

An Overview of Drugs taken During Pregnancy and its Outcome

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Abstract

Aim is to create awareness among the women of reproductive age group about the risks associated with consumption of drugs during pregnancy. More than 90% of pregnant women take prescription or non-prescription drugs at some time during pregnancy. In general, unless absolutely necessary, drugs should not be used during pregnancy because many of them are harmful to the fetus. Pregnancy introduces unique considerations for drug treatment due to its impact on the pharmacokinetics of medications and the potential harm certain drugs can pose to the fetus. While completely avoiding pharmacological treatment in pregnancy is impractical and risky, as some women have pre-existing medical conditions or develop new ones requiring medication, the challenge lies in balancing effective treatment with fetal safety. Historical incidents, such as thalidomide in the 1960s, highlighted the risks, but it's crucial to note that congenital abnormalities from teratogenic drugs constitute less than 1% of total cases. To address these concerns, the Food and Drug Administration (FDA) established a system in 1979 for assessing the teratogenic risk of drugs. This classification, ranging from Category A (considered safest) to Category X (absolutely contraindicated in pregnancy), helps guide clinicians in making informed therapeutic decisions. The article delves into various aspects of drug use during pregnancy, emphasizing the importance of weighing risks and benefits to ensure optimal maternal health while safeguarding the developing fetus.

KEYWORDS: Pregnancy, Medicine, Fetus, Teratogenicity.

Introduction

The misuse of substances by pregnant women remains a significant public health issue, posing risks to child development and placing socioeconomic burdens on society. The impact on the child's brain development is substantial, given the influence of major drug targets on shaping the developing brain (1,2,3,4,5,6). Fetal exposure to drugs has been associated

with various brain deficits. This review addresses several key aspects: (i) the current understanding of substance use patterns among pregnant or childbearing-age women (ii) the cellular and molecular pathways through which prenatal drug exposure affects structural and functional brain development (iii) outcomes in exposed individuals across different areas of functioning (iv) existing experimental animal models and (v) current research limitations

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and potential future avenues^(7,8). Nicotine is the most frequently used substance during pregnancy, with alcohol, marijuana, and cocaine following closely behind according to studies. However, some research indicates that as many as 50% of pregnant individuals engage in the use of multiple substances. In recent years, there has been a notable rise. Despite prevention and education efforts, the rate of illicit drug use among pregnant women aged 15–44 has remained steady at 5.9%. Notably, young adolescent females now surpass males in their age group in non-medical use of psychoactive drugs⁽⁹⁾.

Legal substances like alcohol and nicotine also pose risks to the fetus. The prevalence of reported current alcohol and cigarette use among pregnant women aged 15–44 has not substantially changed in the past decade, with approximately 8.5% reporting current alcohol use during pregnancy. The legality of a drug does not necessarily align with its safety profile, emphasizing the need for improved therapies and educational strategies for pregnant and breastfeeding women.

Various animal species model different drugs and biological processes, each with its unique developmental timeline. Translating findings to humans is complicated due to these differences. Rodents and lagomorphs, born relatively early compared to humans, require postnatal drug administration to model third-trimester human exposure, omitting transplacental transfer observed in human fetal drug exposure. Challenges such as accurate dosing, route of administration, and pharmacokinetics are often overlooked in animal models. Additionally, drugs have the potential to impact fetal development through various mechanisms. When a drug crosses the placenta, which is common for the majority of drugs of abuse, it can directly influence molecular targets in the fetus. Another pathway involves the drug's direct effects on the uterus and/or placenta, potentially altering placental secretory activity or uteroplacental blood flow. Moreover, drugs can induce changes in the mother's physiology, such as increased stress hormone secretion or modifications in maternal health behaviors resulting from addiction, which can subsequently affect the fetus. While not covered in detail here, recent findings suggest that

paternal exposures to drugs like cocaine during spermatogenesis can also impact offspring brain and neurobehavioral development through epigenetic mechanisms in animal models^(10,11,12).

Despite the complexity of this topic, we will strive to provide a comprehensive review, incorporating evidence from animal models as well as clinical and imaging data from longitudinal human cohorts examining the consequences of fetal exposure to specific drugs of abuse.

PHYSIOLOGICAL ALTERATION IN THE BODY'S FUNCTION DURING PREGNANCY:

Pregnancy is initiated by the fusion of a sperm and an egg, known as fertilization, typically occurring in the woman's fallopian tube. Following fertilization, the developing cluster of cells undergoes rapid division. Around 5-7 days after ovulation, the fertilized egg implants into the uterine wall, marking the beginning of placental formation. The placenta plays a crucial role in sustaining and nourishing the baby by facilitating the transfer of oxygen, carbon dioxide, amino acids, fats, vitamins, and minerals between the mother's blood and the growing baby. Waste substances are also exchanged through the placenta. From implantation until approximately the eighth week, the developing entity is referred to as an embryo. During this phase, specialized cells start forming vital organs, the nervous system, bones, muscles, and blood. After the eighth week, it is termed a fetus, measuring 2.4 cm with most internal organs formed and distinct external features emerging⁽¹³⁾.

As the fetus and placenta grow, substantial metabolic changes occur in the mother's body. Obvious physical transformations include weight gain and alterations in body shape. Weight gain is attributed to increased breast tissue, blood volume, and water content. Deposition of fat and protein, along with elevated cellular water, contributes to maternal stores. The average weight gain during pregnancy is 12.5 kg, with 1 kg attributed to protein. Changes in plasma albumin and fibrinogen levels, as well as increased total body fat, are observed. In the second half of pregnancy, plasma lipids increase, but triglycerides, cholesterol, and lipoproteins decrease post-delivery. The ratio of LDL to HDL also rises during pregnancy⁽¹⁴⁾.

The impact of a drug on the fetus depends on the developmental stage and the strength and dosage of the drug. Limited information is available regarding drug effects during conception and implantation. It is recommended that women at risk of conceiving or planning pregnancy should discontinue unnecessary medications 3-6 months before conception. Drugs taken in the early stages of pregnancy may exhibit an all-or-nothing effect, either causing fetal harm or having no impact. The period between the 3rd and 8th weeks, known as organogenesis, is particularly sensitive to drugs, potentially leading to miscarriage or noticeable birth defects. Beyond the 9th week, referred to as the fetal stage, exposure to drugs is not strongly associated with major congenital malformations but may influence the growth and function of normally formed organs and tissues^(15,16,17).

The impact of medication on the fetus is also influenced by the dose reaching the fetus, affected by maternal dose, drug distribution in the maternal bloodstream, placental function, maternal and fetal genetic and physiological factors, and exposure to other drugs, chemicals, or environmental hazards⁽¹⁷⁾.

PREGNANCY AND DRUG:

Medications play a crucial role in enhancing human health and well-being, but their use during pregnancy requires careful consideration. Ideally, pregnant women should avoid unnecessary drug intake as substances can pass through the placenta, potentially harming the developing fetus. However, this may not always be feasible, especially for women with pre-existing medical conditions like asthma, epilepsy, or hypertension, which require ongoing treatment. Additionally, new health issues may arise during pregnancy, necessitating pharmacological intervention⁽¹⁸⁾. While the avoidance of drugs during pregnancy is preferred, it is not always practical or safe. Some essential substances like vitamins, minerals, iron, and dietary supplements are crucial for maternal and fetal health. Statistics reveal that around 8% of pregnant women need drug treatment for various chronic diseases and complications related to pregnancy. Many women inadvertently take medications in the early stages of pregnancy, with over half being prescribed drugs other than vitamins or minerals. Moreover, more than 90% of pregnant women use prescription or over-the-counter drugs, and some may engage in social drug use like tobacco, alcohol, or illicit substances⁽¹⁹⁾. The

challenge in treating pregnant women with drugs stems from limited information, as they are often excluded from medical trials, and results from animal studies may not be directly applicable. Concerns about potential harm to the fetus have restricted the use of drugs during pregnancy, making it challenging to gather comprehensive safety data. Information on medication safety is primarily derived from case reports, epidemiological studies, and animal research, each with its limitations. A study in 2001 highlighted the lack of safety information for over 90% of medications approved by the FDA between 1980 and 2000 when used during pregnancy. This dearth of information makes it challenging for both women and healthcare providers to make informed decisions about medication use during pregnancy.

Despite the limited data on drug safety during pregnancy, the widespread use of over-the-counter and prescription drugs indicates their common usage. While about 2-3% of birth defects may result from drug use, medications are often essential for the well-being of both the pregnant woman and the fetus. Health care practitioners may recommend specific vitamins and minerals, and medications may be prescribed to alleviate common pregnancy symptoms or treat unrelated conditions. Pregnant women may also use medications to manage pre-existing chronic conditions or address pregnancy-related disorders^(20,21,22). Given these complexities, it is crucial to examine the patterns of drug use during pregnancy to identify opportunities for improvement based on current knowledge⁽²³⁾.

THE IMPACT OF DRUG ON THE DEVELOPING FETUS:

The consumption of drugs during pregnancy can impact the developing fetus in various ways. It can have a direct effect, causing harm or abnormal development, potentially resulting in birth defects or even fetal death. Additionally, these substances may influence the placenta's function, often by narrowing blood vessels and diminishing the supply of oxygen and nutrients from the mother to the fetus. This can lead to the birth of a baby who is underweight and not fully developed. Furthermore, drugs can induce strong contractions of the uterine muscles, indirectly harming the fetus by compromising blood supply or triggering premature labor and delivery.

FDA CATEGORIZATION OF DRUGS USE IN PREGNANCY⁽²³⁾ :

TABLE 1: Category Description

A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate effect, but adequate and well-controlled studies in pregnant women have or Animal studies have shown an adverse effect, but adequate and well -controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well -controlled studies in pregnant women .or No animal studies have been conducted and there are no adequate and well -controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus.
X	Studies in animals or humans have demonstrated teratogenic effects. The risk to the fetus clearly outweighs any potential benefit to the mother. Drugs in this category are contraindicated in pregnancy

TABLE 2: Commonly used drugs in pregnancy and their categories⁽²⁴⁾

DRUGS	CATEGORY
ANALGESICS AND ANTIPYRETICS	B AND C
Acetaminophen	B
Phenacetin	B
Aspirin	C
ANTIEMETICS	B AND C
Doxylamine	B
Meclizine	B
Cyclizine	B
Dimenhydrinate	B
ANTIBIOTICS	B,C AND D
Penicillin, Ampicillin, Amoxicillin	B
Cloxacillin, Cephalosporins	B
Erythromycin	B

List of some of the drugs during pregnancy along with their categories as per FDA categorization

TABLE 3: Medications Contraindicated In Pregnancy

DRUG	COMMENTS
Vitamin A and its derivatives,including isotretinein, accutane and etretinate	Significant risk of spontaneous abortion and risk of many significant anomalies ^(25,26)
ACE inhibitors	May cause kidney damage in the fetus when used in II and III trimester, decrease in the amount of amniotic fluid and deformities of face, limbs and lungs ⁽¹⁵⁾ .
Anticoagulants-warfarin	Use during trimester produces defects like nasal hypoplasia and depressed nasal bridge; termed as Fetal warfarin Syndrome. Use during 2 nd and 3 rd trimester is associated with increased risk of fetal malformations ⁽¹⁶⁾ .

List of some drugs whose use is contraindicated during pregnancy along with the harmful /damaging effects they may produce on the fetus.

RECREATIONAL SUBSTANCES AND PREGNANCY:

In addition to advising pregnant women on the use of prescribed and non-prescribed medications during pregnancy, it is crucial to address the potential risks associated with certain substances commonly used during this period.

Smokingof tobacco:

Smoking during pregnancy can cause prenatal morbidity and mortality. Studies also suggest a relationship between tobacco and pregnancy consistently leads to a reduction in birth weight and various birth defects in the heart, brain, face and miscarriage. Additionally, the offspring of smokers face an increased risk of sudden infant death syndrome (SIDS), placental issues, premature births, and other complications. Informing and encouraging pregnant women to quit smoking is vital due to the significant

adverse effects on the fetus⁽²³⁾. Furthermore, the use of e-cigarettes and other nicotine-containing tobacco products is not recommended during pregnancy. Nicotine, the addictive substance present in tobacco, poses health risks for both pregnant women and developing babies, potentially causing damage to the baby's brain and lungs. Additionally, certain flavorings utilized in e-cigarettes may have adverse effects on the development of the baby.

Caffeine:

Caffeine is the most commonly ingested drug during pregnancy, found in various beverages, analgesics, diet aids, and stimulants. While evidence suggests that moderate caffeine consumption poses little or no risk to the fetus, high doses can stimulate the fetus, potentially increasing heart and breathing rates. Moreover, excessive caffeine intake may decrease blood flow across the placenta and interfere with iron absorption, thereby increasing the risk of anemia⁽²³⁾.

Intake of Alcohol beverages:

Drinking during pregnancy can result in Fetal Alcohol Syndrome, a severe condition with a global incidence of 1 in 2000 live births. Women who consume alcohol during pregnancy face a doubled risk of miscarriage, and the birth weight of babies born to such mothers is often below normal. Fetal Alcohol Syndrome encompasses inadequate growth, facial defects, a small head, mental retardation, and abnormal behavioral development. Factors such as poor nutrition, smoking, drug abuse, genetic predisposition, and low socioeconomic status contribute to the severity of this syndrome⁽²³⁾. Fetal Alcohol Spectrum Disorder (FASD) encompasses a spectrum of physical, mental, behavioral, and learning challenges resulting from exposure to alcohol during fetal development. The specific threshold of alcohol consumption leading to FASD remains unknown, underscoring the recommendation to abstain from alcohol during pregnancy as a precautionary measure. The prevalence of FASD in Australia is uncertain, with suspicions of underreporting. The 2016 National Drug Strategy Household Survey revealed that 25% of pregnant women continued drinking after learning of their pregnancy. Consuming alcohol during pregnancy not only poses risks to the fetus but also

endangers the health of pregnant individuals, leading to issues such as vomiting, dehydration, high blood pressure, nutritional deficiencies, and gestational diabetes⁽²⁴⁾.

Illicit use of Drugs:

The use of illicit drugs like cocaine and opioids during pregnancy can lead to serious complications for both the developing fetus and the newborn. Inadequate fetal growth and a higher incidence of birth defects and premature birth are common outcomes. Cocaine, for example, crosses the placenta, constricts blood vessels, reduces blood flow to the fetus, and can lead to complications such as preterm delivery and premature placental detachment⁽¹⁵⁾.

Conclusions

In India, the easy availability of drugs and inadequate health services contribute to a significant proportion of self-medication with over-the-counter (OTC) drugs. While many OTC drugs can be used during pregnancy under medical supervision, caution is necessary. Aspirin and OTC non-steroidal anti-inflammatory drugs like ibuprofen should be avoided in the last three months of pregnancy due to potential complications. The effects of herbs and dietary supplements on a growing fetus are not well understood, emphasizing the importance of consulting a doctor before using such products during pregnancy. The unique physiological nature of pregnancy poses challenges for treating chronic and acute disorders and managing symptoms associated with pregnancy. Healthcare professionals, including pharmacists, bear the responsibility of providing pregnant patients with accurate and current information regarding the risks and benefits of medication use during pregnancy. Counseling on the risks of teratogens involves accurately identifying exposure, and caution is necessary, especially with substances like ethanol, illicit drugs, and OTC medications. Disease without treatment is more risky than appropriate treatment. We should use drugs well known effect on pregnancy without signs of embryotoxicity. Choosing well-established drugs with a history of use in pregnancy is often preferable, even in the presence of newer alternatives, due to established fetal safety.

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