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Review Article

An overview of over the counter drugs in pregnancy and lactation

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Abstract
Over the counter (OTC) drugs are commonly used by pregnant women. Most OTC drugs are safe in pregnancy but some have unproven safety and may adversely affect the growing foetus. The safety profile of some of the medication may change according to the gestational age of the foetus. Because an estimated 10% or more of the birth defects results from maternal drug exposure, the US Food and Drug Administration (FDA) has assigned a risk category to each drugs. Among the commonly used OTC drugs Acetaminophen, Chlorpheniramine, Kaolin and Pectin preparations and most antacids have a good safety record. The drugs like H_2 blockers; Pseudoephedrine and Atropine/ Diphenoxylate should be used with caution. The risk and benefit while using OTC drugs in pregnancy has to be assessed.

Key words: OTC drugs, Pregnancy, Lactation

Prescribing drugs during pregnancy presents a challenge to the physician to balance optimal treatment of the maternal symptoms and disease against possible harm to the foetus. For many drugs including those recently marketed, data are still inadequate to confirm their safety during pregnancy. If adequate information on drug safety is lacking and drug authorities and the industry tend to be cautious in their recommendation, even essential drug treatment may be avoided and chronic illnesses requiring drug treatment may not be treated optimally[1]. It is general principle to avoid drug exposure during the first trimester when organogenesis takes place and harmful exposure may lead to structural abnormalities. In addition to the malformations, other adverse effects are possible.

Drug therapy in pregnancy: Most drugs taken by the pregnant women can cross the placenta and expose the developing embryo and foetus to their pharmacologic and teratogenic effects. Critical factors affecting placental drug transfer and drug effects on the foetus include[2].

1. The physiochemical properties of the drug
2. The rate at which the drug crosses the placenta and the amount of drug reaching the foetus
3. The duration of exposure to the drug
4. Distribution characteristic in different foetal tissue
5. The stage of placental and foetal development at the time of exposure to the drug
6. The effect of drugs in combination

Teratogenic Drug Actions: A single intrauterine exposure to a drug can affect the foetal structure undergoing rapid development at the time of exposure. Thalidomide is an example of a drug that may profoundly affect the development of the limbs after only brief exposure.

Teratogenic Mechanism: The mechanisms by which different drugs produce teratogenic effects are poorly understood and are probably multifactorial. For example, drugs may have a direct effect on maternal tissue with secondary or indirect effect on foetal tissue. Drugs may interfere with the passage of oxygen or nutrients through the placenta and therefore have effect on the most rapidly metabolising tissue of foetus. Finally, drugs may have important direct action on the processes of differentiation in developing tissue.

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For Example, Vitamin A (Retinol) has been shown to have important differentiation directing actions in normal tissue. Several vitamin A analogues (Isotretinone, Etretinate) are powerful teratogens, suggesting that they alter the normal process of differentiation. The deficiency of a critical substance appears to play a role in some types of abnormalities. For Example folic acid supplementation during pregnancy appears to reduce the incidence of neural tube defects e.g. Spina bifida[2].

Continued exposure to a teratogen may produce cumulative effect or may affect several organs going through varying stages of development. Chronic consumption of high doses of ethanol during pregnancy, particularly during the first and second trimester may result in the foetal alcohol syndrome. The knowledge of safety of drug while using in pregnancy and lactation is very important. The lack of knowledge will increase the risk of teratogenecity to foetus. Therefore we have planned inform prescribers about drug safety and risks with emphasis on OTC drugs through this review article.

Table 1: FDA classification of drug safety during pregnancy[18]

Category A	Controlled studies in women fail to demonstrate a risk to the foetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of foetal harm appears remote.
Category B	Either animal reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women, or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of risk in later trimesters).
Category C	Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the foetus.
Category D	There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease in which safer drugs cannot be used or are ineffective).
Category X	Studies in animals or human beings have demonstrated foetal abnormalities or there is evidence of foetal risk based on human experience, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Over the counter medications in pregnancy: Pregnant women commonly use over the counter medications, although most over the counter drugs have an excellent safety profile, some have unproven safety or are known to adversely affect the foetus. Non-prescription drugs account for about 60 percent of medications used in United States, and more than 80 percent of pregnant women take OTC or prescription drugs during Pregnancy[5]. It is estimated that up to 60 percent of patients consult a health care professional when selecting an OTC Product.[1] At least 10 percent of birth defects are thought to result from maternal drug exposures.

The medical community's approach to the use of mediations during pregnancy has changed dramatically since the early 1970s, largely because of the problems with thalidomide and diethylstilbestrol, consequently, extensive testing is required before a drug can be labelled for use during pregnancy.[5]

Pain Medications: The most commonly used OTC pain medications and their effects are mentioned in table-2. Gastrointestinal and renal effects are among the most widely studied and recognized adverse effects of NSAIDs, but reproductive risk, especially from NSAID use in early pregnancy, has not been systematically evaluated. A Danish case-control study linked pharmacy data with birth registry data.[5] The authors selected women with registry reports of miscarriages as cases and live births as controls. They reported an association between use of prescribed NSAIDs & miscarriage. A prospective cohort study of the risk factors for miscarriage among members of the Kaiser Permanente Medical care program an integrated health care delivery system, including hospitals and outpatient clinics showed use NSAIDs during pregnancy increased the risk of miscarriage by

80%. The risk of miscarriage was much higher when NSAIDs were taken around conception.[7]

Salicylates have been associated with increased perinatal mortality, neonatal haemorrhage, decreased birth weight, prolonged gestation and labour, and possible birth defects. So pregnant women should use salicylates only under the guidance of a medical professional. Indomethacin is the most studied NSAIDs that are commonly used during pregnancy. Physicians may employ indomethacin during pregnancy to treat pain from degenerating leiomyomata, or as a tocolytic agent. Unfortunately indomethacin use during pregnancy may result in oligohydramnios, premature closure of the foetal ductus arteriosus with subsequent persistent pulmonary hypertension of the newborn, foetal nephrotoxicity, and periventricular hemorrhage.[5] Other NSAIDs, such as ibuprofen, have been studied less often during pregnancy. However, an analysis of 50 pregnant patients who overdosed on ibuprofen revealed no evidence of foetal abnormalities.[8]

Table 2: Use of Analgesics in Pregnancy[18]

Drug name	FDA pregnancy risk classification by trimester (1st/2nd/3rd)	Drug class	Crosses placenta?	Use in pregnancy
Acetaminophen	B/B/B	Non-narcotic analgesic/antipyretic	Yes	Pain reliever of choice
Aspirin	D/D/D	Salicylate analgesic/antipyretic	Yes	Not recommended except for specific indications
Ibuprofen	B/B/D	NSAID analgesic	Yes	Use with caution; avoid in third trimester
Ketoprofen	B/B/D	NSAID analgesic	Yes	Use with caution; avoid in third trimester
Naproxen	B/B/D	NSAID analgesic	Yes	Use with caution; avoid in third trimester

Decongestants, Expectorants & Antihistamines: Women commonly use cold medications during pregnancy. These medications, like most of the other OTC drugs, have not been studied well in Pregnancy (Table-3). The most commonly used cold medications include decongestants and expectorants such as Pseudoephedrine, Guaifenesin and Dextromethorphan. Commonly used antihistamines are Diphenhydramine, Chlorpheniramine and Clemastine fumarate.

The use of vasoconstrictive agents such as Pseudoephedrine may activate alpha-adrenergic receptors, elevating blood pressure or causing vasoconstriction in the uterine arteries, and potentially adversely affecting blood flow to the foetus. This process could explain the reported association between the use of Pseudoephedrine in the first trimester and the development of gastroschisis, which is debatable, & evidence suggests that this effect is negligible at typical doses.[8] Diphenhydramine is widely used in pregnancy as a sedative, an antihistamine, and an anti-nausea drug, although few data confirm its safety during pregnancy. The drug has been shown to have oxytocin like effects, especially in high doses.[9]

Dextromethorphan has been associated with birth defects in chicken embryos. The collaborative perinatal project[10] monitored 50,282 pregnant women, 300 of whom were exposed to Dextromethorphan in the first trimester. Birth defects did not increase above the baseline rate. Thus, sufficient evidence indicates a lack of adverse effects of Dextromethorphan use during pregnancy. Guaifenesin has been associated with an increased risk of neural tube defects.[11]

Table 3: Decongestants, Expectorants, and Nonselective Antihistamines in Pregnancy[18]

Drug name	FDA pregnancy risk classification	Drug class	Crosses placenta?	Use in pregnancy
Chlorpheniramine	B	Antihistamine	Not known	Antihistamine of choice
Pseudoephedrine hydrochloride	B	Sympathomimetic decongestant	Not known	Oral decongestant of choice, possible association with gastroschisis
Guaifenesin	C	Expectorant	Not known	May be unsafe in first trimester
Dextromethorphan hydrobromide	C	Non-narcotic antitussive	Not known	Appears to be safe in pregnancy
Diphenhydramine	B	Antihistamine/ antiemetic	Yes	Possible oxytocin-like effects at high dosages
Clemastine fumarate	B	Antihistamine	Not known	Unknown safety profile

Antidiarrhoeal Agents: The safety of the various agents is outlined in Table 4. Most commonly used antidiarrhoeal medications include kaolin and pectin preparations, bismuth Subsalicylate, Loperamide[4], and Atropine/Diphenoxylate. A possible association has been identified between the ingestion of clays containing Kaolin and the development of iron deficiency anaemia.[12] Use of bismuth Subsalicylate can result in absorption of salicylate and should be avoided in Pregnancy. Loperamide has not been found to be teratogenic in animals but one study involving first-trimester exposure in humans showed a possible increase in foetal cardiac malformation.

Antacid Preparation: The available antacids contain alginic acid; aluminium, magnesium, and calcium are regarded as safe in pregnancy (Table-5). There have been sporadic reports of foetal maldevelopment and injury associated with prolonged use of high dosages of aluminium- containing antacids during pregnancy.[13] Magnesium compounds contain Magnesium Sulphate, a known tocolytic agent. Despite the minimum magnesium absorption that occurs with antacid ingestion, some clinician prefers the use of calcium containing preparation. Semithicone is not absorbed. The H_2 receptor blockers are effective in treating symptoms of heartburn and gastroesophageal reflux disease in pregnancy. But these drugs readily cross the placenta.[14] Their use is recommended in pregnant women whose symptoms cannot be adequately controlled with lifestyle modification and antacids Nizatidine has been associated with an increased risk of foetal death, spontaneous abortion, and decreased foetal weight in rabbit.

Although studies have indicated that there is probably no increases risk of foetal morbidity or mortality, few studies have evaluated first trimester use of H_2 blockers. Therefore most investigators recommend avoiding these drugs in the first trimester.[15]

Table 4: Antidiarrhoeal Medications in Pregnancy[18]

Drug name	FDA pregnancy risk classification by trimester (1st/2nd/3rd)	Drug class	Crosses placenta?	Use in pregnancy
Kaolin and pectin	B/B/B	Antidiarrhoeal	No	Antidiarrhoeal of choice (not absorbed)
Bismuth Subsalicylate	C/C/D	Antidiarrhoeal	Yes	Not recommended (salicylate absorption)
Loperamide	B/B/B	Antidiarrhoeal	Not known	Probably safe
Atropine/diphenoxylate	C/C/C	Antidiarrhoeal	Not known	Not recommended (adverse animal studies)

Table 5: Antacids, Simethicone, and H_2-Receptor Blocker Antihistamines in Pregnancy[18]

Drug name	FDA pregnancy risk classification	Drug class	Crosses placenta?	Use in pregnancy
Aluminium hydroxide/magnesium hydroxide	B	Antacid	Not known	Generally regarded as safe
Calcium carbonate	C	Antacid	Not known	Generally regarded as safe
Simethicone	C	Antiflatulent	No	Generally regarded as safe
Cimetidine	B	Antihistamine	Yes	Preferred after antacids; generally regarded as safe
Ranitidine	B	Antihistamine	Yes	Preferred after antacids; generally regarded as safe
Nizatidine	C	Antihistamine	Yes	Not recommended (adverse animal studies)
Famotidine	B	Antihistamine	Yes	Probably safe, data needed

Topical antifungal in pregnancy: The commonly used topical antifungal and their safety is shown in Table-6. One of the largest studies to date investigated the teratogenicity of Clotrimazole. The population-based, case-control study of 18515 cases pregnancy and 32804 controlled pregnancies didn't show an association between foetal malformation and the use of Clotrimazole.[16]

The centres for disease control and prevention recommends using only topical vaginal antifungal agents including Butoconazole Clotrimazole Miconazole and the prescription medication Terconazole and Nystatin in pregnancy. Because imidazole agents are likely to be safe when used during pregnancy and may be more effective than Nystatin.[17]

Drugs during lactation: Drugs should be used conservatively during lactation and the physicians must know which drugs are potentially dangerous to the nursing infants. Most drugs administered to lactating are detectable in breast milk. Fortunately the concentration of drug achieved in breast milk is usually low. Therefore the total amount the infant would receive in a day is substantially less than what would be considered as a therapeutic dose .If the nursing mother must take medication and the drug s relatively safe one, she should optimally take 30-60 minutes after nursing and 3-4 hrs before the next feeding. This allows time for many drugs to be cleared out from the mother's blood and the concentration in the breast milk will be relatively low. Drugs for which no data are available on the safety during lactation should be avoided or breast-feeding should be discontinued for a time being.[2]

Since 1975, the US food and drug administration has assigned pregnancy risk factors to all the drugs used in USA3. Unfortunately many drugs have not been adequately researched during pregnancy and because of ethical considerations probably will not be in the future.3 Most antibiotics taken by the nursing mother is detected in milk. Drugs like tetracycline are highly concentrated in mother's milk, up to 70% of maternal serum concentration and presents a risk of permanent tooth staining in the infant.

Chloramphenicol on the other had doesn't get as much into milk so as to cause Gray baby syndrome but presents potential risk to cause bone marrow suppression so it should be avoided during lactation. Anti TB drugs like Isoniazide rapidly reaches equilibrium between breast milk and maternal blood and the concentration reached is high enough to show signs of Pyridoxine deficiency. This can be avoided by giving Pyridoxine supplements to the mother.

As for sedatives and hypnotics they achieve high concentration in milk sufficient to produce pharmacological effect in infants. Drugs like barbiturates, Chloral Hydrate and Diazepam can produce sedation, and poor suck reflex in infants. Opioid such as Heroin and methadone and morphine

enters breast milk, which are potentially sufficient to prolong the state of neonatal narcotic dependence if it the drug is taken chronically by the mother during pregnancy. Lithium enters breast milk in concentration equal to those in the maternal serum. Radioactive substances can cause thyroid suppression and may increase the risk of thyroid cancer. Similarly breast-feeding should be avoided in mothers receiving cancer chemotherapy.[2]

Table 6: Topical Vaginal Antifungal Medications in Pregnancy[18]

Drug name	FDA pregnancy risk classification	Drug class	Crosses placenta?	Use in pregnancy
Butoconazole	C	Imidazole antifungal	Not known	Probably safe
Clotrimazole	C	Imidazole antifungal	Not known	Safe in second and third trimesters (human trials), first trimester probably safe
Miconazole	C	Imidazole antifungal	Not known	Probably safe
Tioconazole	C	Imidazole antifungal	Not known	No data

Table 7: Important Medications in Lactation period [2]

Drug	Effect on infants	Comments
Aspirin	Minimal	Occasional dose is safe, high dose is significant in breast milk
Ampicillin	Minimal	Possible occurrence of diarrhoea, allergic sensitisation
Chloramphenicol	Significant	Low dose doesn't cause Gray baby syndrome, possibility of bone marrow suppression. Not recommended while breast feeding
Chlorpromazine	Minimal	Appears insignificant
Diazepam	Significant	Cause sedation in breast fed infant, accumulation occurs in infants
Digoxin	Minimal	Insignificant quantities in breast milk
Isoniazide	Minimal	Possibility of pyridoxine deficiency in infants
Lithium	Significant	Avoid breast feeding unless levels can be measured
Oral contraceptives	Minimal	May suppress lactation at high dose
Penicillin	Minimal	Very low conc. in milk
Phenobarbitone	Moderate	Hypnotic dose can cause sedation in infant
Phenytoin	Moderate	Amount entering breast milk are not sufficient to cause adverse effect
Prednisone	Moderate	Low dose is safe. Dose 2 or more times physiologic amounts should probably be avoided
Propanolol	Minimal	Very small amount in breast milk
Tetracycline	Moderate	Possibility of permanent staining of developing teeth in infants. Should be avoided during breast-feeding.
Theophylline	Moderate	Can enter breast milk in moderate quantities. not likely to produce significant effects
Tolbutamide	Minimal	Low concentrations in breast milk
Warfarin	Minimal	Very small quantities in breast milk

Conclusion

Prescribing drugs during pregnancy presents a challenge to the physicians. Most drugs taken by the pregnant women can cross placenta and expose the developing embryo and foetus to their pharmacological and teratogenic effects. It is still ambiguous and poorly understood how the different drugs cause its teratogenic effects. Pregnant women very commonly use OTC drugs. Although most OTC drugs have an excellent safety profile, some have unproven safety or are known to adversely affect the foetus. The medical community's approach to the use of medication during pregnancy has changed dramatically since 1970s largely because of the problems with Thalidomide and Diethylstilbestrol. Therefore, extensive testing is required before a drug can be labelled for use during pregnancy. Drugs should be used conservatively used during lactation and physicians must know which drugs are potentially dangerous to nursing infants. Therefore frequent awareness programme to physician is an important aspect for the safe use of drugs.

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