FEATURES OF THE USE OF DRUGS IN PREGNANT AND LACTATING WOMEN

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Abstract. *Medications may be required for a variety of indications during pregnancy. The most commonly used medications include antiemetics, antacids, antihistamines, analgesics, antimicrobials, diuretics, antidepressants, and tranquilizers. They also frequently use (and even abuse) psychoactive substances. Despite this trend, there is still no clear evidence-based recommendation for the safe use of medications during pregnancy.*

Keywords: *Vaccination during pregnancy, Antiviral drugs during pregnancy, Antidepressants during pregnancy, Reference materials, Additional information.*

Introduction

Until the 2010s, the U.S. Food and Drug Administration (FDA) classified prescription and over-the-counter drugs into five safety categories (A, B, C, D, X) for use during pregnancy.

However, only a few well-controlled studies of drug use during pregnancy had been conducted. Most of the information on the safety of drugs during pregnancy came from animal studies and uncontrolled clinical trials, as well as post-marketing surveillance. Consequently, the FDA classification system led to confusion and difficulties in making clinical decisions based on the available data. In December 2014, the FDA responded by requesting that categories A, B, C, D, and X be removed from drug labels.

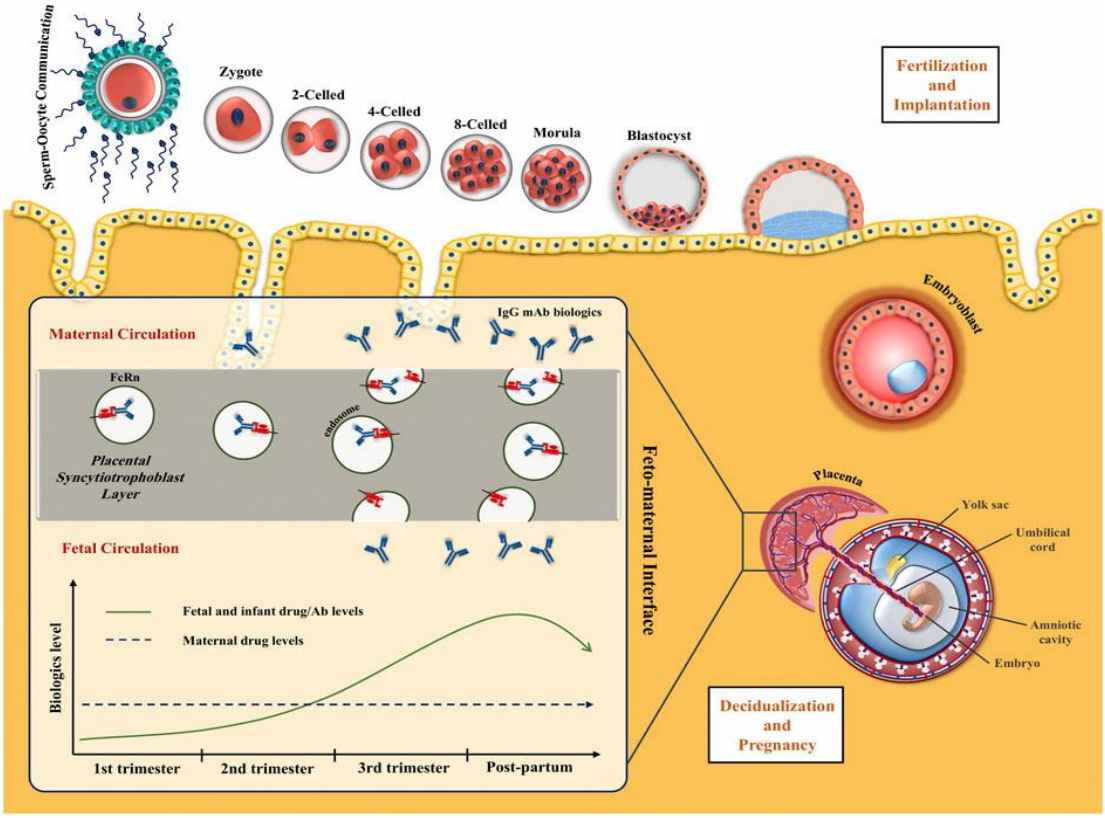
The FDA now requires that, instead of categorical information, drug-specific information be included in a suitable format called the Pregnancy and Lactation (Drugs) Final Rule (PLLR).

The information specified by the FDA includes 3 sections:

Pregnancy: information on the use of the drug in pregnant women (e.g., dosage, risk to the fetus) and the existence of a registry that collects and maintains data on the effects of the drug on pregnant women

Lactation: information on the use of the drug during breastfeeding (e.g., the extent of the drug's penetration into breast milk, possible effects on the nursing infant)

Effects on reproductive potential in women and men: the need for pregnancy testing, contraception, and information on infertility as a result of taking the drug



Each of the pregnancy and lactation sections has 3 subheadings (Risk Summary, Clinical Considerations, and Information) that provide more detailed information. The final rule does not apply to over-the-counter (OTC) drugs.

Drug delivery and metabolism during pregnancy

Drug therapy for certain conditions is often necessary during pregnancy. In general, a drug is considered for use during pregnancy if the potential benefit outweighs the known risks.

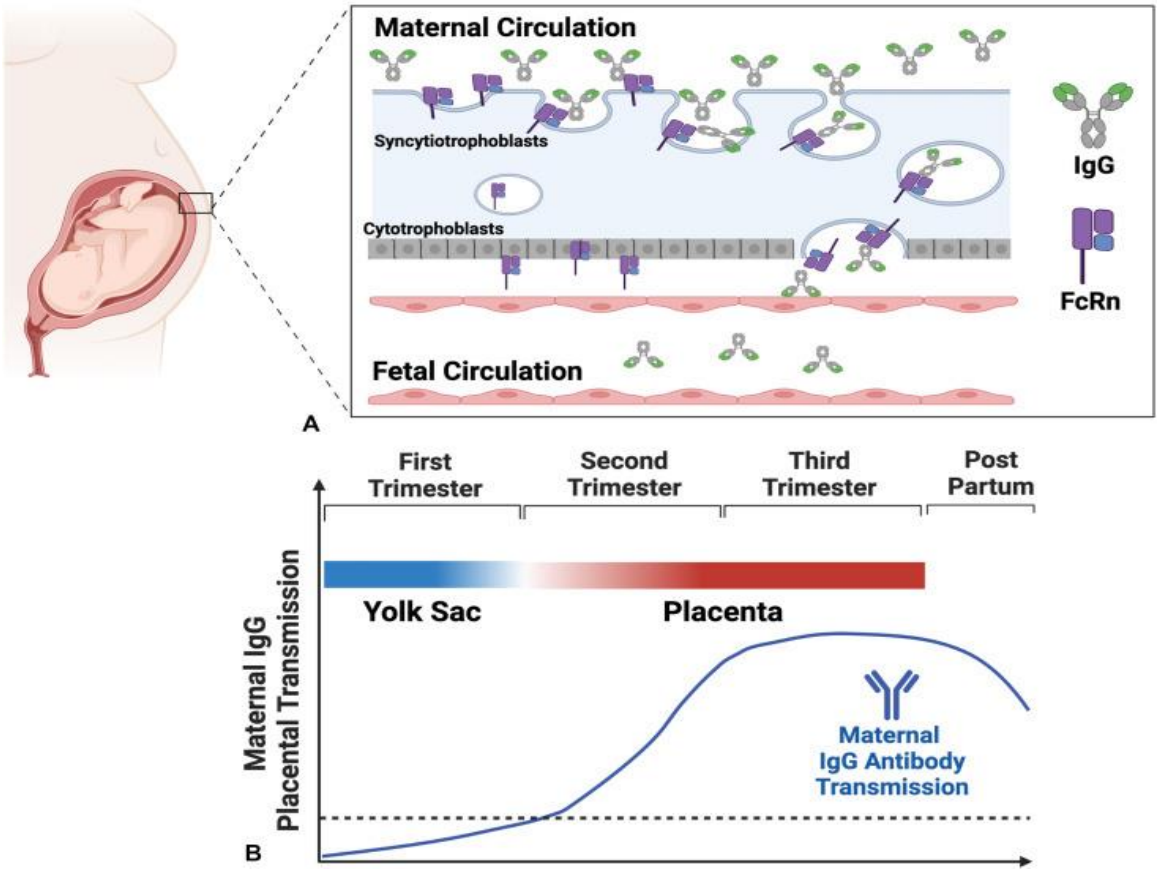
Not all drugs or other substances in the mother's bloodstream cross the placenta to the fetus (transfer). Some drugs that cross the placenta may have direct toxic or teratogenic effects. Drugs that do not cross the placenta may also harm the fetus in the following ways:

Narrowing of the placental vessels, thereby disrupting gas exchange and nutrient metabolism

Causes severe uterine hypertonicity, leading to anoxic injury

Altering maternal physiology (e.g., causing hypotension)

For a list of some medications that may have adverse effects during pregnancy, see the table Safety of Selected Medications During Pregnancy.



Drugs cross the placenta in the same way as they cross other epithelial barriers (see Absorption). Whether and how quickly a drug crosses the placenta depends on the molecular weight of the drug, the degree of its binding to other compounds (e.g., carrier proteins), the available space for exchange in the placental villi, and the amount of drug metabolized by the placenta. Most drugs with a molecular weight of less than 500 daltons readily cross the placenta and enter the fetal circulation. Larger molecular weight drugs (e.g., protein-bound drugs) usually do not cross the placenta. One exception is immunoglobulin G, which can be used to treat conditions such as autoimmune fetal thrombocytopenia or neonatal hemochromatosis. In general, the time between entry into the maternal circulation and entry into fetal tissues is at least 30 to 60 minutes; however, some drugs do not reach the same concentration in the mother's and fetus' blood.

The effect of the drug on the fetus is mainly determined by the gestational age of the fetus, the permeability of the placental barrier, maternal factors, the activity of the active ingredients in the drug, and its dosage.

The age of the fetus affects the type of drug exposure:

Up to 20 days after fertilization: When using drugs during this period, the principle of "all or nothing" is generally applied, which means that either the drug kills the embryo or has no effect on it. At this time, there is no possibility of teratogenesis.

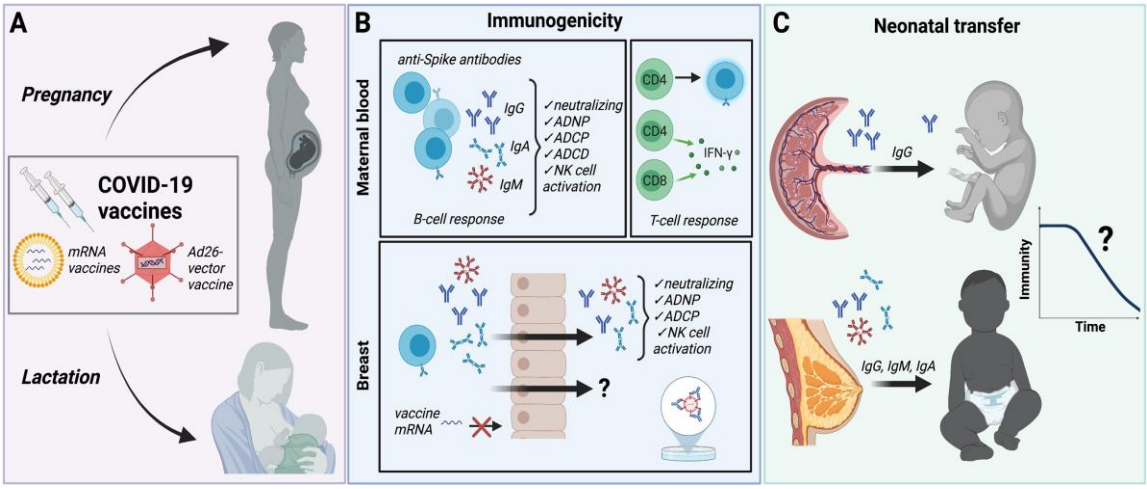
During organogenesis (20 to 56 days after fertilization): Teratogenesis most often occurs during this time. Drugs administered to the embryo during this period may cause spontaneous abortion, severe, near-fatal anatomical defects (true teratogenic effects), occlusive embryopathy (a permanent mild metabolic or functional defect that may manifest later in life), or an increased risk of childhood cancer (for example, when the mother receives radioactive iodine to treat thyroid cancer); or the drugs may have no significant effect.

Research methods and materials

After organogenesis (2nd and 3rd trimesters): Teratogenesis is unlikely, but drugs may disrupt the growth and function of normally formed organs and tissues. Because of increased placental metabolism, doses must be higher to affect the fetus.

Maternal factors that affect the absorption, distribution, metabolism, and excretion of drugs. For example, nausea and vomiting can reduce the absorption of an oral drug.

The overall incidence of major structural congenital malformations in the United States is approximately 3% (1); most of them develop from genetic, environmental, multifactorial, or unknown causes. The overall incidence of birth defects caused by therapeutic drugs is difficult to determine. For example, in one study of 5504 cases of birth defects, only 20% had a known cause, and of those with a known cause, <1% were drug-related (2).



a. Safety of certain medications during pregnancy
b. Vaccination during pregnancy
c. Vaccination in pregnant women is as effective as in non-pregnant women.

During flu season, all pregnant women are recommended to get the flu vaccine.

Adsorbed diphtheria-tetanus-pertussis vaccine (DTP) is recommended for all pregnant women in the 3rd trimester.

CDC recommends the COVID-19 vaccine for everyone 5 years of age and older, including those who are pregnant, breastfeeding, trying to become pregnant, or planning to become pregnant. Evidence is accumulating about the safety and effectiveness of the COVID-19 vaccine during pregnancy. This evidence supports the conclusion that the benefits of getting the COVID-19 vaccine outweigh the known or potential risks of getting the vaccine during pregnancy. (See also: CDC: COVID-19 Vaccines During Pregnancy or Breastfeeding.)

In August 2023, the U.S. Food and Drug Administration (FDA) approved the use of the respiratory syncytial virus (RSV) vaccine in selected pregnant women between 32 and 36 weeks of gestation, and it should not be used before 32 weeks. Following prenatal use of the RSV vaccine, clinical trials have found increased rates of preterm birth, preeclampsia in pregnant women, and low birth weight and jaundice in infants compared with placebo; further studies are needed to assess these potential risks (3).

Vaccinations against other diseases should only be given when the risk of infection to the pregnant woman or fetus is high and the potential side effects of the vaccine are minimal. Vaccinations against cholera, hepatitis A, hepatitis B, measles, mumps, plague, polio, rabies, typhoid, and yellow fever should only be given when there is a moderate risk of infection.

Live virus vaccines should not be given to women who are or may become pregnant. Live attenuated rubella vaccines may cause subclinical infection of the placenta or fetus. However, neonatal defects caused by vaccination have not been documented, and women vaccinated early in pregnancy should be advised to terminate the pregnancy based on the theoretical risk alone. Live attenuated varicella zoster vaccine also has the potential to infect the fetus; the risk is highest between 13 and 22 weeks. This vaccine is contraindicated during pregnancy.

Antiviral drugs during pregnancy

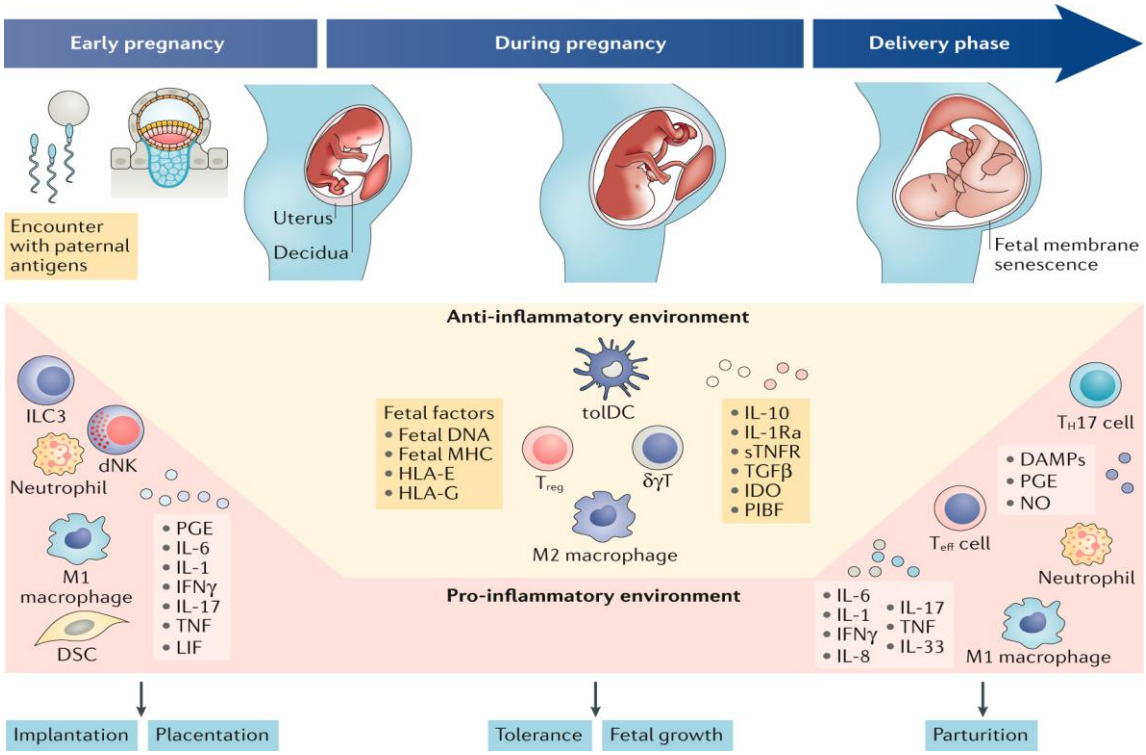
Some antiviral drugs (such as zidovudine and ritonavir for HIV infection) have been used safely during pregnancy for many years. However, some antiviral drugs can pose serious risks to the fetus.

Observation results

Pregnancy is associated with an increased risk of severe COVID-19. The United States National Institutes of Health (NIH) recommends the use of nirmatrelvir-ritonavir (4) or remdesivir (5) in pregnant women with early mild to moderate COVID-19. The American College of Obstetricians and Gynecologists recommends considering the use of nirmatrelvir-ritonavir, especially in patients with at least one additional risk factor for severe disease. For pregnant

women hospitalized with COVID-19, the NIH recommends the use of baricitinib or tocilizumab, if appropriate.

Antiviral drugs for influenza should be started as early as possible, without waiting for test results to confirm the diagnosis, because treatment within 48 hours of illness onset is most effective. However, treatment at any time during infection reduces the risk of serious complications. Controlled clinical trials of zanamivir and oseltamivir have not been conducted in pregnant women; however, multiple observational studies suggest that their use during pregnancy does not increase the risk of adverse events. There is limited information on the safety of peramivir during pregnancy and there is no information on the safety of baloxavir in pregnant women. Health-care providers should tell pregnant women about the signs and symptoms of influenza and advise them to seek medical attention as soon as symptoms begin.



Antidepressants during pregnancy

Antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are commonly used during pregnancy because the prevalence of clinical depression in pregnancy is high (7–12% according to one review) (6). Physiological and psychological changes during pregnancy can affect depression (possibly by worsening it) and may reduce the response to antidepressants. Ideally, depression during pregnancy should be treated by a multidisciplinary team, including an obstetrician and a psychiatrist.

Pregnant women taking antidepressants should be asked about symptoms of depression at each prenatal visit and have an appropriate prenatal evaluation. This may include:

- ***Detailed assessment of fetal anatomy in the 2nd trimester***

Conclusion: If a pregnant woman takes paroxetine, an echocardiogram is performed to evaluate the fetal heart, as some studies suggest that paroxetine increases the risk of congenital heart defects.

To reduce the risk of neonatal withdrawal symptoms, clinicians should consider tapering all antidepressants to the minimum effective dose during the third trimester. However, the potential benefit of dose reduction must be carefully balanced against the risk of worsening symptoms and postpartum depression. Postpartum depression is a very common disorder that is often unrecognized, and treatment should be initiated promptly. Periodic visits with a psychiatrist and/or social worker may be helpful. This document discusses the proposed changes to the pregnancy labels that eliminate the pregnancy categories (A, B, C, D, X) and replace them with more useful and detailed information. " FDA [Food and Drug Administration] Content and Format of Labeling for Drugs and Biological Products for Human Use; Labeling Requirements for Pregnant and Nursing Women." The new label requires a summary of the risks associated with drug use during pregnancy and lactation, evidence to support claims, and information to assist clinicians in making prescribing decisions and to counsel women about taking medications during pregnancy and lactation.

Teratogen Information System: This website provides resources to help healthcare practitioners identify risks associated with drugs (and environmental exposures [e.g., vaccines, infections]) during pregnancy. It provides expert information on over 1,700 drugs (including the 200 most commonly prescribed drugs). It summarizes the clinical and experimental literature and uses this information to determine teratogenic risk. Subscription required.

Newborns of mothers who smoke are more likely to develop anencephaly, congenital heart defects, cleft palate, sudden fetal death, physical and mental retardation, and deviant behavior. Quitting or limiting smoking can reduce the risks.

Exposure to smoke can also harm the fetus.

Alcohol is the most commonly consumed teratogen. Drinking alcohol during pregnancy increases the risk of miscarriage. The level of risk probably depends on the amount of alcohol consumed, but the safe amount of alcohol is unknown. Regular alcohol consumption reduces fetal weight by 1-1.3 kg. Daily consumption of as little as 45 ml of pure alcohol (equivalent to 3 drinks) can lead to the development of fetal alcohol syndrome. This syndrome occurs in 2.2/1000 live births; it includes fetal growth retardation, malformations of the facial skull and cardiovascular

system, and neurological disorders. It is a major cause of mental retardation and can lead to neonatal death due to developmental delay.

Use of stimulants such as cocaine or methamphetamine poses indirect risks to the fetus (e.g., maternal stroke or death during pregnancy). Their use can also cause fetal vasoconstriction and hypoxia. Repeated use increases the risk of the following conditions:

a. Spontaneous abortion
b. Intrauterine growth restriction
c. Placental abruption
d. Premature contractions and birth
e. Stillbirth

Congenital defects (e.g., central nervous system, genitourinary, and skeletal anomalies; isolated atresias)

Although the main metabolite of marijuana can cross the placenta, occasional marijuana use does not necessarily increase the risk of birth defects or fetal growth restriction. Marijuana use during pregnancy has been associated with adverse pregnancy outcomes, including small for gestational age fetuses, premature birth, and neurodevelopmental and behavioral problems in infants. The trend toward recreational marijuana use and its increasing use in several states may lead to a better understanding of its effects over time.

Bath salts are a group of "designer" illegal drugs derived from various amphetamine-like substances; these drugs are increasingly being used during pregnancy. Although the effects are not well studied, there is a potential for fetal vasoconstriction and hypoxia, as well as a risk of stillbirth, premature placental abruption, and possible congenital malformations.

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