinoin embryopathy if daily dosages of 0.5 to 1.5 mg/kg of body weight is maintained. Birth defects, like malformations of the neurological, cardiac, and craniofacial systems, anomalies in cephalic neural crest cell activity may occur when this drug is administered [1].

Sedative/Hypnotics: During pregnancy, benzodiazepines are typically used to treat hypertension or eclampsia and reduce anxiety in addition to issues with insomnia. These drugs are also approved for the treatment of generalized anxiety disorder, panic disorder with or without agoraphobia, and other disorders, along with sedation, mild anaesthesia, anterograde amnesia of perioperative events, seizure control, and skeletal muscle relaxation. Almost every major class of benzodiazepine compound is excreted in milk for lactating mothers, addition to the fact that it quickly crosses the placenta to reach the fetus [1]. Because the fetus is most vulnerable to pharmaceutical side effects, **Table 2**, the first three months of pregnancy should normally be avoided of such drugs [2, 3].

Aminoglycosides: For chronic infections brought on by *Pseudomonas aeruginosa* or cystic fibrosis, bactericidal drugs are often used topically as ear drops, administered parenterally, or nebulized. They can also be taken orally to sterilize the colon before surgery. Ototoxicity has been associated with doses as low as 1 g of streptomycin given twice weekly for 8 weeks during the first trimester. Streptomycin and kanamycin used during pregnancy and by the children of those who did

have congenital deafness have been related. Reports say that nephrotoxicity may increase when cephalosporins and aminoglycosides are combined [1]. Aminoglycosides and curariform medicines should not be used together since this may worsen neuromuscular blockade.

Teratogenic Drugs in Second Trimester of Pregnancy:

Angiotensin Converting Enzyme Inhibitors: As mixed vasodilator, angiotensin converting enzyme (ACE) inhibitor lowers the blood pressure by relaxing the veins and arteries. In case of heart failure, cardiac output is maintained with the help of ACE inhibitors, but blood flow can be increased and glomerular filtration rate be decreased with the use of ACE inhibitors [1]. These drugs when administered to a pregnant patient in the second trimester, especially can cause fetal pathology by inhibiting fetal urine production; although, they are safe during first trimester. ACE inhibitors and AT1-receptor antagonists should be avoided during the second and third trimesters of pregnancy, due to serious fetal malformations [1] such as oligohydramnios, neonatal and foetal renal failure, bony malformations, limb contractures, pulmonary hypoplasia, protracted hypotension, and neonatal death [1, 2].

Diazepam: Diazepam, centrally acting spasmolytic medication is of choicefor pregnant women to reduce anxiety and treat eclampsia in the second trimester of pregnancy [1]. The drug is highly bound to plasma protein, cross blood brain barrier, cross placental barrier, found in milk while lactating [1]. This risk can be tuned by controlling the absorption wherein delayed and decreased absorption is seen when administered with a moderate fat meal. However, babies who are breastfed are bound to get frequent doses, via lactation may develop drug accumulation [1]. Therefore, it is not advisable to use this medicine when pregnant. On the other hand, some infants have been born with facial clefts, heart abnormalities, and other numerous deformities as a result of prenatal exposure to Diazepam [1].

Teratogenic Drugs in Third Trimester of Pregnancy:

Tetracycline: Tetracyclines (e.g., tigecycline, minocycline, doxycycline), are classified as broad-spectrum antibiotics used to manage and treat different bacterial infections. These are assigned to patients falling in pregnancy category D (Evidence of risk pertaining to a risk to the fetus) by the FDA [3]. Tetracyclines act by suppressing bacterial protein synthesis (bacteriostatic) and are advised not to be given to pregnant women. This drug can cause hepatotoxicity in the mother and permanently yellow or brown teeth in the fetus (tooth discoloration in children under the age of eight) [3]. Additionally, they may hinder the growth of the long bones in the fetus [4, 5]. Tetracycline is excreted in very small quantities into breast milk, where it is chelated by the high calcium content to decrease the infant's exposure to it [4].

Chloramphenicol: This antibiotic is typically administered intravenously, and infrequently prescribed in the form of ear drops to treat ear infections. Although there isn't conclusive proof that using this medication during pregnancy leads to birth defects [3], it has been linked to adverse neonatal outcomes (such as grey baby syndrome), and the infant is theoretically at risk for idiosyncratic bone marrow suppression because oral chloramphenicol can cross the placenta [3]. Various authorities advise against using this medication during the week immediately prior to delivery since it is contraindicated. It should only be used when the benefits of using this drug during pregnancy outweigh the risk to the fetus.

Sulfamethoxazole: FDA classifies sulfamethoxazole not to be used in pregnancy category C to treat digestive, respiratory, and urinary tract infections in pregnant women [3]. Sulfonamides have the ability to penetrate the placenta two to three hours after mother's intake, until plasma concentrations in the fetus establishes equilibrium with the maternal serum and gradually, foetal plasma concentration reaches 70% to 90% of the mother's level. Additionally, this might cause hemolytic anaemia and jaundice in the infant [3]. They have the capacity to replace plasma albumin with bilirubin, which in infants during the first month of life can result in kernicterus.

Analgesics: Although analgesics are not known to cause significant problems, late pregnancy is a sensitive to use them. Analgesics fall into categories, systemic non-opioid analgesics (*e.g.*,

acetaminophen, aspirin *etc*.) and opioid analgesics (morphine, codeine, meperidine *etc*). For drugs like acetaminophen, there is no strong evidence of teratogenicity caused. Bleeding time is also not prolonged in contrast to aspirin. Nevertheless, for drugs like aspirin**,** potentially serious perinatal side effects, include a higher risk of gastroschisis and a lower uterine contractility that causes labour to start later and prolongs pregnancy. Aspirin causes bleeding in the fetus and in pregnant women before and during delivery since it reduces platelet aggregation, however, low-dose of aspirin has been shown to be both safe and beneficial [3].

In contrast, nonsteroidal anti-inflammatory drugs (NSAIDS), like indomethacin can delay delivery by at least 48 hours and as much as 7–10 days. Moreover, administration in first-trimester carries a higher risk of miscarriage and birth defects. Even after thirty weeks, NSAIDs can cause oligohydramnios and premature closure of the foetal ductus arteriosus [3]. Various types of opioids such as morphine-like agonists (*e.g.,* morphine, hydromorphone, hydrocodone, codeine, and oxycodone), meperidine-like agonists, and synthetic opioid analogues (*e.g.,* tramadol) has been linked to a number of negative effects on the health of mothers and new-borns, including maternal deaths, preterm birth, stillbirth, and specific birth defects.

CONCLUSION: The current study provides a concise but comprehensive overview of the teratogenesis brought on by numerous medicines during various pregnancy trimesters. Medications are extremely important during pregnancy for managing both the mother's and the fetus' biological systems. Unless specific circumstances are activated, all pregnancy-related medications may not always induce teratogenesis. Only a few of these have been discussed. If mother is taking such known drugs, it should be stopped, altered, or dosed down to the least quantity feasible in order to reduce or totally eradicate this impact. This will depend on the teratogenic pathway and the target organ. Typically, it happens when a fetus is developing during a delicate time. The unique physiology of pregnancy makes it challenging to treat acute and chronic disorders with medication as well as to manage the symptoms of a number of pregnancy-related disorders. Medical professionals need to inform patients about natural ways to manage aches, pains, tension, and viral diseases while pregnant in order to reduce the danger of teratogens damaging the health of the fetus. Congenital disabilities would disappear quickly with more effort and less exposure. Any medication should only be used at the lowest effective dose when the risk-to-benefit ratio supports it, after thorough consultation with a caregiver. It is advised to use caution when taking any medications while pregnant because the long-term consequences of using medications may take years to manifest. With regular and sufficient medical supervision, pregnant women would not only become aware of and understand teratogens, but they would also be far more likely to avoid exposure during pregnancy. To make sure they are not teratogenic or should not be administered to pregnant women, it is crucial to be under the supervision of a medical practitioner all throughout the pregnancy period.

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