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TERATOGENICITY: OVERVIEW, PHYSIOLOGICAL CHANGES DURING PREGNANCY AND EFFECTS OFANTIBACTERIALS ON FETUS

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ABSTRACT

An exposure that could cause a persistent deformity in an organism's structure or function duringthe time it is still embryonic or fetal is known as teratogenic. Any medication can partially or completely pass through the placenta because it is not a rigid barrier. One of the most active biological systems is the embryo, where pharmacological effects are frequently irreversible, in contrast to adulthood. This kind of negative impact came into focus during the thalidomide crisis (1958–61), which left thousands of infants with phocomelia (seal-like limby) and other birth problems. The risk and benefits of pharmaceutical use at the time of pregnancy should be considered for both the mother and the developing fetus. Certain drugs may be contraindicated in certain trimesters and taken cautiously in others, depending on the results of the examination. In 2015, The FDA implemented the Pregnancy and Lactation Labeling Rule (PLLR) to replace the "A, B, C, D, and X" pregnancy labeling categories, with the goal of improving drug safety classification. Foods and beverages in categories A and B are safe, medications in categories C and D should only be used in dire circumstances or when the potential benefit to the fetus surpasses the potential risk. It is often known that one of the most prevalent effects of the physical changes that occur during pregnancy is asymptomatic bacteriuria. Antibacterial medication will consequently assist the mother as well as the infant. As so, the mother receives no direct benefit from the treatment. Antibiotic administration is highly prevalent during pregnancy. It is widely known that there is a lot of pharmacoepidemiological research on the prescribing of medications during pregnancy. Thefindings indicated that the only medications that have been shown to be teratogenic during pregnancy are those used very rarely. Due to the antibiotic's possible risks to the fetus, many pregnant women use extreme caution when taking them. Antibiotics, however, come in a number of classes that are either contraindicated or allowed with restrictions from being used during pregnancy and lactation, or both. The increase in pregnant tuberculosis patients can be attributed to the growing proportion of women of childbearing age. As with any medication, the main concern when it comes to tuberculosis treatment during pregnancy is the potential for teratogenicity, particularly in the first trimester. This review describes the teratogenicity and its mechanism, physiological changes occur during pregnancy and further the use of different antibacterial (Antibiotics, Antitubercular drugs) effects on the fetus.

KEYWORDS: Teratogenicity, Antibiotic, Antitubercular, Infections, FDA category, Placenta, Birth defects, Pregnancy.

INTRODUCTION

When a medicine is given to a pregnant woman, its teratogenicity refers to its ability to result in defects in developing fetus.[1] Thalidomide is well known example of how a drug that seemed to be harmless and was available over the counter to treat morning sickness could have such negative effects on the fetus, including miscarriages and physical deformities.[2] Pregnant women generally take one or more medications during their pregnancy; over 60% of them are prescribed medications.[3] Teratogens can cause physical deformities, behavioral or mental disorders, and a reduction in the cognitive abilities of the offspring, among other effects on an embryo. In addition, it may cause problems like premature labor, robotic reversals, miscarriages, and damage to embryos. Physical agents, metabolic disorders, infections, and early pharmaceuticals and chemicals are the four classes of teratogens.[4] Teratogens are chemicals that have the potential to disrupt a fetus's regular intrauterine growth,

anatomical formation, bodily functions, and postnatal development. This term covers hereditary problems, maternal illnesses, infectiousdiseases, and environmental exposures. Drug exposures are typically at the focus of discusses on teratogens.[5] Most medication administered to the expectant woman can also target the fetus. The condition that is brought about in the fetus depends on the placenta's permeability, the type and dosage of the agent, the mother's illness, and the length of the pregnancy. The first trimester is when organs are developing, making it a high-risk time for the fetus. During this time, any unfavorable circumstance, intrinsic or extrinsic, may negatively affect the development of the embryo, resulting in deformity or death.[6]

Radiation was the first practical experimental method that has been used to cause congenital malformations. Anophthalmia, cleft lip, and other congenital abnormalities were documented in the progeny of pigs fed a diet low in vitamin A, according to a 1933 report by veterinarian Frederick Hale. Some of our most potent drugs have been discovered to be strong teratogens in lower animal species. For instance, the Nobel prize in medicine has been given out no less than four times for the development of exceptional pharmaceuticals like cortisol, penicillin, streptomycin, and insulin, all of which have been found to cause birth defects in experimental animals. The thalidomide experience in humans supports this claim. The medication caused a peculiar and recognizable "thalidomide syndrome."[7]

Drugs can have three different effects on the fetus

Fertilization and implantation - Conception through 17 days- pregnancy failure, which frequently goes unrecognized.

Organogenesis- Which occurs between 18 and 55 days after conception is the most susceptible time.

Growth and development- Starting at 56 days, developmental and functional problems may appear. For example, ACE inhibitors may result in hypoplasia of organs, particularly the lungs and kidneys.[1]

FDA Categorization of Drugs Used In Pregnancy

A. A higher risk of fetal malformations has not been demonstrated by sufficient, carefully monitored research in pregnant women.
B. Studies on animals have not revealed any evidence of harm to the fetus; however, studies on pregnant women have not been sufficiently or adequately controlled, or studies on animals have shown a negative effect but have not been able to demonstrate a risk to the fetus.
C. Alternatively, no appropriate and well-controlled research has been done, no animal research has been done, no sufficient research has been done on pregnant women, and animal research has shown a negative impact.
D. Studies on pregnant women that are sufficiently well-controlled or observational have shown that there is a harm to the fetus. The advantages of treatment, though, might exceed the risk.

X. Research involving sufficient, well monitored, or observational studies in animals or expectantmothers has proven to be positive for fetal malformations.[8]

Figure 1: Effects of Teratogens.

Physiological Changes During Pregnancy

The numerous physiological changes that pregnant women experience, which lead to altered pharmacokinetics, make it more difficult to prescribe.[9] A number of physiological changes might affect the pharmacodynamics and pharmacokinetics of medicaments during pregnancy. (a) Nausea and vomiting during pregnancy can affect how much and how quickly medications are absorbed. (b) Due to the rise in progesterone and estrogen levels during pregnancy, gastrointestinal transit durations are prolonged. (c) Changes in gastric volume and pH brought on by pharmacological treatments used during pregnancy to treat digestive issues, such as histamine-2 receptor antagonists, antacids and proton pump inhibitors. (d) Modification of the expression and activity of transporters and enzymes involved in the biotransformation of medications in the gut.

[10]The penetration of an egg by a sperm results in pregnancy. This process, known as fertilization, typically occurs in a woman's fallopian tube. The fertilized egg starts dividing into a huge mass of cells right away. The fertilized egg implants into the uterine wall between five and seven days following ovulation, beginning the process of placenta formation. Significant metabolic changes take place as the fetus and placenta develop and put more stress on the female reproductive system. Weight increase and changing body shape are the most evident physical changes.[11]

Role of Placenta

Since the placenta connects the maternal and fetal circulations, we typically think of it as the fetus's main nutritional source. The placental barrier notion is crucial when thinking about external substances like medications.[7] Lipophilic drugs typically cross the placenta easily. Additionally, the fetus and amniotic fluid may serve as sites for the accumulation or dissemination of drugs. The human placenta also expresses a variety of xenobiotic metabolic enzymes, including active membrane transporters and several SULT1A1 and SULT1A3 metabolic enzymes (phase I: CYP1, CYP2, and CYP3, phase II: GST alpha and pi, NAT, SULT1A1 and SULT1A3, and some UGT1A and UGT2B).[10] The velocity of transfer is influenced by the chemical characteristics of the medication, including protein binding, pH difference, lipid solubility, and molecular mass.[11] Patients sometimes experience changes in their organ systems throughout pregnancy as a result of the developing fetus, including the cardiovascular, respiratory, gastrointestinal, urinary, and more systems.[12]

Three different kinds of drug transfer occur across the placenta:

A. Type 1 medications (Complete transfer), such as thiopental. Drugs that transfer in this way will cross the placenta quickly, equilibrating in maternal and fetal blood at pharmacologically vital amounts.
B. Type 2 medications (Exceeding transfer), such as ketamine. The amounts of these medications are higher in fetal blood compared to maternal blood because they cross the placenta.
C. Type 3 medicines (Incomplete transfer), such as succinylcholine. These medications have larger amounts in maternal blood than in fetal blood because they cannot penetrate the placenta completely.[13]

In accordance with their physicochemical characteristics, molecules may cross the placenta in a number of mechanisms. Lipid membrane of placenta is first penetrated by tiny, hydrophobic substances that passively diffuse. This group includes a lot of prescription and nonprescription medications. Transcellular transport can also take place by active receptor-mediated transport or endocytosis, in addition to passive diffusion and is the mechanism for nutrients and bigger molecules like immunoglobulins. The paracellular space, or the spaces between the cells in each layer, is another pathway by which some chemicals pass across the placental barrier.[14] A medication that has been partially ionized is able to penetrate the placental barrier in its non- ionized fraction. Drug pKa and maternal blood pH both affect the level of ionization of medications.[13] Compounds with a molecular weight more than 1000 have a limited ability to pass the placenta, such as heparin, iron dextran, and insulin. However, the majority of medications have molecular weights between 250 and 400.[15] Only drugs that are free and unbound pass through the placenta. Fetal albumin rises whereas maternal plasma albumin falls during pregnancy. As a result, there is an increase in the concentration of free medication that passes through the placenta and reaches the fetus.[11]

Mechanism of Teratogenesis

The mechanisms underlying teratogenesis can be broadly classified into two categories based on the etiology of congenital malformations: (a) environmental agents or other factors that interact with an embryo during its developmental stage, such as drugs, chemicals, radiation, infections, abnormal metabolic states of the mother, or mechanical factors; and (b) errors in genetic programming resulting from deviations in the genotype of the embryo or the slight likelihood of error of a normal genotype.[16] In accordance with Wilson (1959), the third teratological concept states that "teratogenic substances function in certain mechanisms on growing cells and tissues to trigger orders of abnormal developmental occurrences."[17] According to certain theories, an embryonic or germinal cell's first response to a harmful environmental influence plays a crucial role in establishing the course of subsequent pathogenesis as well as how the pathogenesis will proceed.[18] A specific pathogenic process may result in different outcomes for chemical or drug exposures based on factors like embryonic age, duration of exposure and dose, and genetic susceptibility, whereas a specific birth defect may be caused by a variety of factors (such as

environmental factors, genetics, medicines, social conditions), as well as by various mechanisms.[19]

On the basis of some analysis of the literature, there are several teratogenesis pathways. Mechanism of tertogenesis

- Mutation
- Chromosomal aberrations
- Mitotic interference
- Changes in nucleic acid composition and protein synthesis
- Decrease in the quantity of vital components needed for biosynthesis
- Less energy available for the development of the embryo and the fetus
- Inhibition of enzyme
- Osmolar imbalance
- Changes in membrane characteristics.

1. The nucleotide sequence of nuclear DNA strands can be altered by the process of mutation, which modifies the ability of progeny cells to divide.
2. Chromosomal abnormalities, such as chromatid loss or translocation and nondisjunction, cause progeny cells to have an apparent excess or lack of chromatin material.
3. The term "mitotic interference" is used for convenience to refer to the various ways that altering the cell cycle might alter the proliferative rate.
4. The term "altered nucleic acid synthesis and function" describes the ways in which different antibiotics and anti-cancer drugs prevent genetic material from being expressed throughout the developmental stage.
5. Reduction in the quantity of components necessary for biosynthesis is the process through which dietary deficit results in aberrant development.
6. In addition to being directly associated with the disruption of both anaerobic and aerobic metabolism, the coenzyme analogues, such as 6-aminonicotinamide and galactoflavin, are both teratogenic and embryo lethal. These analogues reduce the energy supply for embryonic and fetal growth.
7. It is believed that blocking specific metabolic processes by inhibiting particular enzymes, such as carbonic anhydrase, thymidylate synthetase, and dihydrofolate reductase is the main cause of aberrant development.
8. It has been shown that osmolar imbalance, which alters the fluid pressures, viscosities, and composition in different embryonic compartments, can be quickly created and functions as a major mechanism of teratogenesis.
9. Despite the fact that altered membrane properties can cause an osmolar imbalance, it is also likely that they can impair vital transport processes across placental or cell membranes without adversely altering fluid volume or osmotic balance.[18]

Table 1: Some examples of teratogenic agents known to cause birth defects.[20]

AGENTS	MALFORMATIONS
Dietylstilbesterol	Reproductive tract abnormalities
Tetracycline	Teeth anomalies and damage
Warfarin	Intellectual disorder and craniofacial malformations
Cytomegalovirus	Brain and sensory abnormalities
Ionizing radiation	Microcephaly, growth delays, mental weakness
Cadmium	Limb anomalies, cardiovascular disorders, neural tube defects

Table 2: Frequently used drugs in pregnancy.[21]

Group	Drug included	Category
Antibiotics-Cephalosporin	-	B
Penicillins	-	B
Aminoglycoside	Gentamycin, Streptomycin	C, D
Macrolide	Erythromycin, Azithromycin	B
Antihypertensive	Propranolol, Atenolol, Verapamil, Diltiazem	C
Corticosteroids	Cortisone Dexamethasone	D C
Anti-parasitic drugs	Albendazole, Diethylcarbamazine	D/X
Anti-cancer	Vincristine, 5-fluorouracil	D
Antifungal	Miconazole, Salicylic acid	C

Use of Antibacterials During Pregnancy

Antibacterial therapies are among the most frequently recommended medications during pregnancy because of the significance of treating infections for the health of the expectant mother and her fetus.[22] The physiological changes that arise during pregnancy or poorly understood immunological systems make such individuals more susceptible to infection. Due to this relative

immunosuppression, the risk of significant maternal complications from infections with pathogens such malaria and varicella-zoster virus is increased.[9] According to research done on animals, some antibacterial drug types, including some quinolines and metronidazole, may act as genotoxic agents or carcinogens. The offspring's gut colonization may also be impacted by maternal antibiotic use during pregnancy, which alters the bacterial profile. Through interactions with the immune system, and commensal bacteria the microbiome contributes to disease prevention, couldassist in avoiding the development of cancer. The probability of pediatric cancer may also be influenced by exposure to infectious organisms.[23] All medications, according to the FDA, can be divided into five risk classes, or risk factors A, B, C, D, and X. Drugs from categories A and B are safe; drugs from categories C and D ought to be used only in cases where the potential benefit to the fetus justifies the possible risk, such as when safer medications are either ineffective or cannot be used, or when a major disease occurs. Any possible benefits are outweighed by the risks associated with taking drugs from category X while pregnant. Penicillins and cephalosporins are classified as group B drugs by the FDA based on their safety for the fetus. Nonetheless, these drugs may be teratogenic, according to a number of recent publications.[24]

Antibiotics

The usage of antibiotics during pregnancy is on the rise, and they constitute an important proportion of all medications recommended during pregnancy. According to various studies every fourth pregnant woman receives an antibiotic prescription.[25] Prenatal antibiotic exposure has been associated to both immediate (congenital defects) and long-term (gut microbiome changes, asthma, atopic dermatitis) in the infant.[26] Despite the broad adoption of antibiotics during pregnancy, there are still concerns regarding the safety of macrolides, quinolones, tetracyclines, metronidazole, and nitrofurantoin for developing fetuses. There is some conflicting evidence in the literature on the association between prenatal antibiotic use and the possibility of spontaneousabortion. There is no correlation between the usage of macrolides and spontaneous abortion, according to four research that used data from teratology information services. Contrarily, A Danish study based on information from a prescription database discovered that using clarithromycin increased the incidence of spontaneous abortion.[27]

Table 3: Antibiotics that should not used during pregnancy.[28]

Aminoglycoside 5- nitroimidazoles Tetracyclines Vancomycin	Gentamicin, Streptomycin Metronidazole Doxycycline, Tetracycline etc.

Gentamicin

Many severe Gram-negative bacillary infections are treated with gentamicin. Following topical treatment, there is a significant absorption, and it has been discovered to cause nephrotoxicity in newborns.[29] UTI is the primary medical condition for which gentamicin is used. Since there areno published epidemiological studies of congenital malformations, the extent of teratogenic risks for infants born following gentamicin exposure during pregnancy is unknown. There is only one case report available online: a mother who had a 10-day regimen of gentamicin (300 mg/d) and prednisolone in gestational week 7 reported having a child with renal cystic dysplasia at the age of 4.5 years. It is unclear how these findings relate to the usage of clinical gentamicin levels during human pregnancy. In animal studies, high gentamicin dosages were linked to higher rates of embryonic death, hearing loss, and nephrotoxicity.[30]

Tetracyclines

Tetracycline concentrations in umbilical cord blood are roughly 50% higher than those in mother blood. Following intrauterine exposure, the fetus likewise showed the usual negative effects of tetracyclines in accordance with these concentrations.[28] Due to its affinity for calcium, tetracycline is integrated into calcified tissue as a chelated compound and as a complex known as tetracycline-calcium orthophosphate.[31] Since tetracyclines are FDA category D drugs, they should only be used in cases where no other treatment option is available, such as for syphilis patients who are allergic to penicillin.[32] Numerous publications on the topic have been published in the dentistry and medical literature since the first report of tetracycline-induced tooth discoloration in 1958. Children who get tetracycline or a derivative throughout the enamel- building process for permanent or deciduous teeth have been shown to experience severe tooth discoloration. It was demonstrated by Douglas that tetracycline penetrated the placental barrier and discolored the permanent teeth of infants whose mothers used the medication during the pregnancy.[31]

The effect of tetracyclines on DNA synthesis was investigated in an organ culture system in order to determine the drug's growth-depressing concentration. This indicates that tetracycline significantly reduced DNA synthesis at 100 µg/ml but had no effect on the absorption of labeled thymidine at 10 µg/ml.[33]

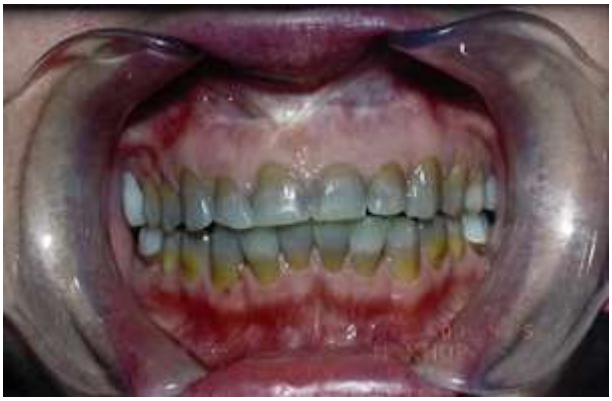

Figure 2: Tetracycline - induced discoloration of teeth.

Sulphonamides

Since infections during pregnancy may result in serious complications for both the pregnant woman and the fetus, sulfonamides are an extremely important class of drugs. They have been utilized as first-line treatments for urinary tract infections and other diseases brought on by susceptible microorganisms in the second and third trimesters. Sulfonamides have diuretic, antibacterial, antithyroid, hypoglycemic, and many other pharmacological activities. Trimethoprim - sulfamethoxazole (TMP-SMX) is the sulfonamide that is most frequently administered during pregnancy.[34] It is possible for the sulfonamides to cross the placenta as well. Unconjugated bilirubin can be displaced from plasma albumin by administering sulfonamides to infants or expectant women in third trimester of pregnancy. A condition known as kernicterus may then result from the released bilirubin entering the tissues and brain.[28]

Macrolides

Macrolides are bacteriostatic antibiotics that reversibly bind to the bacterial 50SRibosomal subunit and inhibit protein biosynthesis.[35] There is a higher chance of serious birth malformations, especially heart defects, in children whose mothers used macrolide antibiotics during the early stages of their pregnancies. Macrolide antibiotics, such as azithromycin, clarithromycin, and erythromycin, are alternatives to penicillin for people with penicillin allergies and are used to treat common bacterial infections. Out of 8632 children whose mothers used macrolides, 186 had major abnormalities.[36] Erythromycin belongs to the macrolide class of medications and is consideredto be very safe to use while pregnant. Rarely, a transient hearing impairment could develop. Because clarithromycin has been reported to cause cardiovascular abnormalities in rats and to have teratogenic effects in animals, it should be taken with caution.[35]

Antituberculosis Drugs

The diagnosis of tuberculosis in pregnant women is more complex due to the similarity of the disease to physiological symptoms of pregnancy, including exhaustion, sweating, shortness of breath, coughing, and a slight fever. The four first-line anti-tuberculosis drugs are categorized as categories B and C according to the USFDA risk classification of pharmaceuticals during pregnancy. Category C includes pyrazinamide, isoniazid, and rifampicin; category B includes only ethambutol. Category D drugs are those that are presently being phased out of the market, such as streptomycin.[37] It is possible for a woman to become pregnant while receiving tuberculosis treatment; in such cases, her obstetrician and the pregnant woman should discuss the risks to the growing fetus.[38] The CDC recommends using first-line agents such as isoniazid, rifampicin, and ethambutol during pregnancy.[39]

Table 4: Tb treatment regimens for pregnant women.[40]

Diagnosis	Treatment
Latent TB	• RIF and INH on a 3- months daily regimen. • Rifampin dosage of 4 months per day. • 3 month weekly INH and rifapentine regimen is no advised for pregnant women or women expecting to become pregnant during the course of treatment because it has not been evaluated to be safe.
TB disease	• Streptomycin has been shown to have harmful effects on the fetus, so it should not be used during pregnancy. • Isoniazid, rifampin, and ethambutol taken daily for two months is the recommended starting treatment regimen. After that, the medication should be taken either daily or twice a week for seven months.

Second line antituberculosis drugs

Streptomycin

The antibiotic streptomycin is an aminoglycoside that has been isolated from the Streptomyces griseus bacteria. It is the first antibiotic aminoglycoside to be found. Although streptomycin was once among the first and most successful therapies for pulmonary tuberculosis, nowadays it is mostly used as an adjuvant therapy, second only to the "RIPE" regimen (rifampin, isoniazid, pyrazinamide, and ethambutol). Because streptomycin has documented ototoxic effects and can penetrate the placenta, it is contraindicated during pregnancy. Streptomycin is therefore regarded as teratogenic.[41] Aminoglycosides and penicillins have been used together to treat Pseudomonas aeruginosa infections during pregnancy. The only documented teratogenic effect of these drugs particularly streptomycin and kanamycin during the first trimester of pregnancy is ototoxicity.

Because of numerous previous cases of ototoxicity and nephrotoxicity in newborns whose mothers took the streptomycin throughout the first trimester of pregnancy, the FDA has classified streptomycin as a category D agent.[42] Streptomycin can pass through the placental barrier in a variety of ways, with fetal concentrations up to 50% higher than maternal concentrations. This amount is influenced by a number of factors, such as deficits in maternal detoxification or excretion, structural defects that enhance the permeability of the placenta, and various illnesses ofthe mother or fetus. [43]

According to research in *R.* clamitans and *Rana pipiens*, external application of streptomycin sulfate decreases normal embryonic development in a direct proportion to drug concentration and duration of exposure up to toxicity. The most common abnormalities seen were extreme tiredness, dizziness, enlarged bodies, tissue disintegration, especially in the gills, and abnormalities of the mouth and eyes. Streptomycin at a hazardous level of 0.9 mg/ml for *R. pipiens* and 1.3 mg/ml for *R. clamitans* was found. Equally clear was the impact of streptomycin on regeneration. Tail fin regeneration is inhibited in *R. clamitans* larvae of all ages, and regeneration capacity is directly correlated with drug concentration. At doses of 1.2 mg/mL, the greatest suppression of epidermal proliferation and decrease in vascularization were observed.[44]

Kanamycin

An aminoglycoside antibiotic called Kanamycin A was derived from Streptomyces kanamyceticus and is used to treat a variety of pathogens, including Mycobacterium TB.[45] The FDA has classified kanamycin as pregnancy category D.A pregnant female or a female who becomes pregnant while receiving therapy should be informed of the possible danger to the developing fetus before beginning kanamycin treatment. The use of kanamycin during pregnancy is advised only in situations where the benefits outweigh the risks.[46] A study by Yehoash Raphael et al. showed the ototoxicity of kanamycin in guinea pigs after the pregnant mothers were given 200 or 400 mg/kg body weight kanamycin sulfate for 8 consecutive days at various stages of gestation. Surface view analysis of Corti's organ revealed moderate damage from treatment during the middle trimester and severe damage from therapy during the last trimester of pregnancy. Studies in humans have shown that therapy with aminoglycosides can cause ototoxic effects in adult human ears. Because kanamycin acts on fetal and maternal cochlear cells in a comparable manner, it is important to consider the potential teratogenic risk of kanamycin treatment, particularly in the third trimester of pregnancy.[47]

Fluoroquinolones

As an antibiotic class, fluoroquinolones work by inhibiting bacterial DNA gyrase. When it comes to their use during pregnancy, a number of factors come together to cause teratogenic and fetotoxic concerns. Micropathogens and mammals have comparable topoisomerases in their DNA. In addition to crossing the human placenta, fluoroquinolones may potentially cause cancer and mutagenesis in the growing fetus. Moreover, the quinolones exhibit a strong affinity for cartilage.[48]

The weight and length of the fetus significantly decreased when norfloxacin was administered to pregnant female rats during the organogenesis phase. Norfloxacin, administered orally, can cause skeletal abnormalities such as impaired ossification of the skull, dislocation or absence of the sternebrae, reduction or absence of the caudal vertebrae, and absence of the forelimb and hindlimbdigit bones, along with portions of the metatarsal and metacarpal bones. It is possible to link the fetotoxicity, high resorption ratio, fetal loss, and deformities to the suppression of DNA transcription in the rapidly dividing fetal cells. Fluoroquinolones therefore impede both DNA gyrase and mitosis. A fully damaged DNA molecule may cause embryonic loss or resorption, but a partially damaged molecule may cause fetal deformity.[49]

Ethionamide

Since 1956, ethionamide has been used as a second-line therapy for tuberculosis. It is an inactive prodrug. Ethionamide is a category C drug. It can cross the placenta. Ethionamide usage during pregnancy is debatable.[50] Thiomide derivatives, such as prothionamide and ethionamide, have high tissue penetration, including the cerebrospinal fluid. Rats utilized in animal experiments showed an increase in central nervous system complications, whereas mice and rabbits did not show an increase in induced birth malformations.[51] Studies on humans have also shown an increase in CNS abnormalities following early prenatal use of this medication. Therefore, it is not advised to use it during pregnancy.[52]

CONCLUSION

Pregnancy causes a number of physiological changes that may affect the pharmacokinetics and pharmacodynamics of medications and increase the risk of birth abnormalities. Antibiotics that cause birth malformations include gentamicin, tetracycline, sulfonamides, and macrolides. Additionally, second-line antitubercular medicines have been identified as teratogenic.

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