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SAFE USE OF MEDICINES IN PREGNANCY

Magdum Jyoti*[1], Shelake Sardar[2], Patil S. S.[2], Narvekar Namita[2]

[1]Ashokrao Mane Institute of Diploma in Pharmacy, Peth-Vadgaon, Kolhapur, MS, India.416112

[2]Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, MS, India.416112

Email ID: jyotimagdum2016@gmail.com

Abstract:

Pregnancy is a special physiological condition which affects the pharmacokinetics of medicines used and certain medications reach to fetal circulation which may cause adverse effects and also teratogenic effects. But complete avoidance of medical treatment during pregnancy is not possible because some women enter pregnancy with some medical problem or some are arises during gestation period. In this review we summarize basic principles of teratology, classification of drugs according to FDA and provide information regarding safe and effective use of medication during pregnancy.

Keywords: *Teratogens, Teratogenic effects, FDA categories of drugs, fetal circulations, Placental barrier, adverse effects, safe use of medications.*

Corresponding author:

Magdum Jyoti*,

Ashokrao Mane Institute of Diploma in Pharmacy,
Peth-Vadgaon, Kolhapur,
MS, India.416112

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INTRODUCTION:

In the pregnancy drug treatment presents a special concern because many physiology of pregnancy affects the pharmacokinetics of medication used which may reach to fetus and may cause harm. It has been estimated that about 10% of congenital anomalies may be caused due to exposures to medications, alcohol or other exogenous factors that have adverse effects on developing embryo or fetus. Total avoidance of pharmacological treatment in pregnancy is not possible and may be dangerous because some women enter pregnancy with medical conditions that require ongoing treatment (e.g. asthma, epilepsy, and hypertension). Also during pregnancy new medical problems may be arises (e.g. migraine, headache) requiring pharmacological therapy. We all know about thalidomide disaster in 1960's pregnant ladies who ingested thalidomide gave birth to children with phocomalia. Various other examples of teratogenic effects of drugs are known. It has been documented that congenital abnormalities caused by human teratogenic drugs account for less than 1% of total congenital abnormalities. Hence in 1979, Food and Drug Administration developed a system that determines the teratogenic risk of drugs by considering the quality of data from animal and human studies. FDA classifies various drugs used in pregnancy into five categories, categories A, B, C, D and X. Category A is considered the safest category and category X is absolutely contraindicated in pregnancy.

PHYSIOLOGY OF PREGNANCY

Placental barrier: Pregnancy occurs when a sperm penetrates an egg. This is called fertilization and usually takes place in the woman's fallopian tube. The fertilized egg immediately begins to divide into a growing cluster of cells. Between 5-7 days after ovulation the fertilized egg implants into the wall of uterus and starts forming the placenta. The placenta maintains and nourishes the baby by enabling the transfer of O_2, CO_2, amino acids, fats, vitamins and minerals from the mother's blood. It also allows transfer of waste substances from the growing baby.

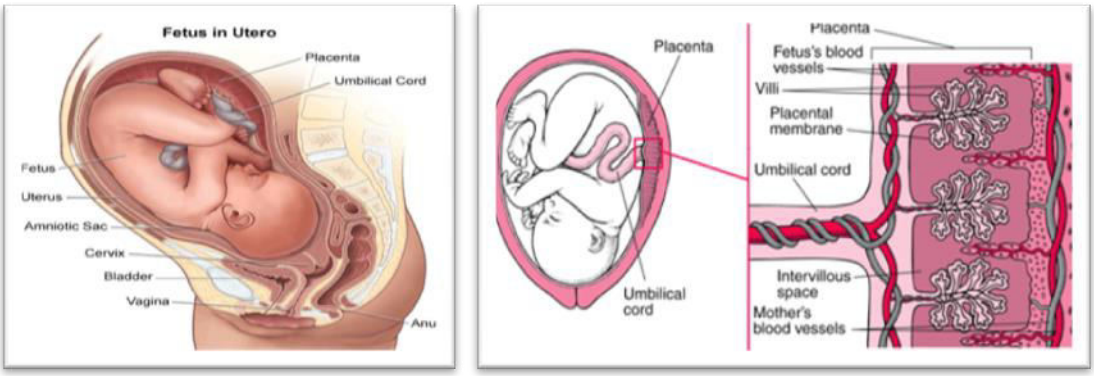

Fig. 1: Placental barrier

FACTORS AFFECTING DRUG TRANSPORT

In order for a drug to cause a teratogenic or pharmacological effect on the fetus, it must cross from maternal circulation to fetal circulation through the placenta by diffusion. The rate of transfer depends on the chemical properties of the drug such as protein binding, pH difference, lipid solubility and molecular weight of the drug.

- Only free unbound drug crosses the placenta. During pregnancy maternal plasma albumin decreases while fetal albumin increases. As a result the concentration of free drug increases which crosses the placenta to reach the fetus.
- Fetal pH is slightly more acidic than maternal pH and so weak bases are more likely to cross the placenta.
- Moderately lipid soluble drugs can easily diffuse across the placental membrane.
- Drugs with low molecular weight (<500 g/mol) diffuse freely across the placenta. Drugs with a higher molecular weight (between 500-1000 g/mol) cross the placenta less easily, while a few drugs with a high molecular weight (>1000 g/mol) do not cross the placenta.

PREGNANCY MEDICATION RISK: TERATOLOGY AND ADVESRE EFFECTS OF DRUGS

The damage caused by medications can be classified into 2 broad categories: those that are teratogens and those that cause adverse fetal affects. The term “teratogen” is sometimes used to describe an agent that can produce structural or functional abnormalities in a developing embryo or fetus. And teratogenicity is actually a property of the exposure which is depending on:

- The physical and chemical nature of the agent,

- Route of administration
- Timing in gestation
- Concurrent exposure to other agents and biological susceptibility of the mother and embryo or fetus.

The developmental stage of the embryo or fetus at the time of exposure is critical. During conception and for about 2 weeks thereafter, most cells of the conceptus are not yet committed to a specific developmental program. One damaged cell can be replaced by another, and normal development will usually ensue, although the embryo will not survive if too many cells are damaged or killed. This is known as the "all-or-nothing" period, but even during this period some exposures can adversely affect the development of surviving embryos .The subsequent period of organogenesis, from 18 to 60 days after conception (about 4.5–11 weeks after the start of the last normal menstrual period) is the time of greatest sensitivity to most teratogenic exposures. The most common teratogenic effects are neural tube defects, congenital heart abnormalities, cleft lip or palate and fetal stillbirth.

Fig. 2: Neural tube defects, congenital heart abnormalities, cleft lip or palate and fetal stillbirth.

Adverse fetal effects which includes dysfunction of an organ or tissue after that organ or tissue has been formed. Some examples include difficult postnatal adaptation, withdrawal, electrolyte abnormalities, and altered glucose metabolism. Medications that may cause adverse fetal effects include some antipsychotic, antidepressant, and opioid medications. There are only few medications are known teratogens. And it is also find out that only 2-3 % birth defects are related to medications or drugs used during pregnancy, remaining 97-98% defects are due to other causes. Although the number of mediations associated with teratogenicity is small, it is important because many of the underlying causes of congenital anomalies cannot be affected or changed, whereas drug exposure can be controlled.

PREGNANCY AND DRUG USE

Drugs play an important role in improving human health and promoting well-being. However to produce the desired effect, they have to be safe, efficacious. In general, drugs unless absolutely necessary should not be used during pregnancy because drugs taken by a pregnant woman can reach the fetus and harm it by crossing the placenta, the same route taken by oxygen and nutrients, which are needed for the growth and development of fetus. While avoiding medications when pregnant may be desirable, it is often not possible and may be dangerous because some women enter pregnancy with medical conditions that require ongoing and episodic treatment (e.g. asthma, epilepsy, hypertension). Also during pregnancy new medical problems can develop and old ones can be exacerbated (e.g. migraine headache) requiring pharmacological therapy. Failure to manage conditions like these may affect the health of both the mother and her infant. Also some drugs like vitamins, minerals, iron and dietary supplements are essential for the health of pregnant woman and the fetus. It has been reported that about 8% of pregnant women need drug treatment due to various chronic diseases and pregnancy related complications. Many women take medications in the early weeks of pregnancy before realizing that they are pregnant. About 59% of pregnant women are prescribed a medication other than a vitamin or mineral supplement. About 13% of pregnant women take a dietary herbal supplement.

More than 90% of pregnant women take prescription or nonprescription (over-the-counter) drugs or use social drugs such as tobacco or alcohol or illicit drugs at sometime during pregnancy which is harmful to fetus and mother also. Pregnant women are usually excluded from medical trials and results from animal studies need not apply to human population. Hence treating pregnant women with some drugs is a problem and most clinicians have a rather restricted approach to the use of drugs during pregnancy. Fear of causing fetal harm and death through medication use in pregnancy has resulted in many challenges to clinical research about the safety of drugs in pregnancy. Therefore medication safety information in pregnancy is actually obtained through case reports, epidemiological studies and animal studies; all of which have limitations that make determining risks of a drug use during pregnancy difficult. Despite the paucity of information on the safety of drugs in pregnancy, the statistics on over the counter (OTC) and prescription drugs used in pregnancy indicate that drug use in pregnancy is wide spread. About 2-3% of all birth defects result from use of drugs. However drugs are sometimes essential for the health of pregnant women and fetus. A health care practitioner may recommend that women take certain vitamins and minerals during pregnancy. Drugs are also used for treatment of some common symptoms associated with pregnancy such as aches and pains, nausea and vomiting, and edema. Medications may also be prescribed to treat conditions occurring during but unrelated to pregnancy such as upper respiratory infections, urinary tract infections and gastrointestinal upsets to name some. Also pregnant woman may be using medications to treat pre existing chronic conditions such as epilepsy, hypertension or psychiatric disorders or to treat pregnancy related disorders such as pregnancy induced hypertension, to induce labor or to facilitate lung maturity in the fetus expected to be delivered preterm. Also this patient population may be exposed to any other agents that may have an adverse effect on fetus. It therefore becomes important to examine the pattern of drug use in pregnancy.

FDA CATEGORIES FOR DRUG USE IN PREGNANCY

In 1979, the Food and Drug Administration developed a system determining the teratogenic risk of drugs by considering the quality of data from animal and human studies. It provides therapeutic guidance for the clinician. Category A is considered the safest category but some drugs from categories B, C and D are also used during pregnancy. Category X is the only rating that denotes a drug is absolutely contraindicated for use during pregnancy (Table 1). Some of the drugs commonly used during pregnancy and their categories (as per FDA categorization) are mentioned in the table given below (Table 2). Some of the drugs have been proved to be harmful to the fetus and so their use during pregnancy is contraindicated. (Table 3)

TABLE 1: FDA CATEGORIZATION OF DRUGS FOR USE IN PREGNANCY

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well controlled studies in pregnant women. Or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlle. or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities.

TABLE 2: COMMONLY USED DRUGS IN PREGNANCY AND THEIR CATEGORIES

Drugs	Category
Analgesics and Antipyretics	B and C
Acetaminophen	B
Phenacetin	B
Aspirin	C
Antiemetics	B and C
Doxylamine	B
Meclizine	B
Cyclizine	B
Dimenhydrinate	B
Antibiotics	B,C and D
Penicillin, Ampicillin, Amoxycillin,	B
Cloxacillin Cephalosporins	B
Erythromycin	B
Gentamicin	C
Amikacin	C/D
Streptomycin	D
Sulphonamides	B/D
Tetracyclines	D
Amoebicides	B
Anthelmentics	B
Antimalarials	C
Antifungals	C
Anti TB Drugs	B and C
Ethambutol	B
INH	C
B,C,D,E,folic acid	A
Thyroxin	A
Androgens	X
Estrogens	X
Norethindrone	X
Norgestrel	X

TABLE 3 MEDICATIONS CONTRAINDICATED IN PREGNANCY

Drug	Comments
Vitamin A and its derivatives including isotretinein, accutane and etretinate.	Significant risk of spontaneous abortion and risk of many significant anomalie.
ACE inhibitors	May cause kidney damage in the fetus when used in II and III trimester, decrease in the amount of amniotic fluid and deformities of face, limbs and lungs.
Anticoagulants- warfarin	Use during I trimester produces defects like nasal hypoplasia and a depressed nasal bridge; termed as Fetal warfarin Syndrome. Use during II and III trimesters is associated with increased risk of fetal malformations.
- Heparin	Safe but if taken for long time osteoporosis and decrease in number of platelets in pregnant women occurs
Estrogen and Androgens	Genital tract malformations.
Thyroid preparations	
Methimazole	Overactive and enlarged Thyroid gland.
Carbimazole	Overactive and enlarged Thyroid gland.

Drug	Comments
Radioactive iodine	Underactive Thyroid gland in fetus.
Propylthiouracil	Safe.
Anticonvulsants	
Carbamazepine	Risk of birth defects.
Phenytoin, Phenobarbitone	Bleeding problem in the newborn which can be prevented if pregnant woman takes Vit. K by mouth every day for a month before delivery or if the newborn baby is given an injection of Vit. K soon after birth Risk of birth defects.
Trimethadione	Increased risk of miscarriage in the women
Sodium valproate	Increased risk of birth defects in fetus; including a cleft palate and abnormalities of the heart, face, skull, hands or abdominal organs
Antidepressants- Lithium	Birth defects (mainly of the heart), lethargy, decreased muscle tone, underactivity of Thyroid gland and nephrogenic diabetes insipidus in the new born. Ebstein's anomaly (tricuspid valve malformation) has been reported in a number of foetuses exposed to this drug.
NSAIDs	
Aspirin and other Salicylates	Delay in start of labor, premature closing of ductus arteriosus, jaundice, brain damage in the fetus and bleeding problems in the woman during and after delivery and in the newborn.
Antibiotics- Tetracycline	Slowed bone growth, permanent yellowing of the teeth and increased susceptibility to cavities in the body.
Chloramphenicol	Gray Baby Syndrome.
Ciprofloxacin	Possibility of joint abnormalities (seen in animals).
Kanamycin and Streptomycin	Damage to fetus's ear resulting in deafness (risk of ototoxicity).
Sulfonamides	Jaundice and brain damage in newborn.
Antineoplastic agents	
Busulfan	Birth defects such as less than expected growth before birth, underdevelopment of lower jaw, cleft palate, abnormal development of skull bones, spinal defects, ear defects and club foot.
Oral Hypoglycemic drugs	A very low level of sugar in the blood of newborn. Inadequate control of diabetes in the pregnant woman.

SAFE AND EFFECTIVE USE OF MEDICATIONS DURING PREGNANCY

Preconception care: Serious congenital anomalies, including chromosome abnormalities and Mendelian disorders, can be identified in about 2% of infants at birth. However, some anomalies do not become apparent until later in life. While most birth defects are not preventable, some can be avoided through appropriate planning and medical interventions. The following components of preconception care can help minimize the risk of birth defects:

- Optimize health before conception occurs. This includes counseling women to avoid smoking, use of excessive alcohol and illicit drugs, and exposure to potentially toxic environmental or occupational hazards before they are pregnant.
- Establish effective treatment for chronic conditions before conception occurs.
- Carefully manage all chronic conditions and illnesses throughout pregnancy.
- Counsel women to avoid the use of nonessential medications, including prescription and over-the-counter medications and dietary or herbal supplements.
- Avoid the use of medications with high teratogenic risk when equally effective treatments with lower risks are available.
- Limit the use of essential medications to the smallest number of drugs possible that will

effectively treat maternal disease without compromising the health of the woman or her fetus.

- Limit each essential medication to the smallest dose that can be used to effectively treat maternal disease without compromising the health of the woman or her fetus.
- Recommend that all women who are capable of becoming pregnant take a vitamin supplement or eat nutritional foods to assure consumption of 0.4 mg (400 micrograms) of folic acid per day.

Effective pregnancy management in women with chronic conditions requires careful planning, close medical supervision before and during pregnancy, and continuous communication between the pregnant woman and her health care providers.

Examples of approaches to preconception planning for the use of medications during pregnancy in different clinical settings

Exactly how the components of preconception planning for the use of medications during pregnancy are implemented depends on the nature of the condition requiring treatment, the known risks and safety of use of the specific drugs during pregnancy, and the woman's individual circumstances, among other factors. In this section, we provide three examples of approaches to planning for the safe and effective use of medications in clinical settings where these factors vary accordingly.

Avoiding teratogenic treatments for non life-threatening maternal conditions—Isotretinoin

Isotretinoin is indicated for the treatment of severe nodular cystic acne unresponsive to other therapy but is also used to treat non-nodular, but scarring, acne. A single course of therapy typically lasts 15–20 weeks and can result in complete and prolonged remission of the acne in many patients. However, isotretinoin treatment in the first trimester of pregnancy is teratogenic. Exposed infants can have craniofacial, cardiac, thymic, and central nervous system malformations .Research has also shown a high incidence of developmental delay in children whose mothers used isotretinoin early in the first trimester, regardless of whether the children had structural malformations.

Managing maternal conditions that require continuous treatment—epilepsy

At least one in every 250 pregnant women, or about 0.4%, takes an anticonvulsant drug. Approximately half take the drugs to prevent seizures, but anticonvulsants are also used to manage mood disorders, migraine headaches, and chronic pain. Anticonvulsant drugs have several different modes of action, such as targeting a specific receptor or enzyme. As a result, anticonvulsant medications vary in their effectiveness for specific types of epilepsy. Individuals with epilepsy may respond differently to particular medications, reflecting genetic differences such as polymorphisms in the cytochrome P450 enzymes. It is not yet possible to screen for pharmacogenetic differences that would help select the appropriate anticonvulsant for individual use. Physiologic changes during pregnancy also can affect the disposition of anticonvulsant drugs and the dose needed to prevent seizures. While not all anticonvulsant drugs have been studied in pregnancy, a number of adverse effects have been identified in infants and children of women treated with these medications during pregnancy. Major malformations, midface and digit hypoplasia, microcephaly, growth restriction, and deficits in IQ are sometimes seen, although the pattern of abnormalities and specific effects vary for individual drugs. For example, spina bifida occurs in approximately 1% of fetuses exposed to carbamazepine and in 2 to 5% of fetuses exposed to valproic acid. Preconception care provides an opportunity to choose a plan of anticonvulsant treatment that will pose the least risk to the fetus while appropriately managing maternal symptoms. New data about the effects on the fetus of anticonvulsant medications are emerging steadily, and the latest information should always be sought. The treatment plan must be individualized for each woman in collaboration with her neurologist, psychiatrist, or other specialist. Primary considerations include assessing whether taking an anticonvulsant drug is essential to the mother's health; using the fewest number of anticonvulsant drugs possible; using the lowest dose for each drug that will effectively treat maternal symptoms .establishing the most effective blood level of each drug before conception; and monitoring drug levels throughout pregnancy. For carbamazepine, phenobarbital, phenytoin, primidone, and valproic acid, levels of the non-protein bound, or "free," concentration should be measured. Because abrupt cessation of a medication may result in increased seizures or exacerbation of other symptoms, the number and dose of medications should be adjusted, and the woman's response stabilized, over a period of time before attempting conception.

Managing maternal conditions with intermittent symptoms—asthma

Asthma is a chronic condition with intermittent symptoms, for which treatment during pregnancy is essential to safeguard the health and well-being of both the mother and fetus. Abrupt cessation or

undertreatment of asthma during pregnancy can endanger both. Studies suggest that maternal asthma during pregnancy can increase the risk for perinatal mortality, preeclampsia, preterm delivery, and low birth weight. Maternal asthma can lead to alkalosis with decreased blood flow to the uterus, decreased venous return, and a leftward shift of the oxyhemoglobin dissociation curve, all of which may contribute to fetal hypoxia. In the extreme, maternal hypoxia can result in decreased umbilical blood flow, increased systemic and pulmonary vascular resistance in the fetus, and decreased fetal cardiac output. Fetal compromise may occur well before maternal symptoms become severe .A variety of medications are available to treat acute and chronic asthma. They include $beta_2$-agonoists, corticosteroids, theophylline, and anticholinergics. Before attempting conception, it is important to maximize asthma control using medications that can also be used to manage asthma symptoms during pregnancy. This will ensure maximum oxygen delivery to the developing embryo and fetus while avoiding unintended medication exposures.

CONCLUSION:

The unique nature of physiology of pregnancy presents challenges for pharmaceutical treatment of chronic and acute disorders and for symptom management of many complaints associated with pregnancy. It is the responsibility of all clinicians including pharmacists to counsel patients with complete, accurate and current information on the risks and benefits of using medications during pregnancy. Counseling women who have had exposure to drugs about risk of teratogens involves accurately identifying exposure and quantifying the magnitude of exposure. This may be straightforward for prescribed drugs but it can be much more difficult with ethanol or other illicit substances or OTC drugs. Also, when selecting drugs to be used in pregnancy effectively, drugs that have been in use for a long time are often preferable because fetal safety has been established even though newer alternatives may be available.

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