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Review Article

Drugs In Pregnancy

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Abstract

In 1991 WHO International Survey of Drug Utilization in Pregnancy is 86% of women took medication during pregnancy, Average of 2.9 prescriptions and despite this high rate of medication intake, most drugs are not labeled for use during pregnancy. Most women use a number of different medications during pregnancy, many of which are self-administered. It is essential to consider the following factors before prescription of drugs during pregnancy. A) Dose and duration of drug exposure is important. The larger the dose is more likely the effects. The longer the duration of drug exposure is greater chance of susceptible periods of organogenesis and developmental problem. B) Timing of exposure is very crucial. Certain organ systems may have only limited period of susceptibility for damage. C) Pathogenetic mechanism, teratogens produce their adverse effect by specific mechanism. D) Host susceptibility, variability in the genetic factors related to mechanism of certain drugs. All drugs can affects the health of the mother and fetus, therefore any drugs should be administer with care during pregnancy.

Key words : Drug, pregnancy, congenital malformation, fetus

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: 1) Consider all drugs have the potential for affecting the fetus except heparin and insulin. 2) All the patients are at risk in pregnancy during reproductive years. 3) Risk –benefit ratio should justify the use of a particular drug, and the minimum effective dose. 4) Drugs should be used only when necessary, and avoids long term use. 5) No drugs are considered totally safe in pregnancy due to lack of sufficient reports.

The drugs are uses in pregnancy must follow the 'obstetrics rules' are follows: 1) "First does no harm" 2) "Never be the first to use the new". 3) "Never the last to use the old". 4) "Remember that all women are pregnant until proved otherwise".

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Objectives

1) To review general principles regarding drugs in pregnancy. 2) Increased public awareness and concern since the thalidomide tragedy. 3) Only prescribe medicines if absolutely necessary.

The effects of drug: All the drugs should be avoided if possible during the 1st trimester[1]. During the 1st trimester drugs may produce congenital malformations (teratogenesis), and the greatest risk is from the 3rd to 11th week of pregnancy (stage of organogenesis). Wilson's six general principles of teratogenesis are 1) Genotype and interaction with environmental factors, 2) Timing of exposure, 3) Mechanisms of teratogenesis, 4) Manifestation, 5) Agent, and 6) Dose effect[2].

Maternal pharmacokinetics

Absorption: 1) Pregnancy can alter the absorption of oral drug; hyper-emesis gravidarum does not retain the drug. 2) Gastrointestinal transit is prolonged owing to slow emptying of the stomach and reduced gut motility.

Distribution: 1) Lipid solubility and protein binding affect the distribution of drugs. 2) Plasma drug concentration is greatest for drugs with low lipid solubility that are highly bound to plasma protein.

Drug metabolism: 1) Water soluble drugs are eliminated unchanged. 2) Lipid –soluble drugs are metabolized by

oxidation, or conjugated in the placenta and fetal liver before being excreted in bile or urine.

Drug excretion: 1) Renal plasma flow (RPF), 2) Glomerular filtration rate (GFR), 3) Creatinine clearance are all increased in pregnancy; drugs excreted unchanged and more quickly.

Fetal pharmacokinetics

Distribution, metabolism, and fetal excretions occur in the fetus and placenta.

Placental Transfer of Drugs: 1) The human placenta allows bi-directional transfer of most molecules below molecular weights of 1500. 2) The great majority crosses the placenta by simple diffusion. 3) Highly fat-soluble molecules that are uncharged 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.

Teratogenic period: 1) The pre-implantation and pre-somatic stages, from "0 to 31 days" following conception, drugs exert an "all –or- none effect". 2) If a toxic exposure occurs between day 31 and 81, the pregnancy either survives the insult without harm, or terminates. 3) 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".

Drug Categories

The USA Food and Drug Administration (FDA) classify the drugs for use in pregnancy using 5-letters system.

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."

Analgesics: Backache, leg cramps and abdominal pain is common complaints in pregnancy that arise due to both physical and physiological change s in the mother. All trimester of pregnancy may be associated with different types of pain. Paracetamol seems to be safest for use during pregnancy, of 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 infant. Prolonged use may also lead to withdrawal symptoms in the infant. Both NSAIDs and Cox-II 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 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 Timolol. C/D: Aspirin, Mefenamic, COX—II Inhibitors- Celecoxib, Rofecoxib, Valdecoxib.

Anti-ulcerative drugs: 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, Domperidone.

Antispasmodics drugs: B: Tiemonium Methylsulphate, Drotaverine. C: Hyosine butylbromide, Mebeverine, Metoclopramide.

Drugs acting on rectum and colon: B/D: Mesalazine, Salfasalazine, Tegaserod.

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, Prochlorperazine maleate, Promethazine theoclate.

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. D: Gentamycin, Streptomycin, Tobramycin, Amikacin, Kanamycin.

Antimalarials drugs: C: Chloroquine, Mefloquine, Primaquine, Sulphadoxine +pyrimethamine.

Anthelmintics drugs: C: Pyrantel, Albendazole, Levamisole, Mebendazole.

Antiviral drugs: B: Aciclovir, C: Lamivudine, Interferon beta, Interferon gama.

Tranquilizers : Some-times tranquilizers are indicated, when the patients are very nervous in case unwanted pregnancy and 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[3].

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.

Laxative: Constipation is an effect of physiological changes during pregnancy,mechanical obstruction by the gravid uterus, reduced motility because of smooth muscle relaxation and increased water absorption from the colon. B: Lactulose, Bisacodyl, Magnesium Hydroxide, Magnesium Sulphate, Magnesium carbonate. C: Magaldrate[4].

Pregnancy with pituitary tumour: B: Bromocriptine, Carbergoline.

Antidiabetic drugs: Pregnancy is associated with gestational diabetes mellitus, clinical diabetes mellitus & 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 associated with essential hypertension. B: Methyldopa. C: Amlodipine, Nifedipine, Varapamil, Ramipril, Lisinopril, Captopril, Enalapril, Labetalol. D: Atenolol[5].

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)[6].

Anti-allergy drugs: B: Cetrizine, Loratadine.

Vitamins/ Iron: B: Calcium. C: Iron.

Tocolytic drugs: B: Retordine, Magnesium Sulphate[8].

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: 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.

Conclusion

Most pregnant wo men required medicine. Drugs use in pregnancy remains clear, simple, and straightforward. 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[9]. During pregnancy each medication must have the maternal and fetal risks and benefits evaluated to determine if the medication use is indicated.

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