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Review Article

Drugs and Pregnancy: A Careful Concern for Mother and Child

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Abstract

Drugs used during pregnancy may have temporary or permanent effects on the fetus. More than 90% of pregnant women take prescription or nonprescription (over-the-counter)drug.About 2% to 3% of all birth defects result from the use of drugs during pregnancy. However, drugs are sometimes inevitable for the wellbeing of the pregnant women and fetus. In everyday practice, the healthcare professionals are very much concern about the safety of a drug to be prescribed in pregnancy. Pregnancy Index will be a good reference of different drugs to be prescribed in pregnancy by physicians with confidence. Drugs can impair intrauterine growth by interfering with fetal metabolic processes. This may take the form of a simple inhibition of essential pathways, such as the utilization of folic acid, or may involve more complex alterations in genetic structure and expression. Fetal death and abortion can be caused by drugs.If drugs are given during the stage of organogenesis structural damage to the fetus may result. Preconception counseling and education regarding drugs will become increasingly important. It is important to screen systematically for such concerns as early as possible in pregnancy. Preconception planning only rarely provides an opportunity to identify exposures of concern as example. Oral hypoglycemic agents should be changed before pregnancy into injection insulin; any antihypertensive drugs should be changed as methyldopa, nidifine, labetolol. Anaemia should be corrected before pregnancy.

Key words: Drug, Congenital malformation, Teratogens.

Introduction

Prescribing in pregnancy has remained a problem to practicing physicians over the years. Most women use a number of different medications during pregnancy, many of which are self-administered. Only a small percentage of these drugs are reported to health professionals. General principles of drug uses in pregnancy are as follows i.e. consider all drugs have the potential for affecting the fetus except heparin and insulin, all the patients are at risk in pregnancy during reproductive years, risk benefit ratio should justify the use of a particular drug, and the minimum effective dose, drugs should be used only when necessary, and avoids long term use and no drugs are considered totally safe in pregnancy due to lack of sufficient reports[1].

The drugs are uses in pregnancy must follow the 'obstetrics rules' like. "First does no harm". "Never be the first to use the new". Never the last to use the old" and "Remember that all women are pregnant until proved otherwise"[2].

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The effects of drugs

All the drugs of various categories mentioned below should be avoided if possible during the 1st trimester. During the 1st trimester drugs may produce congenital malformations (teratogens), and the greatest risk is from the 3rd to 11th week of pregnancy (stage of organogenesis). Therefore Wilson's six general principles of teratogenesis like genotype and interaction with environmental factors, timing of exposure, mechanisms of teratogenesis, manifestation, agent and dose effect needs to be careful consideration.

Maternal pharmacokinetics also be in careful consideration in regards to absorption as pregnancy can alter the absorption of oral drug; hyper-emesis gravidarum does not retain the drug. Gastrointestinal transit is prolonged owing to slow emptying of the stomach and reduced gut motility[3].

In regards to distribution; lipid solubility and protein binding affect the distribution of drugs. Plasma drug concentration is greatest for drugs with low lipid solubility that are highly bound to plasma protein are also the important point for consideration as well.

Moreover, Drug metabolism e.g. Water soluble drugs are eliminated unchanged. Lipid soluble drugs are metabolized by oxidation, or conjugated in the placenta and fetal liver before being excreted in bile or urine.

In addition, Drug excretion depends on renal plasma flow (RPF), Glomerular filtration rate (GFR), Creatinine clearance and those all increased in pregnancy; drugs excreted unchanged and more quickly.

The points of fetal pharmacokinetics e.g. distribution, metabolism and fetal excretions occur in the fetus and placenta in particulars.

It is to be noted that placental transfer of drugs can also be considered due to the facts that the human placenta allows bi-directional transfer of most molecules below molecular weights of 1500. The great majority crosses the placenta by simple diffusion. Highly fat-soluble molecules that are unchanged reach the fetus more rapidly than drugs with a low fat solubility, which are ionized. Teratogenic agents usually affect organ systems at very specific points in development. The heart, central nervous system, palate, and ear are most commonly affected system and organs due to careless choosing drugs in pregnancy. Prescribing needs to consider teratogenic period like the pre-implantation and pre-somatic stages, from "0 to 31 days" following conception, drugs exert an "all or- none effect". If a toxic exposure occurs between day 31 and 81, the pregnancy either survives the insult without harm, or terminates. After 81, organs growth continues but malformation due to a maternally ingested medication is less likely. The pre-implantation and pre-somatic stages, from "0 to 18 days" following conception, drugs exert an "all or- none effect"[4].

Therefore in the USA Food and Drug Administration (FDA) classify the drugs for use in pregnancy using 5-letters system (drug categories) as follows for drug use in pregnancy. A = adequate controlled studies in pregnant women fail to demonstrate a risk to the fetus. Very few drugs in this category. B= "Best" No risk seen in animals, but no controlled trials in pregnant women. C= "Caution "Adverse fetal effects in animals, no controlled trials in humans. Most drugs are category C. D = "Danger "Evidence of human fetal risk should be reserved for life-threatening disease. X= strong evidence of fetal abnormality, No therapeutic indication in pregnancy. Teratogenic Drugs; "Most Teratogenic FDA-approved medications are in categories D or X, some drugs in C."

A drug is identified as a teratogen if exposure in utero cause directly or indirectly, structural or functional abnormalities in the fetus or in the child after birth. One example is the beta blockers (most notably atenolol), which have been associated with intrauterine growth retardation (IUGR),[5,6] probably due to increased fetal and uteroplacental peripheral vascular resistance and reduced placental blood flow.

Diethylstibestrol which was used to prevent recurrent miscarriage is now known to cause transplacental carcinogenicity[7], in utero exposure is associated with problems in later life such as infertility in both female and male offspring and a rare form of vaginal cancer[8].

Neuropsychological and behavioral abnormalities may also occur after drug exposure. Some anti-epileptic drugs and drugs of abuse have been associated with learning and behavioral problems following in utero exposure[9,10].

Drugs like analgesics used in pregnancy for the relief of backache, leg cramps, and abdominal pain that arise due to both physical and physiological changes in the mother. All trimester of pregnancy may have associated with different types of pain. Paracetamol seems to be safest for use during pregnancy, among all the analgesics, which is a category B. NSAIDs are safe in the 1st and 2nd trimesters (cat-B) but are best avoided during the last trimester (cat- D). Opioids can cross the placenta and may cause respiratory depression in the newborn. Prolonged use may also lead to withdrawal symptoms in the infant. Both NSAIDs and CoxII inhibitors inhibit the synthesis of Prostaglandin's and may result in the premature closure of the fetal ductus arteriosus, leading to fetal pulmonary hypertension.

Drugs under category; B - (Paracetamol), B/D - (Diclofenac, Diclofenac sodium & Misoprostol, Aceclofenac, Ibuprofen, Indomethacin, Ketoprofen, Naproxen, Ketorolac, Tromethamine, Meloxicam Prioxicam), C-Codeine+ paracetamol, Opioids/Opioid-related-Pethedine Morphine Tramadol, Timololandunder category C/D- Aspirin, Mefenamic, COX-II Inhibitors-Celecoxib, Rofecoxib, Valdecoxib needs to be choose approximately[11].

Heart burn is a common complaint in pregnancy because of relaxation of the esophageal sphincter. The anti-ulcerative drugs are used during first trimester of pregnancy, when pregnancy is more complicated by vomiting. B- Ranitidine, Famotidine, Pantoprazole, Lansoprazole, Esomeprazole Rabeprazole- Omeprazole. X- Misoprostol and Domperidone.

The other group of drugs like e.g. (Category-B) Tiemonium Methylsulphate, Drotaverine. C- Hyosinebutylbromide, Mebeverine, Metoclopramide.

Drugs acting on rectum and colon; Category (B/D)- Mesalazine, Salfasalazine, Tegaserod also be used carefully.

The anti-emetic drugs; Ginger appears safe and effective easing nausea in pregnancy (on trial). A-Pyridoxine. B-Cyclizine hydrochloride, Cyclizine lactate, Meclizine hydrochloride, Metoclopramide, Diphenhydramine, Ondansetron. C- Chlorpromazine hydrochloride, Prochlorperazinemaleate, Promethazine theoclate[12].

Sulfasalazine and other 5-ASA compounds such as mesalamine, balsalazide and olsalazine do not appear to increase complications or harm the fetus. Sulfasalazine may cause nausea and heart burn. As sulfasalazine lowers folic acid levels, women should be on at least 2 mg of folic acid daily. Women can breastfeed while taking 5-ASA compound.

Prednisolone and other corticosteroid are low risk during pregnancy. Antibiotic should be avoided during pregnancy. Because thalidomide can cause birth defects and fetal death, it should always be avoided during pregnancy.

Immunomodulators, such as Azathioprine, 6-mercaptopurine and cyclosporine A appear low risk during pregnancy in standard doses. Both men and women should avoid methotrexate.

Most biologics such as infliximab, adalimumab and certolizumab are considered low risk. They also do not appear in breast milk.

As Antibiotics are commonly used to treat or prevent infection in pregnancy. B-Cloxacillin, Cefo-taxime, Cefixime, Ampicillin, Amoxicillin + Clavulanic acid, Nitro-furantoin, Cephalosporins, sulfonamides, Penicillin's, Erythromycin, Clindamycin, Azithromycin. D-- Tetracycline, Doxycycline, Ciprofloxacin, Lomefloxacin, Gatifloxacin, Ofloxacin, Norfloxacin. C/D-- Co-trimoxazole. Aminoglycosides; D- Gentamycin, Streptomycin, Tobramycin, Amikacin, Kanamycin. Antimalarials drugs; C- Chloroquine, Mefloquine, Primaquine, Sulphadoxine +pyrimethamine. Anthelmintics drugs; C- Pyrantel, Albendazole, Levamisole, Mebendazole. Antiviral drugs; BAciclovir, C-- Lamivudine, Interferon beta, Interferon gama.

The following group of drugs are indicated like tranquilizers demands careful administration during pregnancy when the patients are very nervous in case unwanted pregnancy. Pregnancies, which are associated with hyper-emesis gravidarum, toxaemia of pregnancy. Benzodiazepines; Are most commonly used anxiolytic and hypnotic. D-- Diazepam, Lorazepam (oral + parental), Midazolam (oral + parental), Nitrazepam, Bromazepam, Alprazolam, Phenobarbital. Anticoagulants; Pregnancy itself is a hypercoagulable condition, due to increase level of fibrinogen, VII, X factors. It is indicated in pregnancies associated with prosthetic heart valve, previous history of deep venous thrombosis. C -- Heparin, Protamine sulfate. D- Warfarin. X- Coumarin. Cough syrup; C- Dextromethorphan, Dextroamphetamine.

Laxatives: Constipation is an effect of physiological changes during pregnancy, Mechanical obstruction by the gravid uterus. Reduced motility because of smooth muscle relaxation> (Progesterone). Increased water absorption from the colon (>Aldosterone). B-Lactulose, Bisacodyl, Magnesium Hydroxide, Magnesium Sulphate, Magnesium carbonate. C-- Magaldrate. Pregnancy with pituitary tumour; B-Bromocriptine, Carbergoline.

Antidiabetic drugs: Pregnancy is associated with gestational diabetes mellitus, clinical diabetes mellitus condition. Pregnancy is associated with increase peripheral resistance to insulin, primarily mediated by human placental lactogen, oestrogen, progesterone, and cortisol. Insulin resistance is increases as pregnancy advances. B-- Acarbose, Metformin, Pioglitazone. C- Rapaglinide, Pioglitazone, Rosiglitazone, Glibenclamide, Glimepride, Glipizide, Insulin.

Antihypertensive drugs: Pregnancy with toxaemia is a common medical problem. Pregnancies are associated with toxaemia, essential hypertension. B- Methyldopa. C- Amlodipine, Nifedipine, Varapamil, Ramipril, Lisinopril, Captopril, Enalapril, Labetalol. D-Atenolol.

Diuretics: Usually prescribed, when pregnancies are associated with Eclampsia with pulmonary edema, anasarca. B- Amiloride + hydrochlorothiazide. B/D-Amiloride. C- Spironolactone, Acetazolamide, Furosemide.

Bleeding disorder: C- Aminocaproic acid.

Antifungal drugs: Usually required, when pregnancy is associated with diabetes mellitus. B- Clotrimazole. C- Nystatin, Griseofulvin, Fluconazole, Miconazole (topical +vaginal).

Anti-allergy drugs: B- Cetrizine, Loratadine. Vitamins/ Iron; A-- Vit D, Vit E, Thiamine, Folic acid, Ascorbic acid. B-Calcium. C- Iron.

Tocolytic drugs: B- Retordine, Magnesium Sulphate.

Hormones: Hormones are sometimes required to prevent Abortion, Systemic Lupus Erythrometosus. X-Estrogen (All categories), Progestins (except megestrol and norethindrone), Danazol, Misopristol, and Raloxifene. C- Coticosteroids. D- Mifepristone.

Antiepileptic drugs: Pregnancy with epilepsy has an increased risk of malformation and further increased by taking anti epileptic drugs. C- Carbamazine. D- Phenytoin, Phenobarbitone, Valproate.

Anti-thyroid drugs: When pregnancy is associated with hyperthyroidism. D- Propythiouracil, Carbimazole, Methimazole.

Antineoplastics drugs: X- Flurauracil, Methotrexate.

Anti-tubercular drugs: B- Ethambutal. C-Isoniazid, Pyrazinamide, Rifampicin, Rifampicin +Isoniazid. D-- Streptomycin Antidepressant drugs; C- Imipramine, Fluoxetine, Escitalopram, Amitriptyline, Nortriptyline.

Antidysentry drugs: B-Metronidazole, Nitazoxanide[13].

Conclusion

Most pregnant women required medicine. Drugs use in pregnancy remains clear, simple, and straightforward and should have clear and specific indications for drug use. Maternal and fetal benefit should be evaluated unless use of drug should be stopped. 50% of pregnancies are unplanned, it is important to minimize exposure to unnecessary medications in reproductive aged women regardless of their plan for pregnancy. During pregnancy, each medication must have the maternal and fetal risks and benefits are to be evaluated to determine when the medication is indicated.

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