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(REVIEW ARTICLE)

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Drug use in pregnancy: A review

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Abstract

Drugs play an important role in improving health and promoting well-being. However to produce desired effect, they have to be safe, efficacious and have to be used rationally. Every pregnant women is advised to take supplements which include vitamins and minerals for the healthy development of the fetus and mother. In case, of any co-morbidity occurrence use of non-supplements that is medications use becomes essential to treat the underlying medical condition.

The appropriate medication use in pregnancy should follow the USFDA drug risk category. This classification explains about the A, B, C, D, X and N categories which specify the safety profile of various medications of each category, where drugs of category A are considered the safest and category X drugs are contraindicated in pregnancy or can be also called as teratogenic drugs. Hence, this provides physicians better prescribing guidelines. Some women may develop medical complications in pregnancy such as asthma, hypertension, epilepsy, gestational diabetes etc which would require continuous and episodic treatment. This requires the following up of USFDA drug risk category for safe prescribing of drugs so to cause no harm to the mother and fetus.

Also, immunizing the pregnant women with vaccination plays an important role in protecting the mother and fetus during pregnancy. However, live-virus vaccines should be avoided in women who are or may be in pregnancy process, such as rubella vaccine and varicella vaccine. The decision to treat pregnancy-associated conditions should be based factors such as safety, symptom severity, and potential for quality-of-life improvement.

Keywords: Pregnancy; Fetus; USFDA drug risk category; Drug use in pregnancy; Teratogenic drugs

1. Introduction

Pregnancy is when sperm and egg fuse together, leading to the development of a fetus in a woman's womb. The period of pregnancy, known as gestation, involves the growth of one or more fetuses [1]. Early pregnancy symptoms include nausea, vomiting, mood swings, missed periods, and tender breasts. The pregnancy is divided into three trimesters: the first trimester (1-12 weeks) involves conception and potential miscarriage, the second trimester (13-28 weeks) is when fetal movement can be felt, and the third trimester (29-40 weeks) requires essential parental care [2].

Some pregnant women require medication due to chronic diseases and pregnancy-related problems[3]. Pregnant women also need to take vitamin or mineral supplements [4]. However, pregnant women are often excluded from clinical trials, making it challenging to determine the safety of drugs during pregnancy [5]. Medication safety information during pregnancy is typically derived from case reports, epidemiological studies, and animal research, which has limitations in assessing drug risks [6]. The decision to use medications during pregnancy should be based on

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evaluating the benefits and risks to both the mother and the fetus [7]. Some drugs may be used sparingly in certain trimesters but contraindicated in other trimester due to the risk-benefit ratio [8].

1.1. USFDA Drug Risk Category

The safety of drug use in pregnancy is given as per these below categories:

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. [9]

FDA classifies 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 contraindicated in pregnancy. This provides therapeutic guidance for the physicians in prescribing [10].

- **Category A**: Drugs have adequate, well-controlled studies in pregnant women that have not shown any increased risk of fetal abnormalities. Considered safest during pregnancy.
- **Category B**: Animal studies have shown no evidence of harm to the fetus. But, adequate and well-controlled studies in pregnant women have not demonstrated a risk to the fetus. While these drugs are generally considered safe, there may be a lack of comprehensive human data.
- **Category C**: Animal studies have shown adverse effects on the fetus. There are either no adequate and well-controlled studies in pregnant women or animal studies have not been conducted. These drugs may be used if the potential benefits outweigh the risks.
- **Category D**: Adequate well-controlled or observational studies in pregnant women that have demonstrated a risk to the fetus. However, in certain situations, the benefits of therapy may outweigh the potential risks.
- **Category X**: Show positive evidence of fetal abnormalities in animal or human studies. The use of these products is contraindicated in women who are or may become pregnant.

1.2. Physiological changes in pregnancy in women [11]

Weight increases and changes body shape (due to increases in breast tissue, blood volume in the extra vascular and extra cellular fluid), the average weight gain in pregnancy is 12.5 kg. During normal pregnancy 1 kg weight due to protein. Fibrinogen levels are increased and total body fat also increased. The ratio of LDL and HDL increases in pregnancy. Increased cardiac output.

1.3. Pharmacokinetic changes in pregnancy [12]

The drug effect can be changed by the changes in pharmacokinetics in pregnancy. Hydrophobic drugs are more soluble in pregnant women. The free drug have therapeutic or adverse effects on the mother and for placental transfer to the fetus. Excretion of drugs is increased by kidneys, mainly which are excreted primarily unchanged in the urine (digoxin, lithium). The increased size of uterus decreases renal blood flow in supine position.

1.4. Effect of Drug use during pregnancy [12]

When potential benefit outweighs known risks, drugs may be considered for treatment of various medical conditions during pregnancy.

Not all maternal drugs cross the placenta and reach fetus. Some drugs that cross the placenta may have a direct toxic effect or a teratogenic effect. Drugs that do not cross the placenta may still harm the fetus by constricting placental vessels and thus impairing gas and nutrient exchange producing severe uterine hypertonia that results in anoxic injury altering maternal physiology (e.g, causing hypotension).

The faster a drug crosses the placenta depends on the drug's molecular weight, extent of its binding to another substance (carrier protein), area available for exchange across the placental villi, and amount of drug metabolized by the placenta.

Most drugs with a molecular weight of < 500 daltons readily cross the placenta and enter the fetal circulation. Substances with a high molecular weight (eg, protein-bound drugs) usually do not cross the placenta. One exception is immune globulin G, which may be used to treat disorders such as fetal alloimmune thrombocytopenia. Generally, equilibration between maternal blood and fetal tissues takes at least 30 to 60 minutes.

1.5. Potential complications of high- risk pregnancy [13]

A high- risk pregnancy can be life threatening for the pregnant women or fetus. Serious complications can include:

- Preeclampsia (high blood pressure from pregnancy).
- Eclampsia (seizure from pregnancy).
- Preterm delivery.
- Cesarean delivery-(C- section).
- Excessive bleeding during labor and delivery, or after birth.
- Low or high birth weight.
- Birth defects.
- Problems with the fetus's brain development.
- Miscarriage.
- Stillbirth.

2. Various complications of pregnancy [14]

- **Ectopic pregnancy:** A condition where the fertilized egg implants outside your uterus (usually in Fallopian tube). This requires surgery or medication to remove the ectopic tissue.
- **Hyperemesis gravidarum (HG):** It is severe and persistent vomiting during pregnancy. It can lead to dehydration or losing too much weight.
- **Congenital disorders:** If the fetus is suspected with a health issue or congenital disease, there is risk for complications during pregnancy. This requires additional monitoring or baby needs special care at birth.
- **Gestational diabetes**: The pregnancy hormones don't maintain the body metabolism to keep the blood sugar levels stable. A glucose screening test needs to be done to detect diabetes in pregnancy. Most people can keep their blood sugar levels under control with diet and exercise, but some need medication. The condition usually resolves once your baby is born.
- **Infections**: Many viral and bacterial infections can complicate a pregnancy. These include urinary tract infections (UTIs), yeast infection group B strep and bacterial vaginitis. Sexually transmitted infections (STIs) can also cause pregnancy complications.
- **Vaginal bleeding**: Heavy or excessive bleeding during pregnancy requires immediate care.
- **Low amniotic fluid (oligohydramnios):** Low amniotic fluid means the fetus is surrounded by less amniotic fluid than it should have for its age. This increases risk for premature birth. It's more common than polyhydramnios (too much amniotic fluid), which can also cause complications.
- **Depression and anxiety:** Extreme sadness or worry during pregnancy (or postpartum, after the baby's born) can affect fetal development.
- **Anemia**: Low levels of red blood cells to carry oxygen in your body. May feel tired and weak. Iron deficiency is a common cause of anemia. Treatment is by taking supplements or eating more iron-rich foods.

2.1. How Drugs effect the fetus [15]

Drugs can directly act on the fetus causing damage or abnormal development leading to birth defects or death. The can result in a baby that is underweight and underdeveloped and can also trigger preterm labor and delivery.

2.2. Mechanism of Drugs effects on fetus [16]

Drugs that do not directly cross the placenta may still harm the fetus in following ways:

- **Constricting placental vessels:** Some drugs narrow the blood vessels in the placenta, leading to reduced gas and nutrient exchange between the mother and the fetus which deprives the fetus of essential oxygen and nutrients for proper development.
- **Producing severe uterine hypertonia:** Certain drugs may cause excessive contractions of the uterus, resulting in a lack of blood flow to the placenta and, consequently, causing anoxic (lack of oxygen) injury to the fetus.
- **Altering maternal physiology**: Some drugs can affect the mother's blood pressure or other physiological processes, indirectly impacting the fetus's well-being.

2.3. Vaccines in Pregnancy [17].

Immunization is as effective in women who are pregnant as in those who are not.

2.3.1. To Be Taken

Influenza vaccine is recommended for all pregnant women in the 2nd or 3rd trimester during influenza season.

The tetanus-diphtheria-pertussis (Tdap) vaccine is recommended for all pregnant women during the 3rd trimester.

The CDC recommends **COVID-19 vaccination** for all people 5 years and older, including people who are pregnant, breastfeeding, trying to get pregnant now, or might become pregnant in the future. Evidence about the safety and effectiveness of COVID-19 vaccination during pregnancy has been growing. Research data suggest that the benefits of receiving a COVID-19 vaccine outweigh any known or potential risks of vaccination during pregnancy.

2.3.2. To Be Avoided:

Live-virus vaccines should not be given to women who are or may be in pregnancy process. Rubella vaccine, an attenuated live-virus vaccine, may cause sub-clinical placental and fetal infection. However, no defects in neonates have been attributed to rubella vaccine, and women vaccinated inadvertently during early pregnancy need not be advised to terminate pregnancy based solely on theoretical risk from the vaccine.

Varicella vaccine is another attenuated live-virus vaccine that can potentially infect the fetus. Risk is highest between 13 weeks and 22 weeks gestation. This vaccine is contraindicated during pregnancy.

The list of drugs given in pregnancy and their US-FDA risk category is given in Table 1.

Table 1 Commonly Used Drugs In Pregnancy and their Categories[18].

Drugs	**Category**
Analgesics and Antipyretic	
Acetaminophen	B
Phenacetin	B
Aspirin	C
Antiemetics	
Doxylamine	B
Meclizine	B
Cyclizine	B
Dimenhydrinate	B
Antibiotics	
Penicillin, Ampicillin, Amoxycillin	B
Cloxacillin, Cephalosporins	B
Erythromycin	B
Gentamicin	C
Amikacin	C/D
Streptomycin	D
Sulphonamides	B/D
Tetracyclines	D
Amoebicides	B
Metronidazole	B
Anti-helminthics	

Piperazine	B
Mebendazole	B
Antimalarials	C
Antifungals	C
Anti TB Drugs	
Ethambutol	B
Isoniazid	C
Rifampicin	C
Pyrazinamide	C
Para-aminosalicylic acid	C
Vitamins	
B, C, D, E, Folic Acid	A
Hormones	
Thyroxin	A
Androgens	X
Estrogens	X
Progestogens-	
Hydroxyprogestrone	D
Medroxyprogestrone	D
Norethindrone	X
Norgestrel	X
Bronchodilators	C

Table 2: Depicts the medications that are contraindicated in pregnancy as follows:

Table 2 Medications Contraindicated In Pregnancy[19]

Drugs	**Comments**
Vitamin A and its derivatives including isotretinoin, accutane and etretinate.	Significant risk of spontaneous abortion and risk of many significant anomalies.
ACE inhibitors	May cause kidney damage in the fetus when used in 2nd and 3rd trimester, decrease in the amount of amniotic fluid and deformities of face, limbs and lungs.
Anticoagulants	
Warfarin	Use during 1st trimester produces defects like nasal hypoplasia and a depressed nasal bridge; termed as Fetal warfarin Syndrome. Use during 2nd and 3rd 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
Radioactive iodine	Underactive Thyroid gland in fetus
Propylthiouracil	Safe.
Anticonvulsants	
Carbamazepine	Risk of birth defects.
Phenytoin and Phenobarbitone	Bleeding problem in the newborn which can be prevented if pregnant woman takes Vitamin K by mouth every day for a month before delivery or if the newborn baby is given an injection of Vitamin 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.
Non-steroidal anti-inflammatory drugs	
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.

3. Management of Pregnancy

Management for a high risk pregnancy depends on specific risk factors such as:

- Frequent follow-up with obstetrician.
- Consultation with a maternal fetal medicine (high risk pregnancy) specialist.
- Consultation with other medical specialists.
- More ultrasounds and closer fetal evaluation.
- Home blood pressure monitoring.
- Careful monitoring of medications used to manage preexisting conditions

If the pregnant women's health or the health of the fetus is in danger,the healthcare provider may recommend labor induction or a C- section.

3.1. Prescribing Principles in Pregnancy [20]

- Drugs should be prescribed only for clear indications where the benefits (usually for the mother) outweigh the potential risks (usually to the fetus).
- All drugs in the first trimester preferably to be avoided.
- Medication should be used in the smallest effective dose for the shortest required duration.
- Medications must be prescribed which are widely used in pregnancy and have a good safety track record.

4. Conclusion

Pregnant women take medications either supplements or non-supplements during pregnancy. So it is, essential for healthcare professionals to consider the potential risks and benefits of drug use in pregnancy, as it may effect the mother and fetus. For this purpose, selecting the use of drugs in pregnancy should be based on the fact that it has been used for a long period of time, so as to know the establishment of fetal safety even though alternative treatment options maybe available. Therefore, medical practitioners must be consulted for appropriate medical advice on drug use in pregnancy. Hence, this review gives a summary about various drugs that are safe and unsafe to use in pregnancy.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] G Curtis, J Schuler (2000). Your Pregnancy Week by Week Fisher Books. https://books.google.com/books/about/Your_Pregnancy_Week_by_Week.html?id=1pBXnVrW5nAC.

[2] RS Waddell, (2006). "Fertility Plus.org".Home Pregnancy Test hCG Levels and FAQ. Available at: HTTP://www.fertilityPlus.org/faq/hpt.html.

[3] The Sensible Guide to a healthy pregnancy. Available at: www.phac-aspc.gc.ca/hp-gs/pdf/hpguide- eng.pdf.

[4] Sharma R, Kapoor B, Verma U. Drug Utilization pattern during pregnancy in North India. J Med sci. 2006; 0:277-87.

[5] Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, et al. Prescription Drug Use Pregnancy. Am J Obstet Gynaecol. 2004; 19.:398:407.

[6] Ward RW. Difficulties in the study of adverse fetal and neonatal effects of drug therapy during pregnancy. Semin Perinatol.2002; 25:191-5.

[7] Taking Medicine During Pregnancy. Available at: http://www.webmd.com/baby/guide/taking-medicineduring-pregnancy.

[8] Drugs contraindicated in pregnancy. Available at: http://www.empr.com/drugs contraindicated-in pregnancy/article/125914/9.

[9] Pangle BL. Drugs in Pregnancy and Lactation. In: Herfindal ET, Gourley DR, editors. Text book of Therapeutics, Drug and Disease Management. 8th ed. Philadelphia: Lippincott William Wilkins; 2006. pp. 434–48.

[10] Punam Sachdeva, et al.: Pregnancy and Drug use 2009, Jan- Feb;71.1-7

[11] Moore PJ.Maternal Physiology during Pregnancy. In De Cherney A, Pernoll ML, editors. Current obstetrics and gynecological diagnosis and treatment. 8thed.New York: McGraw-Hill; 1994. pp.146-54.

[12] Hansen W, Yankowitz J, Nie by lJR. Pharmacological therapy for medical disorders during pregnancy. Clin Obstet Gynaecol. 2002; 45:136-52.

[13] National Institutes of Health Eunice Kennedy Shriver, National Institute of Child Health and Human Development. High Risk pregnancy. (https://www.nichd.nih.gov/health/topics/high-risk).

[14] PregnancyComplications.(2020).https://www.cdc.gov/reproductivehealth/maternalinfanthealth/Pregnancy-Complications/html

[15] Pangle BL. Drugs in Pregnancy and Lactation. In: Herfindal ET, Gourley DR, editors. Text book of Therapeutics, Drug and Disease Management. 8th ed. Philadelphia: Lippincott William Wilkins; 2006. pp. 434–48.

[16] Porter RS, editor. The Merck Manual's Online Medical Library. White house Station: Merck Research Lab; 2004.

[17] Ravindu Gunatilake, MD, Valley Perinatal Services; Avinash S. Patil, MD, University of Arizona College of Medicine, Reviewed/Revised Mar 2021| Modified Sep 2022

[18] Nanavati MS. Obstetrics Handbook for Maternal Health. 1st ed. Mumbai: Niche Laboratories Ltd; 1994.

[19] Briggs GG. Drug effects on the fetus and breastfed infants. Clin Obstet Gynaecol. 2002;45:6–21.

[20] Obstetrics, Gynaecology & Reproductive Medicine; Volume 28, Issue 5, May 2018, Pages 136-140.