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ПРИМЕНЕИЕ ЛЕКАРСТВ ПРИ БЕРЕМЕННОСТИ

Кодирова Муножатхон Набижоновна
Исаков Кобилжон Комилжон угли
Соатова Наргиза Эргашалиевна

Перед продажей нового препарата производитель практически никогда не тестирует продукт на беременных женщинах, чтобы определить влияние этого препарата на плод. Следовательно, большинство лекарств не назначают во время беременности. Как правило, описание лекарственного средства, указанного в «Справочнике врача» и аналогичных источниках, включает такие слова, как «Нельзя использовать во время беременности, не рекомендуется во время беременности, если только это не представляет опасности для плода». Поскольку риск достаточно определен только для нескольких лекарств, врачи, осуществляющие уход за беременными женщинами, имеют очень мало информации, чтобы помочь определить, перевешивают ли потенциальные преимущества для матери риски для плода. Хотя эти общие отказы понятны с точки зрения медицинского права, они трудны для многих женщин и их врачей по ряду причин.

Ключевые слова: беременность, вероятность, рецепт, без рецепта, новорожденный.

DORI VOSITALARINING HOMILADORLIKKA TA'SIRI

Ishlab chiqarilgan yangi dori vositalarini sotishdan avval, ishlab chiqaruvchi ushbu preparatning homilaga ta'sirini aniqlash uchun homilador ayollarda mahsulotni deyarli hech qachon sinovdan o'tkazmaydi. Binobarin, ko'pchilik dorilar homiladorlik paytida foydalanish uchun belgilanmagan. Odatda, "Shifokorlarma'lumotnomasi"davashungao'xshashmanbalardakeltirilgandori-darmonlarning tavsifida "Homiladorlik paytida foydalanish mumkin emas, agar homila uchun xavf tug'dirmasa, homiladorlik paytida foydalanish tavsiya etilmaydi" kabi so'zlar mavjud. Xavf faqat bir nechta dorilar uchun yetarli darajada aniqlanganligi sababli, homilador ayollarga g'amxo'rlik qilayotgan shifokorlar onaning potentsial foydalari homila uchun xavfdan ustunligini aniqlashga yordam beradigan juda kam ma'lumotga ega. Ushbu odatiy rad etishlar tibbiy qonun nuqtai nazaridan tushunarli bo'lsa-da, ko'p sonli ayollar va ularning shifokorlariga bir necha sabablarga ko'ra qiyinchilik tug'diradi.

Kalitso'zlar: Homiladorlik, potensial, retsept, retseptsiz, neonatal.

EFFECTS OF DRUGS ON PREGNANCY

Before marketing a new drug, the manufacturer almost never tests the product in pregnant women to determine its effects on the fetus. Consequently, most drugs are not labeled for use during pregnancy. Typically, descriptions of drugs that appear in the Physicians' Desk Reference and similar sources contain statements such as, "Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus." Since the risk has been adequately established for only a few drugs, physicians caring for pregnant women have very little information to help them decide whether the potential benefits to the mother outweigh the risks to the fetus. These typical disclaimers, although understandable from the medicolegal standpoint, put large numbers of women and their physicians in difficult situations for several reasons.

Keywords: Pregnancy, potential, prescription, over-the-counter, neonatal.

Introduction: In addition to the risk associated with fetal exposure to teratogenic drugs, there is a risk associated with misinformation about the teratogenicity of drugs, which can lead to unnecessary abortions or the avoidance of needed therapy. The medical community and drug manufacturers should make a concerted effort to protect women and their unborn babies from both risks.Use of drugs in pregnancy is often associated with great uncertainty, since it can affect both the mother and the fetus. In addition, drugs and their metabolites may be present at higher concentrations in the fetus than in the mother. The uncertainty originates from the thalidomide scandal in the 1960s. Thalidomide was a drug used to treat hyperemesis but was later shown to be a

potent teratogenic leading to thousands of children being born with severe malformations. The thalidomide scandal has since often raised concern in both health care professionals and pregnant women when using medication during pregnancy. However, the concern may mistakenly lead to nonharmful drugs being attributed teratogenic effects. Studies have shown that pregnant women with chronic conditions, such as asthma and hypothyroidism as well as common acute infections, are treated insufficiently in pregnancy. Furthermore, some pregnant women choose themselves not to take their medication, due to fear of exposing their unborn child. It is therefore important that pregnant women and health care professionals are aware that most drugs used during pregnancy safely can be used without any concern of harming the fetus.

According to Andersen and Futtrup [1] assessing the fetal risk of a drug causing malformation is complicated by the fact that the background risk of a child being born with a major congenital malformation is 3.5%, and most often without a known cause. Based on this, it can be statistically estimated that 200 pregnancies exposed to a drug during the 1st trimester provide enough power (80% strength and 5% significance level) to exclude an increased risk of more than three times higher than the background risk; 700 exposed provide enough power (80% strength and 5% significance level) to exclude an increased risk of more than twice the background risk. Assessing the risk of specific malformations, however, requires data from many thousands of exposed pregnancies since the background risks are even lower. Only few drugs with high teratogenic potential are known; the group includes retinoids (e.g., isotretinoin) and thalidomide, which cause malformations in up to 35% of women exposed in the 1st trimester.[2-9] When exposed to these drugs in the 1st trimester, the main concern is whether the pregnant woman should consider an abortion. The patient should therefore be referred to a physician with expertise and experience in teratology for evaluation, guidance and follow-up. Accidental exposure to virtually all other medicines should not be the reason for terminating the pregnancy. It is estimated that 1% of congenital malformations are due to exposure to drugs during pregnancy. [10] If exposure to a drug during pregnancy is suspected to have had a teratogenic effect it should be reported to the local authorities. Approximately 65% of pregnant women in Denmark are exposed to at least one prescription drug in pregnancy. Women over 40 years of age have the highest rate. The rate has been stable over the past 10 years.In addition to the use of prescription drugs, there is a substantial use of over-thecounter drugs that is not estimated among pregnant women. The most frequently redeemed prescription drugs account for approx. 40% of the use in pregnancy (**Table 1**). These are primarily antibiotics for the treatment of urinary tract infection and upper and lower respiratory tract infections, painkillers, treatment of hypothyroidism as well as disorders that occur frequently in pregnancy such as hemorrhoids, nausea and gastroesophageal reflux [11].

The views expressed by scientists on this subject a few years ago are still noteworthy [12]: Many pregnant women require drug therapy because of pregnancy-induced conditions such as nausea and vomiting, chronic conditions diagnosed before pregnancy, or acute conditions (e.g., those that require surgical treatment with the use of anesthetic agents). Several principles should guide the selection of therapy during pregnancy. Since fetal safety is a major concern, effective drugs that have been in use for long periods are preferable to newer alternatives. **Table 5** lists selected drugs considered to be safe on the basis of either single large cohort studies or meta-analyses of several studies. Newer drugs may be more

specific or have fewer adverse effects in adults, but their safety for fetuses is less likely to be known. For example, although acetaminophen with or without codeine may not be effective in many patients with migraine, it is widely used during pregnancy. Other, more potent antimigraine drugs are either too new (e.g., sumatriptan) or have known reproductive risks (e.g., ergotamine alkaloids that cause uterine contraction).

To minimize the fetal risk, drug doses at the lower end of the therapeutic range should be prescribed during pregnancy. However, because of increased body weight and more rapid clearance of many drugs (e.g., lithium, digoxin, and phenytoin) during late pregnancy, some women may need higher-than-normal doses [13].

Table 1.

The twenty most commonly dispensed prescription drugs during pregnancy in Denmark in 2017

Drug	Indication	Rate of Users During Pregnancy
Pivmecillinam	Urinary tract infection	18.0%
Penicillin V	Upper and lower respiratory infection	11.4%
Fluocortolone and lidocain	Hemorrhoids	7.7%
Paracetamol	Pain	5.6%
Progesterone	Fertility treatment	5.3%
Levothyroxine	Hypothyroidism	3.0%
Metoclopramide	Nausea	2.9%
Hydrocortisone	E.g. eczema	2.8%
Nasal mometasone	Allergic rhinitis	2.3%
Omeprazole	Gastroesophageal reflux	2.2%
Choriongonadotropin	Fertility treatment	2.1%
Clotrimazole	Vulvovaginal candidiasis (topical)	2.0%
Imidazole crème	Candidiasis (topical)	1.9%
Estradiole	Topical hormone treatment	1.8%
Hydrocortisone	Hemorrhoids	1.7%
Aciclovir	Herpes	1.7%
Pivampicillin	Infection	1.7%
Miconazole	Vulvovaginal candidiasis	1.6%
Ondansetron	Nausea	1.5%
Ibuprofen	Pain	1.5%

Pregnant women should be discouraged from taking over-the-counter drugs, and such drugs should not be taken without counseling, since many factors, including the stage of pregnancy, can influence the risk to the fetus. For example, a nonsteroidalantiinflammatory drug may be taken safely for pain during the first trimester of pregnancy, but there is increasing evidence that some nonsteroidalantiinflammatory drugs constrict or even close the fetal ductusarteriosus during late pregnancy [14].

Pregnant women with chronic disorders should plan their pregnancy if possible, and it is essential to ensure that the condition is optimally treated before pregnancy. Conditions such as asthma, infections, diabetes or epilepsy should always be treated during pregnancy, but care should always be given to ensure that the indication is correct and nonpharmacological treatment should always be considered. Prescription of a drug during pregnancy should be based on the amount and quality of available safety data, if possible. In addition, the lowest effective dose and monotherapy should be chosen. Women becoming pregnant during treatment should be offered a review of their medication. A well-founded individual risk assessment can prevent unnecessary concern for the pregnant woman and her family, and unnecessary diagnostics and possible termination of a healthy pregnancy can be avoided.

Table 5.

Selected drugs that can be used safely during pregnancy, according to condition

Condition	Drugs of Choice	Alternative Drugs	Comments
Acne	Topical: erythromycin, clindamycin, benzoyl peroxide	Systemic: erythromycin, topical tretinoin (vitamin A acid)	Isotretinoin is contraindicated
Allergic rhinitis	Topical: glucocorticoids, cromolyn, decongestants, xylometazoline, oxymetazoline, naphazoline, phenylephrine; systemic: diphenhydramine, dimenhydrinate, tripelennamine, astemizole		
Constipation	Docusate sodium, calcium, glycerin, sorbitol, lactulose, mineral oil, magnesium hydroxide	Bisacodyl, phenolphthalein	
Cough	Diphenhydramine, codeine, dextromethorphan		
Depression	Tricyclic antidepressant drugs, fluoxetine	Lithium	When lithium is used in first trimester, fetal echocardiography and ultrasonography are recommended because of small risk of cardiovascular defects
Diabetes	Insulin (human)	Insulin (beef or pork)	Hypoglycemic drugs should be avoided
Headache			
Tension	Acetaminophen	Aspirin and nonsteroidal antiinflammatory drugs, benzodiazepines	Aspirin and nonsteroidal antiinflammatory drugs should be avoided in third trimester
Migraine	Acetaminophen, codeine, dimenhydrinate	β-adrenergic–receptor antagonists and tricyclic antidepressant drugs (for prophylaxis)	Limited experience with ergotamine has not revealed evidence of teratogenicity, but there is concern about potent vasoconstriction and uterine contraction
Hypertension	Labetalol, methyldopa	β-adrenergic–receptor antagonists, prazosin, hydralazine	Angiotensin-converting–enzyme inhibitors should be avoided because of risk of severe neonatal renal insufficiency
Hyperthyroidism	Propylthiouracil, methimazole	β-adrenergic–receptor antagonists (for symptoms)	Surgery may be required; radioactive iodine should be avoided
Mania (and bipolar affective disorder)	Lithium, chlorpromazine, haloperidol	For depressive episodes: tricyclic antidepressant drugs, fluoxetine, valproic acid	If lithium is used in first trimester, fetal echocardiography and ultrasonography are recommended because of small risk of cardiac anomalies; valproic acid may be given after neural-tube closure is complete
Nausea, vomiting, motion sickness	Diclectin (doxylamine plus pyridoxine)	Chlorpromazine, metoclopramide (in third trimester), diphenhydramine, dimenhydrinate, meclizine, cyclizine	
Peptic ulcer disease	Antacids, magnesium hydroxide, aluminum hydroxide, calcium carbonate, ranitidine	Sucralfate, bismuth subsalicylate	
Pruritus	Topical: moisturizing creams or lotions, aluminum acetate, zinc oxide cream or ointment, calamine lotion, glucocorticoids; systemic: hydroxyzine, diphenhydramine, glucocorticoids, astemizole	Topical: local anesthetics	
Thrombophlebitis, deep-vein thrombosis	Heparin, antifibrinolytic drugs, streptokinase		Streptokinase is associated with a risk of bleeding; warfarin should be avoided

Antibiotics. Bacterial infections can not only threaten the mother, but also complicate the pregnancy with, e.g., spontaneous abortion or premature birth. Certain microorganisms can affect the fetus and directly damage it. In addition, bacterial infections may be associated with high fever suspected of contributing to malformations. Long-term high fever should therefore be lowered with paracetamol or in the 2nd trimester with ibuprofen. Penicillins are the best studied antibiotics. They cross the placental barrier and can be measured in the amniotic fluid. Data from many thousands of pregnancies show that penicillin V, amoxicillin, flucloxacillin, pivmecillinam and ampicillin can be used throughout pregnancy. The cephalosporins, such as cephalexin, can also be used, but due to limited data on the treatment of pregnant women they should only be used if the benefits outweigh the risks. Macrolides should not be used during pregnancy due to limited data, but penicillin allergy or bacterial antibiotic resistance may require their usage. Among the macrolides, erythromycin is the best studied drug during pregnancy. Tetracyclines pass the placental barrier

but are not associated with malformations. However, they bind to calcium in the fetus' developing teeth, which mineralize from the 16th week of pregnancy. This leads to tetracycline being incorporated into the teeth and potentially causing permanent discoloration. Doxycycline has a lower affinity to calcium than the older tetracyclines, and the risk is theoretically lower when using doxycycline. Tetracyclines can, if circumstances necessitate treatment in the first trimester, be used [15,16].

Analgesics. Paracetamol is considered safe throughout the entire pregnancy, and ibuprofen can be used in the 2nd trimester. When ibuprofen is used in the 1st trimester, there is a slightly increased risk of miscarriage and cardiac malformations in the fetus. Ibuprofen is contraindicated in the 3rd trimester due to the risk of cardiopulmonary toxicity and impaired renal function in the fetus and prolonged bleeding time and decreased uterine contraction in the mother. Opioids can be used if necessary but should be avoided in the 3rd trimester. Especially during the weeks before birth, use of opioids should be avoided due to risk of respiratory depression and withdrawal symptoms in the newborn. Based on the amount of safety data available, morphine and methadone should be preferred [17,18].

Antiemetics. Nausea and vomiting in pregnancy occur in up to 70–80% of pregnancies. The symptoms are self-limiting, and in 60% of women the symptoms disappear by the end of the 1st trimester and in 90% by the 20th week. In 2% of pregnancies, the symptoms are more severe: hyperemesis gravidarum is characterized by frequent vomiting, dehydration, weight loss of more than 5% of body weight and electrolyte disorders. It is the most common cause of hospitalization in the first half of pregnancy. The exact cause has not been established, but may be due to elevated levels of HCG, vitamin B deficiency, decreased tone of the esophageal sphincter or Helicobacter pylori infections. Pharmacological recommendations differ from country to country, but a recommendation could be to start with vitamin B6 (pyridoxine) alone, or in combination with a sedating antihistamine (meclizine or cyclizine). If enough reduction of nausea is not obtained, metoclopramide, followed by ondansetron, could be used [19].

Asthma. Treatment of asthma in pregnancy follows the same guidelines as for nonpregnant women. Pregnant women with moderate to severe asthma should be referred to a specialist in lung diseases and to obstetric control to optimize treatment. All inhaled drugs for the treatment of asthma are safe during pregnancy. In general, the theoretical risk of birth defects associated with the use of antiasthmatic drugs is considered to be significantly lower than the risk associated with under-treated asthma. However, due to limited data, tiotropium should preferably be avoided during pregnancy [20].

Allergy. Up to 20% of pregnant women suffer from hay fever. Often, allergic rhinitis is exacerbated by nasal obstruction due to increased levels of estrogen during pregnancy. A distinction between allergic rhinitis and pregnancy-related rhinitis is usually possible based on the medical history. Exposure to known allergens such as house dust mites should be avoided if possible. In pregnancyrelated rhinitis, nasal saline can often reduce symptoms. Allergy in pregnancy can often be treated with topical or oral antihistamines, e.g. cetirizine or loratadine, cromoglicic acid or topical glucocorticoids such as budesonide nasal spray.Detumescent drops like xylometazoline can be used if necessary, but the use should be limited to a maximum of 10 days [21-23].

Thyroid agents. Hypothyroidism in pregnancy is always treated with levothyroxine and adjustment of levothyroxine dosage to achieve TSH <2.5

mIU/l is recommended. The dosage of levothyroxine should be increased by 30–50% when the pregnancy is recognized, as pregnant women with hypothyroidism cannot achieve the physiological increase in thyroid hormone production that normally occurs during pregnancy. No increased fetal risk when using levothyroxine during pregnancy has been reported. Conversely, there is an association between untreated hypothyroidism and impaired fertility, increased abortion risk, and impaired fetal brain development. In case of treatment-requiring thyrotoxicosis during pregnancy, antithyroid medication can be administered as monotherapy (propylthiouracil in the 1st trimester, thiamazole in the 2nd and 3rd trimesters). If possible, the patient should be referred to a specialist to ensure optimal treatment [24].

Antimycotics. Pregnancy increases the risk of vulvovaginal candidiasis. Despite this, the diagnosis should at least be confirmed by clinical assessment before starting any treatment. For treatment indication, topical treatment with clotrimazole vaginal tablets or cream is recommended. Systemic treatment with fluconazole has been shown to be associated with a 50% increased risk of spontaneous abortion as well as an increased risk of cardiac malformations and should therefore only be used on compelling indication [25,26].

Antidepressants. Use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has been debated. Like other serious illnesses, serious mental illness can threaten pregnancy. A psychotherapeutic treatment or possibly medical treatment should therefore be considered. In Denmark, sertraline and citalopram are the most frequently used SSRIs. Both drugs are drugs of choice for treatment-requiring depression in pregnant women and should be preferred, although a slight increased risk of cardiac malformations, irritative neonatal symptoms or persistent pulmonary hypertension in the newborn cannot be ruled out. However, the increased risk of malformations seen in several studies is probably due to confounding as previously described. Possible longterm effects on the child's development are currently not adequately investigated. Advantages and disadvantages must therefore be thoroughly discussed when counseling the patient and preferably in collaboration with a psychiatrist. Acid-neutralizing medicines Many pregnant women will need acid-neutralizing medicines due to gastroesophageal reflux, in part due to external pressure against the ventricle toward the end of pregnancy. Antacids and anti-reflux agents are primarily locally acting drugs and can be safely used in pregnancy. Ranitidine (H2 receptor antagonist) may also be used. If a proton pump inhibitor is needed, there is most data on the safety of omeprazole, where data is available for thousands of exposed 1st trimester pregnant women. Pantoprazole, esomeprazole and lanzoprazole can also be used, although there are fewer safety data [27-31].

Local-acting drugs. During pregnancy, the venous return of the anal canal is inhibited by the growing uterus, and up to 85% of pregnant women in 2nd and 3rd trimester have hemorrhoids. Topical hemorrhoid agents containing combinations of, for example, adrenal cortex hormone, analgesics and/or antibiotics can be used. Constipation is also common in pregnancy. Hormonal changes cause relaxation of the smooth muscle of the intestinal tract. Transit time and fluid absorption increase, and up to 40% of pregnant women complain of symptoms of constipation. If fiber-rich diets, sufficient fluid intake (2 L daily) and exercise, wheat bran and special fiber are not enough, the osmotically active laxatives such as lactulose or macrogol-containing preparations are the drugs of choice during pregnancy. In the absence of efficacy, shortterm treatment with the

peristaltic promoters bisacodyl or sodium picosulfate may be attempted [32,33].

Conclusion: The unique nature of the physiology of pregnancy presents challenges for the pharmaceutical treatment of chronic and acute disorders and 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 the 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. The use of herbal medicine during pregnancy is a common phenomenon. Different studies revealed that using herbal medicine during the first 12 weeks and the past 12 weeks of gestation is dangerous for the fetus. Pregnant women should consult doctors or pharmacists before using any herbal medicines. The untoward effects of using herbal medicine during pregnancy need further investigation for many herbs. Thus, researches, especially a clinical trial study, should be conducted to identify the untoward effect of herbal medicine use during pregnancy. We found through our study that there are some problems in advising pregnant women and not giving importance even though it is dangerous. Therefore, we recommend more attention by the pharmacists syndicate by giving specialized educational courses to all members of the medical staff and women in general and follow-up pharmacists in private pharmacies and health institutions by giving the correct instructions using drugs.

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