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"PHARMACEUTICAL ASSESSMENT FOR MATERNAL AND NEONATAL SAFETY: DRUG MONITORING IN PREGNANCY AND LACTATION"

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ABSTRACT

Pharmacovigilance in pregnant and lactating women is a crucial yet often underrepresented area in drug safety surveillance. Due to physiological changes during pregnancy and the potential transfer of drugs to the fetus or infant, this population is at increased risk for adverse drug reactions. Traditional clinical trials rarely include pregnant or breastfeeding women, resulting in limited safety data. However, recent advancements such as the use of real-world evidence, artificial intelligence, and physiologically based pharmacokinetic modeling are helping to bridge these knowledge gaps. Strengthening pregnancy exposure registries, promoting patient-centred reporting tools, and encouraging ethical inclusion of these populations in research are vital steps forward. A collaborative global approach, supported by regulatory reforms and technological innovation, is essential to ensure the safe and effective use of medications for mothers and their children. Ultimately, improved pharmacovigilance will lead to better clinical decisions and health outcomes for this vulnerable group.

KEYWORDS: Adverse drug effect, lactation, teratogenic, pharmacovigilance, foetus, breastfeeding, pregnancy.

1. INTRODUCTION

"Pharmacovigilance plays a vital and indispensable role in clinical research, ensuring drug safety from early trials through post-marketing surveillance. Monitoring safety during clinical trials and after a product reaches the market is essential at every stage of its lifecycle.

Pharmacovigilance is "defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines. India is still in the early stages of pharmacovigilance, and very little is known about the field. Not much has been accomplished in India, despite significant breakthroughs in the field of pharmacovigilance occurring in western nations. Understanding the significance of pharmacovigilance and its effects on the product's life cycle is crucial. This will make it possible to incorporate sound pharmacovigilance practices into the processes and procedures to increase post-marketing surveillance, clinical trial safety, and regulatory compliance.[1]

Adverse Drug Reaction (ADR) regarding Pharmacovigilance reaction to a medicine that is unpleasant and unexpected, and that happens at dosages typically used in humans for illness diagnosis, treatment, or prevention, or for altering physiological performance. A significant adverse or disagreeable reaction brought on by a medication-related intervention that foretells a risk from subsequent administration and calls for prevention, targeted treatment, adjustments to the dosage schedule, or product withdrawal. Any unanticipated, unintended, undesirable, or excessive reaction to a medication that necessitates stopping the medication (therapeutic or diagnostic), altering the drug therapy, adjusting the dosage (apart from small dosage changes), requiring hospitalization, extending hospital stay, requiring supportive treatment, making diagnosis highly difficult, adversely affecting prognosis, or causing temporary or permanent harm, disability, or death. harm that a medication at typical dosages directly causes.[2]

Adverse Drug Event (ADE) Any undesirable outcome that might arise when taking a medication, even if it is not directly related to the treatment. harms brought on by medication-related medical procedures. Medication errors or adverse drug reactions (ADRs) that did not involve an error can cause adverse drug events.[3]

Pregnancy: During pregnancy, physiological changes can affect drug absorption, distribution, metabolism, and excretion. These changes can influence drug safety and efficacy. Pharmacovigilance involves tracking adverse drug reactions (ADRs) to identify any potential risks to the fetus.

Lactation: Medications can be excreted into breast milk, potentially affecting the nursing infant. Pharmacovigilance in this context focuses on identifying and managing any adverse effects that might arise from drug exposure through breast milk.

pregnant women & lactating mother may intentionally or inadvertently be exposed to various prescription drugs for pregnancy and non-pregnancy indications. Priorities in birth-defects research with significant public health implications are established by current use surveys that identify the most frequently used medications during pregnancy.[4] Pregnancy-related studies in the United States and several European nations reveal that pregnant women are frequently exposed to pharmaceutical drugs, including ones with recognized teratogenic potential.[5]

There is, however, a lack of information regarding the safety of a medication used while pregnant and the impact of ADRs on the fetus at the time of marketing. Before a medicine is put on the market, reproductive toxicity studies in animals provide preliminary information about its safety profile when used during pregnancy. These studies are very reliable for identifying a drug's teratogenic potential since very few medications that did not induce teratogenic effects in animals are later discovered to cause teratogenic effects in humans. The findings on hazardous dosages in animals may only be partially generalized to humans due to particular species variations in pharmacokinetic characteristics. Additionally, for ethical considerations, pregnant women usually get excluded from clinical trials in medication development. The significance of continuous assessment of risks in the post-marketing stage is heightened by these variables. Indeed, post-marketing observational studies have found links between a number of regularly used medications and different abnormalities in birth.[6]

Using data from the Swiss national ADR database, this study aimed to present the first update on post-marketing pharmacovigilance data on drug-associated fetal abnormalities

2. IMPORTANCE OF DRUG SAFETY MONITORING IN PREGNANT AND LACTATING MOTHER

Research on drug safety during pregnancy and lactation is mainly ignored.[7] The systematic exclusion of pregnant and breastfeeding women from pharmaceutical research is thought to be made possible by genuine concerns about the possible dangers of exposure to fetuses and infants. nevertheless, this method has significantly contributed to the paucity of safety and pharmacokinetic information available for these groups. Given the typical physiological

changes that occur during pregnancy, which may result in major modifications in medication metabolism with significant safety and efficacy consequences, this lack of information is particularly significant" Pregnancy and lactation medication safety research is becoming increasingly accepted as a public health issue. The Food and Drug Administration of the US (FDA) recently released draft advice that emphasizes the benefits of include pregnant women in safety studies during drug development, especially when it comes to anti-human immunodeficiency virus (HIV) vaginal microbicides.[8]

Given the well-established history of pregnant women's heightened vulnerability to influenza-related morbidity and mortality, the drawbacks of excluding pregnant women from early-stage therapy studies were particularly evident during the 2009 H1N1 influenza pandemic. Later studies have started to guide the best oseltamivir treatment for women who are expecting. However, more thorough and inclusive research on pharmacokinetics and safety might have led to better outcomes for both the mother and the fetus. Here, a distinct illustration of the necessity of medication research during pregnancy and breastfeeding is given, along with a framework for such study.[9]

Pregnant and lactating women constitute a distinct patient population requiring meticulous monitoring due to profound physiological changes that influence pharmacokinetics and pharmacodynamics. Pregnancy induces alterations in drug absorption, distribution, metabolism, and excretion, primarily driven by increased plasma volume, enhanced renal clearance, modified hepatic enzyme activity, and altered gastrointestinal motility. These changes necessitate careful dose adjustments to ensure therapeutic efficacy while minimizing the risk of toxicity. Moreover, the transplacental passage of drugs presents a significant concern, as certain pharmacological agents may exert teratogenic effects, disrupt fetal development, or contribute to adverse pregnancy outcomes, including intrauterine growth restriction, congenital anomalies, or preterm labour. Consequently, drug selection during pregnancy must be guided by risk-benefit assessments, incorporating established safety classifications such as the FDA pregnancy categories or the newer Pregnancy and Lactation Labelling Rule (PLLR).[10]

Lactation further necessitates stringent pharmacovigilance, as many drugs are excreted into breast milk in varying concentrations, potentially affecting neonatal physiology. Given the immature hepatic and renal function of neonates, exposure to pharmacological agents through breastfeeding may lead to accumulation, resulting in adverse effects such as central nervous

system depression, gastrointestinal disturbances, or metabolic imbalances. The decision to administer medication during lactation must therefore consider factors such as the drug's molecular weight, lipid solubility, protein binding capacity, and half-life, alongside the infant's ability to metabolize and eliminate the compound effectively.[11]

Beyond pharmacological considerations, pregnant and lactating women exhibit increased nutritional demands, requiring adequate intake of essential micronutrients such as folic acid, iron, calcium, and vitamin D. Deficiencies in these nutrients, whether due to increased physiological requirements or medication-induced depletion (e.g., enzyme-inducing antiepileptics reducing folate levels), necessitate targeted supplementation to prevent complications such as neural tube defects or maternal anemia. Additionally, conditions prevalent in pregnancy, such as gestational diabetes mellitus, hypertensive disorders, and thyroid dysfunction, necessitate careful therapeutic modulation to optimize maternal-fetal outcomes.[12]

Physiological Changes Affecting Drug Pharmacokinetics

Absorption: Gastric emptying and motility may be altered, affecting drug absorption.

Distribution: Increased plasma volume, body fat, and reduced plasma protein levels can alter drug distribution, leading to changes in drug concentration. Metabolism: Hepatic enzyme activity may be altered, increasing or decreasing drug metabolism.

Excretion: Increased renal blood flow during pregnancy enhances drug elimination, potentially

Potential Teratogenic Effects on the Fetus Some drugs can cross the placenta and harm fetal development, leading to congenital disabilities, growth retardation, or miscarriage. The FDA pregnancy risk categories (A, B, C, D, X) classify drugs based on their potential risks to the fetus.

Impact on Breastfeeding Infants Many drugs can pass into breast milk, potentially affecting the infant's growth, development, and organ function. Infants have immature liver and kidney function, making them more vulnerable to drug toxicity. **(**Ex CNS depressants such as benzodiazepines, opioids, and barbiturates can cause profound sedation, respiratory depression, and failure to thrive, raising concerns about their routine use in lactating mothers. The case of **codeine and tramadol**, where maternal metabolism variations have led to fatal opioid toxicity in neonates, highlights the critical need for individualized risk assessment**).**

Changes in Nutritional Requirements Pregnant and lactating women require higher levels of essential nutrients like folic acid, iron, calcium, and vitamin D. Some drugs (e.g., antiepileptics) may interfere with nutrient absorption or metabolism, requiring supplementation. Ex Dietary counselling and prenatal supplementation.

Increased Risk of Adverse Effects Certain conditions, such as gestational diabetes, hypertension, and preeclampsia, require careful drug selection to ensure maternal safety while minimizing fetal risk. Pain relievers, antibiotics, and anticoagulants must be chosen carefully to balance efficacy and safety.

Clinical Implications Medication Review: Always assess the safety of drugs before prescribing. Dose Adjustments: Some drugs require dose modifications due to altered metabolism and clearance. Alternative Therapies: In some cases, non-pharmacological treatments (e.g., lifestyle modifications) may be preferred. Monitoring & Counseling: Regular follow-ups and patient education are essential to minimize risks.

3. FDA Pregnancy Risk Categories & Their Role.

The FDA replaced the old danger of conception letter categories with new information in 2015 to give individuals and healthcare providers an improved comprehension of prescription and biological medication labeling. Information submitted to the FDA claims that the prior five-letter system misled doctors and patients and caused them to draw inaccurate conclusions about the letters' actual meanings.[13]

Better patient-specific counselling and well-informed decision-making for expectant mothers seeking pharmaceutical therapy are made possible by the new labelling system. Even though the new labelling is an advancement over the previous format, it typically does not offer a clear "yes" or "no" response. On an individual basis, clinical interpretation is still necessary.

On June 30, 2015, the Pregnancy and Lactation Labelling Final Rule (PLLR) comes into force; nevertheless, there are differences in the deadlines for putting this new information on medicine labels, also called package inserts.

While labelling for prescription drugs approved on or after June 30, 2001, will be gradually phased in, prescription medications submitted for FDA approval after that date will adopt the new format immediately. The PLLR rule does not apply to medications approved before June 29, 2001; nonetheless, by June 29, 2018, the pregnant letter category must be eliminated. The

abbreviated new drug application (ANDA) labelling for generic medications must be changed if the final rule results in changes to the labelling of a reference listed drug. Since the new FDA pregnancy labelling regulations do not apply to over-the-counter (OTC) medication goods, their labels will remain unchanged.[14]

Narrative parts and subsections have taken the place of the 1979-era A, B, C, D, and X risk categories.

Pregnancy (includes Labor and Delivery):
Pregnancy Exposure Registry
Risk Summary
Clinical Considerations
Data

Lactation (includes Nursing Mothers)
Summary of risk
Considerations of Clinical
Data

Females and Males of Reproductive Potential
Testing of Pregnancy
Contraception
Infertility

The Pregnancy chapter will include details on the amount taken, possible hazards to the developing fetus, and registry data that gathers and keeps track of information on the effects of pharmacological or biological product use in pregnant women. Although previously advised, information on the accessibility of pregnancy registries on drug labels has not yet become mandatory. Furthermore, the registers' contact details will be provided. Women are urged to sign up in order to contribute data regarding the impact of biologics or drug use during pregnancy.[14,15]

The previous label's "Nursing Mothers" subsection will be replaced with the Lactation subsection. Known human or animal evidence about active metabolites in milk, medications that shouldn't be taken while nursing, and clinical effects on the baby will all be covered" Additional information includes items like a section on risks and benefits, pharmacokinetic

information like metabolism or excretion, and nursing time to lessen exposure for the infant.[16] When available, pertinent information about hormonal contraception or pregnancy testing before, during, or after medication therapy, as well as how a medication affects fertility or pregnancy loss, will be included under the chapter labeled Females and Males of Reproductive Potential.[17]

FDA Pregnancy Risk Categories Prior to 2015

In 1979, the FDA established five categories of risk (A, B, C, D, or X) to indicate a drug's potential to cause birth defects if used while pregnant. The categories were established by evaluating the risk to advantage ratio and the reliability of the documentation. Risks from prescription medications or their metabolites in breast milk were not considered in these categories. This information was located in the "Use in Specific Populations" section of the medicinal product label.[18]

The former pregnancy categories

Category A

In the first trimester of pregnancy, adequate and well monitored trials have not shown any risk to the fetus (and there is no evidence of risk in subsequent trimesters).

Examples of chemicals or drugs: Folic acid, liothyronine, and levothyroxine

Category B

There are no sufficient and carefully monitored trials in pregnant women, and research on animal reproduction has not shown any danger to the fetus. Examples of medications include amoxicillin, cyclobenzaprine, hydrochlorothiazide, and metformin.

Category C

There are no sufficient and well-controlled studies in humans, and animal reproduction studies have demonstrated a negative effect on the fetus; nonetheless, possible advantages might justify the drug's usage in pregnant women despite possible dangers. Examples of medications are trazodone, amlodipine, and gabapentin.[19]

Category D

Adverse reaction data from human trials or investigative or marketing experience provide positive proof of human fetal risk; however, possible benefits might outweigh the risks in pregnant women. Sample medications: The Losartan.

Category X

Fetal abnormalities have been shown in animal or human studies, and adverse reaction information from marketing or experimental experience has provided positive proof of human fetal danger and it is obvious that the risks of using the medication while pregnant outweigh any potential advantages. Examples of medications include finasteride, methotrexate, atorvastatin, and simvastatin.[20]

4. Commonly Monitored Drugs In Pregnancy / Lactation.

The FDA's final rule, also known as the Pregnancy and Lactation Labelling (Drugs) Final Rule [PLLR], mandates that drug labels now include information about the particular drug in a uniform format.

Pregnancy: Details about the medication's use in expectant mothers, such as dosage and fetal hazards and details regarding the existence of a registry that gathers and keeps track of information regarding the drug's effects on expectant mothers.

Breastfeeding: Details regarding the drug's use while nursing, such as the drug's concentration in breast milk and any possible negative effects on the nursing infant.

Males and females with the capacity to procreate: Details regarding infertility, pregnancy testing, and contraception in relation to the medication. Three additional detailed subheadings—risk overview, clinical considerations, and data—are included in each of the pregnancy and lactation subsections. Over-the-counter, or nonprescription, medications are exempt from the final rule.[21]

Drug Transfer and Metabolism During Pregnancy Medication is frequently needed to manage various conditions during pregnancy. Generally speaking, drugs may be used for the treatment of conditions during pregnancy when the possible benefits outweigh the known hazards. Not every drug or other chemical in the mother's bloodstream transfers to the fetus through the placenta. Certain medications that pass through the placenta may be teratogenic or directly harmful. The fetus may nevertheless be harmed by medications that do not get through the placenta by

1. Restricting placental vessels, which hinders the flow of gases and nutrients
2. Creating extreme uterine hypertonia that causes anoxic damage
3. Modifying the physiology of the mother (e.g., producing hypotension)

Similar to how they pass through other epithelial barriers, drugs diffuse across the placenta. The drug's molecular weight, degree of binding to another material (such as a carrier protein), area accessible for exchange across the placental villi, and quantity of drug processed by the placenta all affect whether and how rapidly a medication crosses the placenta. The majority of medications that have a molecular weight less than 500 Daltons easily pass through the placenta and enter the fetal bloodstream. High molecular weight substances, such as medications attached to proteins, typically do not pass through the placenta. Immunoglobulin G is an exception, as it can be used to treat conditions like prenatal hemochromatosis or fetal alloimmune thrombocytopenia. Although it usually takes somewhere between 30 to 60 minutes for the mother's blood and the fetus's tissues to settle into equilibrium, some medications do not achieve equivalent amounts in the mother's and fetus' circulations.[22]

A drug’s effect on the fetus is determined largely by fetal age at exposure, placental permeability, maternal factors, drug potency, and drug dosage.

Fetal age affects the type of drug effect:

- Prior to the twentieth day following fertilization: Medications used at this time usually have a binary impact, either killing the embryo or having no effect at all. It is improbable that teratogenesis will occur at this point.
- Teratogenesis is most likely to occur during organogenesis, which occurs 20–56 days after fertilization. Drugs that enter the embryo at this point can result in spontaneous abortion, a sublethal gross physiological defect (true teratogenic effect), covert embryopathy (a subtle, permanent metabolic or functional defect that may manifest later in life), or an increased risk of childhood cancer (for instance, when the mother is treated for carcinoma of the thyroid with radioactive iodine). Alternatively, the medications may fail to deliver any noticeable results.[23]
- Teratogenesis is unlikely to occur after organogenesis (in the second and third trimesters), although medications may change the development and functionality of normally developing fetal organs and tissues. Adverse prenatal effects require greater doses as placental metabolism rises.

Drug distribution, metabolism, excretion, and absorption are all influenced by maternal variables. For instance, vomiting and feeling sick may reduce an oral substance's absorption.[24]

The majority of malformations are caused by genetic, environmental, multifactorial, or unidentified factors, and the total rate of significant structural birth abnormalities in the US is about 3%.[25] The overall rate of congenital abnormalities brought on by medicinal medications is hard to estimate. For instance, out of 5504 birth defect cases in one study, only 20% had a recognized cause, and less than 1% of cases with known causes were caused by drugs.[26]

Vaccines During Pregnancy- Immunization works just as well for pregnant women as it does for non-pregnant women. Additionally, during influenza season, all pregnant women are advised to get vaccinated against influenza. It is advised that all expectant mothers receive the tetanus-diphtheria-pertussis (Tdap) vaccination during the third trimester.

Everyone aged 5 and up, including those who are pregnant, nursing, trying to conceive, or may become pregnant in the future, should obtain the COVID-19 vaccine, according to the CDC. There is mounting evidence that the COVID-19 vaccine is safe and effective during pregnancy. According to these findings, the advantages of getting the COVID-19 vaccine during pregnancy exceed any known or possible dangers. For further information, see CDC: COVID-19 Vaccines During Breastfeeding or Pregnancy.[27]

A respiratory syncytial virus (RSV) vaccine was authorized by the US Food and Drug Administration in August 2023 for use in pregnant women between 32 and 36 weeks of gestation, with a warning not to use it before 32 weeks. After prenatal RSV vaccination versus placebo, clinical trials have reported higher incidences of preterm birth, hypertension in pregnant patients, and low birth weight and jaundice in infants; more research is required to assess these possible dangers.

Other vaccines should only be administered when there is a minimal chance of side effects from the shot and the woman or fetus is at high risk of contracting a dangerous infection. During pregnancy, vaccinations against cholera, hepatitis A, hepatitis B, measles, mumps, plague, poliomyelitis, rabies, typhoid, and yellow fever may be administered if there is a significant risk of infection.

Women who are pregnant or may become pregnant should not receive live-virus vaccinations. Subclinical placental and fetal infections can result with the rubella vaccine, which is an attenuated live virus vaccine. However, the rubella vaccine has not been linked to any birth

malformations, and women who receive the vaccine accidentally in the early stages of pregnancy do not necessarily need to be counseled to end their pregnancy based only on the vaccine's potential danger. Another attenuated live-virus vaccine that may infect the fetus is varicella; the risk is greatest between weeks 13 and 22 of pregnancy. During pregnancy, this vaccine should not be administered.[28]

Antivirals During Pregnancy

For many years, several antivirals (such as zidovudine and ritonavir for HIV infection) have been used successfully during pregnancy. Certain antivirals, however, might pose serious dangers to the developing fetus.

An elevated risk of severe COVID-19 is linked to pregnancy. The National Institutes of Health (NIH) in the United States advises using either nirmatrelvir-ritonavir (4) or remdesivir (5), if warranted, for pregnant individuals with early mild to moderate COVID-19. Nirmatrelvir-ritonavir may be used, according to the American College of Obstetricians and Gynaecologists, especially for patients who have at least one other risk factor for severe illness. The NIH advises using baricitinib or tocilizumab, if necessary, for pregnant individuals admitted to hospitals for COVID-19.[29]

Since therapy is most effective when administered within 48 hours of the commencement of the illness, Without awaiting outcomes from tests to confirm the diagnosis, antivirals for influenza ought to get started right away. However, the risk of serious consequences is decreased if therapy is received at any stage of the infection. Although zanamivir and oseltamivir have not been the subject of controlled clinical trials in pregnant women, numerous observational studies suggest that using these medications during pregnancy does not raise the risk of side effects. Baloxavir's safety in pregnant women is unknown, and there are fewer data about peramivir's safety. Health care providers should educate expectant mothers about the warning signs and symptoms of influenza and encourage them to get help as soon as symptoms appear.

Acyclovir (oral and topical) appears to be safe during pregnancy.[30]

Antidepressants During Pregnancy

Because clinical depression at the time of pregnancy is so common (7 to 12% in one analysis), antidepressants particularly specific inhibitors of serotonin reuptake (SSRIs), are

frequently taken during pregnancy (6). Pregnancy-related physiological and psychological changes may have an impact on depression (making it worse) and perhaps lessen the effectiveness of antidepressants. Depression during pregnancy should ideally be managed by a multidisciplinary team that includes a psychiatric professional and an obstetrician. At every prenatal visit, pregnant women on antidepressants should be questioned about their depression symptoms, and the proper fetal testing should be performed. It could consist of the following[31]:

A detailed evaluation of fetal anatomy during the second trimester.

Because paroxetine has been linked in certain studies to an increased risk of congenital cardiac defects, echocardiography is used to assess the fetus's heart if the pregnant woman takes it.

Clinicians should think about reducing the dose of all antidepressants to the lowest effective dose throughout the third trimester in order to lower the neonate's risk of experiencing withdrawal symptoms. The advantages of tapering must be carefully weighed against the possibility of postpartum depression and symptom return. Postpartum depression is widespread, frequently goes undiagnosed, and needs to be addressed right away. Seeing a psychiatrist and/or social worker on a regular basis could be beneficial.[32]

Commonly Monitored Drugs in Pregnancy

Drugs used during pregnancy must be carefully selected to minimize risks to the developing fetus. Some categories of drugs that require close monitoring include:

Drug Class	Examples	Potential Risks
Antibiotics	Tetracyclines, Fluoroquinolones, Sulfonamides	Teratogenicity, fetal bone/tooth discoloration, kernicterus
Antiepileptics	Valproate, Phenytoin, Carbamazepine	Neural tube defects, cognitive impairment, fetal hydantoin syndrome
Antihypertensives	ACE inhibitors, ARBs, Beta-blockers	Fetal renal dysfunction, growth restriction, neonatal hypotension
Antidepressants	SSRIs (e.g., Paroxetine), TCAs	Risk of congenital heart defects, withdrawal symptoms
Anticoagulants	Warfarin, Heparin	Warfarin embryopathy, bleeding complications
NSAIDs	Ibuprofen, Aspirin, Diclofenac	Premature closure of ductus arteriosus, oligohydramnios
Diabetes Medications	Insulin, Metformin, Sulfonylureas	Neonatal hypoglycaemia, macrosomia (with poor control)
Hormonal Medications	Estrogen, Progestins	Congenital abnormalities, feminization of male foetus
Thyroid Medications	Levothyroxine, Propylthiouracil (PTU), Methimazole	PTU preferred in 1st trimester (methimazole risk of aplasia cutis), hypothyroidism

Commonly Monitored Drugs in Lactation

Many drugs can pass into breast milk, affecting the newborn. These drugs require monitoring based on their transfer rate, half-life, and infant metabolism.

Drug Class	Examples	Potential Risks to Infant
Antibiotics	Metronidazole, Tetracyclines, Chloramphenicol	GI disturbances, bone development issues, Gray baby syndrome
Antidepressants	Fluoxetine, Sertraline, Amitriptyline	Infant sedation, irritability, poor feeding
Anticonvulsants	Phenobarbital, Carbamazepine, Valproate	Drowsiness, poor sucking reflex, hepatic toxicity
Analgesics	Codeine, Tramadol, NSAIDs	Respiratory depression (opioids), bleeding risk (NSAIDs)
Hormonal Contraceptives	Estrogen-containing pills, Progestins	Possible reduction in milk supply (estrogen)
Beta-Blockers	Propranolol, Atenolol	Bradycardia, hypotension
Diuretics	Furosemide, Hydrochlorothiazide	Reduced milk production, electrolyte imbalances
Antithyroid Drugs	Methimazole, PTU	Hypothyroidism in infants

5. Monitoring and Risk Assessment Strategies

Therapeutic Drug Monitoring (TDM) in Pregnancy & Lactation

Therapeutic drug monitoring (TDM) is a particular clinical pharmacology technique that uses drug serum concentration measurements, interpretation, and close collaboration with doctors to track therapy. Pregnancy exposes almost all expectant mothers to some kind of medicine. Teratogenic effects were found to be significantly correlated with maternal or umbilical cord concentrations of some medications, but not dose. Because of this, TDM in the mother during pregnancy is more useful than the prescribed dosage for calculating and potentially avoiding the teratogenic risk of these medications on the fetus. Information about the transplacental transit of most drugs is still lacking, however. As a more accurate surrogate marker for fetal exposure, it was said that analytical models should also consider the type and dosage of medicines as well as the levels of those drugs in the mother and the newborn after birth. It is advised to measure the umbilical cord/maternal serum drug level ratio during birth in order to evaluate transplacental transfer. A significant interindividual variation in the impact of pregnancy on the kinetics of certain medications was also noted, along with the decrease in plasma concentrations during pregnancy. Therefore, to maximize treatment for women taking these medications during the time of instable kinetics, regular TDM is required during pregnancy and after delivery. Only a small number of studies have actually evaluated the blood levels of the newborns, and there is still a dearth of information regarding the transfer

of medicines to milk and the risk of exposure to breastfed infants. It was stated that, above all other calculations, the monitoring of breastfed infant concentrations seems to be the most pertinent approach for analyzing drug exposure in breastfed infants (particularly in those with certain clinical issues like sedation, poor suckling, and life-threatening rashes).[33]

Why is TDM Important in Pregnancy & Lactation?

Pregnancy-related changes in maternal physiology can potentially affect how well therapeutic medications are absorbed, distributed, and eliminated by expectant mothers. Examples of these physiological changes include increases in extracellular fluid space, total body water, and plasma volume. decreased plasma albumin content; compensatory respiratory alkalosis; elevated cardiac output accompanied by variations in regional blood flow; elevated renal blood flow linked to enhanced glomerular filtration; modifications in the enzymes that the liver uses to metabolize drugs; and alterations in gastrointestinal function. The third trimester of pregnancy is when these changes are most noticeable, however they start in the early stages of pregnancy. Additional changes to the mother's physiology take place throughout the postpartum period; some of them return to normal within 24 hours after delivery, while others take 12 weeks to do so. Pregnancy-related pharmacokinetic investigations are necessary because of these physiological changes.[34]

How is TDM Performed?

1. Blood Sample Collection.

2. Laboratory Analysis High-Performance Liquid Chromatography (HPLC) or Mass Spectrometry is used to measure drug levels.

3. Dose Adjustments Based on drug concentration, dose modifications are made to maintain safe and effective levels.

Physiological Change	Impact on Drug Metabolism
Increased Blood Volume (~50%)	Dilution of drugs, reducing plasma concentration.
Increased Renal Clearance (↑ GFR)	Faster elimination of renally excreted drugs (e.g., antibiotics, digoxin).
Increased Hepatic Metabolism	Faster breakdown of drugs metabolized by the liver (e.g., anticonvulsants).
Decreased Plasma Proteins (Albumin)	Higher free drug levels for protein-bound drugs (e.g., phenytoin).

TDM helps adjust drug doses to compensate for these changes and prevent treatment failure or toxicity.[35]

Benefits of Therapeutic Drug Monitoring (TDM) in Pregnancy & Lactation

Therapeutic Drug Monitoring (TDM) plays a crucial role in ensuring the safety and efficacy of medications taken by pregnant and breastfeeding women. Due to physiological changes in pregnancy and the risk of drug transfer into breast milk, careful monitoring of drug levels is essential.

1. Ensures Maternal Safety & Therapeutic Effectiveness

Pregnancy significantly alters drug absorption, metabolism, and elimination, which may lead to subtherapeutic drug levels or toxicity. TDM helps adjust drug doses to maintain optimal therapeutic effects while avoiding side effects. Example Antiepileptics (Lamotrigine, Carbamazepine): Pregnancy increases metabolism, lowering drug levels, which may cause breakthrough seizures. TDM helps adjust dosing accordingly.

2. Prevents Fetal & Neonatal Drug Toxicity

Some drugs cross the placenta and can cause fetal malformations or toxicity if levels are too high. TDM ensures that only the necessary amount of drug reaches the fetus, reducing teratogenic risks. Example: Warfarin: High doses are teratogenic (causing fetal warfarin syndrome). Monitoring INR ensures safe dose adjustments to prevent bleeding risks.

3. Reduces the Risk of Neonatal Withdrawal & Drug Accumulation

Some medications pass into breast milk, potentially leading to drug accumulation in the infant. TDM helps monitor drug levels in breast milk to prevent neonatal toxicity or withdrawal symptoms after birth. Example: Opioids (Morphine, Methadone): High maternal doses can lead to neonatal withdrawal syndrome (NAS). TDM helps adjust dosing to minimize withdrawal risks in newborns.

4. Optimizes Drug Dosing in High-Risk Medications

Certain drugs have a narrow therapeutic index (NTI), meaning that small changes in dosage can result in either toxicity or treatment failure. TDM ensures precise dose adjustments for drugs with NTI, balancing safety and efficacy. Example: Lithium:-Used for bipolar disorder, but excessive levels can cause fetal cardiac defects or neonatal toxicity. TDM helps maintain safe levels.

5. Improves Pregnancy Outcomes & Reduces Complications

Proper monitoring ensures stable maternal health, which is essential for fetal growth and development. Prevents preterm labor, fetal growth restriction, or congenital malformations caused by improper drug dosing.

6. Minimizes Drug Interactions & Unpredictable Pharmacokinetics

Pregnancy alters liver enzyme activity, which may lead to drug interactions or unpredictable metabolism. TDM helps adjust doses when multiple drugs are prescribed, reducing adverse effects. Example:- HIV Medications (Antiretrovirals): Pregnancy alters metabolism of protease inhibitors, requiring dose adjustments to prevent treatment failure and mother-to-child transmission.[36]

Limitations of Therapeutic Drug Monitoring (TDM) in Pregnancy & Lactation

While Therapeutic Drug Monitoring (TDM) is a valuable tool for optimizing drug therapy in pregnant and lactating women, it has several limitations. These include technical, clinical, and practical challenges that affect its widespread use.[37]

1. Limited Availability for All Drugs.
2. High Cost & Limited Accessibility.
3. Invasive & Uncomfortable for Patients.
4. Variability in Drug Metabolism & Individualized Responses.
5. Delayed Results & Interpretation Challenges.
6. Drug Monitoring in Breast Milk is Limited.
7. Ethical & Logistical Challenges in Pregnancy Studies.
8. Not Always Necessary for Every Drug.[37]

6. Pregnancy Exposure Registries

A pregnancy exposure registry is an observational prospective cohort of women who are willingly enrolled during pregnancy, before results are known, and who are receiving a biopharmaceutical product or products of interest on the basis of their regular clinical care. In order to systematically gather data on particular pregnancy outcomes and assess their frequency in comparison to a scientifically valid reference population, participants are monitored until the conclusion of their pregnancy or longer.[38] The Food and Drug Administration (FDA) has specific examples of pregnancy registries.

The "why, how, and who" of running pregnancy registries are reviewed in this. It begins by outlining the necessity of pregnancy registries for evaluating the advantages and disadvantages of prescription drugs during pregnancy. We next go over the unique methodological features of these registries, such as their design, research population, pregnant women's enrollment and follow-up, exposure and outcome definition and ascertainment, reference groups, statistical power, and validity concerns. Third, adopting a more practical stance, we outline important operational elements such protocol structure, participant recruiting and retention, data collection techniques, findings release schedule, advisory board function, and global design problems. Lastly, we outline factors to take into account when assessing pregnancy registries.[39]

Pregnant women are often excluded from clinical trials due to ethical concerns. , Many medications lack sufficient safety data regarding their effects on pregnancy and fetal development.

PERs help fill this knowledge gap by collecting real-world data on drug safety in pregnancy.

Pregnancy Registry Objectives

Pregnancy exposure registries are primarily used to collect human data regarding the safety of biopharmaceutical drugs during pregnancy. Specific primary and secondary goals should be defined in a scientifically sound study design for pregnancy registries. The main goal of many exposure registries is to "assess the risk of major congenital malformations" in children born to women who were exposed to a particular substance just before or during pregnancy. Determining if that risk is larger or lower than anticipated is implied in this goal. Registries can evaluate multiple maternal, obstetrical, fetal, and infant outcomes, from pregnancy complications to developmental delays. Moreover, they may provide an opportunity to evaluate not only the safety, but also the effectiveness of drugs, as well as the risks associated with untreated diseases during pregnancy. They can also evaluate the effects of dose and gestational timing of exposure, as well as effect modification by maternal characteristics.[40]

Since the ultimate goal is to inform patients and healthcare professionals about their decisions, it is in the best interests of all parties to begin the registry as soon as possible after marketing authorization, use proactive recruitment strategies (i.e., if possible, broaden the source population to obtain, for example, 1,000 prospective women in 1 year rather than 100 per year for 10 years), analyze the data, and publish the results on a regular basis. More

assurance of relative safety or more accurate quantification relative risks can result from the registry's ability to provide narrower margins of uncertainty around the point estimates as more data accumulates over time.[41]

Assess drug safety – Determine if a medication increases the risk of birth defects, pregnancy complications, or neonatal health issues.

Monitor fetal outcomes – Track birth weight, congenital anomalies, preterm birth, and developmental milestones.

Support healthcare decision-making – Help doctors and patients make informed choices about medication use during pregnancy.

Identify patterns of drug use – Understand how medications are prescribed and taken by pregnant women.[42]

Pregnancy Exposure Registries Work

Enrollment – Pregnant women taking a specific medication voluntarily join the registry.

Data Collection – Information is gathered from medical records, patient interviews, and physician reports.

Follow-Up – Health outcomes of both the mother and baby are monitored throughout pregnancy and after birth.

Analysis & Reporting – Researchers analyse the data to determine any risks associated with the drug exposure.

Enrollment and Follow up

Women should be enrolled at conception and monitored for months after delivery in an ideal pregnancy cohort. For logistical reasons, this sequence is rarely followed, and as a result, pregnant cohorts have some degree of unintentional truncation on both sides of the optimal follow-up. The reason for left truncation is that follow-up can only begin once women become aware of their pregnancy (in patient-initiated registries) or when medical professionals discover a patient's pregnancy (in clinician-initiated registries). Additionally, the enrollment process itself may cause additional delays in inclusion.Right truncation occurs because follow up would end with unknown outcomes when there are losses to follow up or pregnancy terminations without fetal autopsy.[43]

Examples of Pregnancy Exposure Registries

1. FDA Pregnancy Exposure Registry Program
2. Antiretroviral Pregnancy Registry (APR)
3. Mother To Baby Pregnancy Studies
4. European Network of Teratology Information Services (ENTIS)

7. Post-Marketing Surveillance & ADR Reporting in Pregnancy & Lactation

PMS is the ongoing monitoring of drug safety and efficacy after a medication has been approved and marketed. It helps detect rare, long-term, and population-specific adverse effects that were not identified during pre-market clinical trials.[44]

Safety investigations must be carried out after approval because pregnant and nursing women have traditionally been omitted from medication development trials. In order to identify trends and possible future prospects, this study assessed the FDA's Post Marketing Requirements for pregnancy and lactation studies from 2007 to 2020. The number of new medications approved within the same time period was compared to the number of studies that had to be carried out in the post-marketing environment. Drugs that were authorized for use in postmenopausal women, men, or children were not included in our analysis. The number of pregnancy and lactation studies that must be carried out after clearance has increased since 2007. Just 16% of medications that might be used in women with the capacity to procreate, however, had a post-marketing requirement for a pregnancy and/or lactation research. Pregnancy registry studies accounted for 37% of all required pregnancy safety studies, followed by descriptive pregnancy safety studies (27%), and retrospective cohort studies (26%). In conclusion, more thorough data collecting on pregnant and lactating people is required in order to better educate patients and prescribers about the safety of using medications during these times so that they can make well-informed decisions.[45]

With over 20 biopharmaceutical member businesses, TransCelerate BioPharma is a non-profit association dedicated to expediting and streamlining global research and development of novel treatments.7. Biopharmaceutical research and development companies that work on novel drug discovery, development, and manufacturing can become members of TransCelerate. The following objectives guided the formation of the TransCelerate Pharmacovigilance Pregnancy and Breastfeeding Topic Team 10:[46] to map and comprehend the global landscape of guidelines and regulations regarding the use of medications during pregnancy and lactation, and (2) to suggest patient-centered solutions that would make it

easier to create procedures and instruments for efficient adherence to the demands of health authorities.

Globally, including in the US, Europe, Africa, and Asia Pacific, regulatory guidelines and laws were examined for the landscape evaluation. National safety laws and recommendations were based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines and the International Conference of Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards. As part of this effort, a survey was sent to TransCelerate's member companies to gather additional insights on the current gaps, ambiguities and challenges they have encountered in the pregnancy and breastfeeding safety environment. A third-party consultant conducted the survey, compiled responses, and blinded and aggregated the responses before sharing the results with the TransCelerate Topic team. The 35 items on the survey were broken down by interest-related subjects (see Table 1) and permitted both free-text and structured response options. Ninety percent (18 of 20) of the TransCelerate member companies that were questioned at the time responded to the survey.[47]

8. Future Directions in Risk Assessment

Future Directions in Risk Assessment: Improving Drug Safety in Pregnancy and Lactation

Drug safety during pregnancy and lactation remains one of the most complex challenges in clinical pharmacology. Pregnant and breastfeeding women are often excluded from clinical trials, leading to significant gaps in data. As a result, healthcare professionals must often make decisions based on limited evidence. However, emerging technologies and global collaboration are paving the way for more precise and reliable methods to assess drug risks during these critical periods.[48]

One of the most promising developments is the integration of Artificial Intelligence (AI) and Big Data into pharmacovigilance. AI can analyse vast amounts of data from electronic health records (EHRs), insurance claims, and patient registries to detect patterns and predict adverse outcomes. Machine learning algorithms can identify subtle associations between drug exposure and complications such as birth defects, preterm labor, or neonatal withdrawal syndromes. Furthermore, natural language processing (NLP) tools can mine unstructured data—like case reports and published research—to extract safety signals that might otherwise go unnoticed.[49]

In parallel, real-world evidence (RWE) gathered from pregnancy registries and population-level data is becoming increasingly important. These registries collect longitudinal data on drug exposure during pregnancy and track outcomes for both mothers and infants. By analyzing such data, researchers can gain insights into long-term safety profiles that clinical trials may miss. Additionally, mobile apps and patient portals now allow pregnant women to report side effects and track medication use in real time, providing valuable patient-centered data.[50]

Real-world Evidence (RWE) & Pregnancy Registries

RWE involves using observational data gathered outside randomized clinical trials.

Types

- Pregnancy Exposure Registries: Voluntary databases tracking medication use during pregnancy and outcomes (e.g., birth defects, preterm birth).
- Healthcare Claims Databases: Analysing insurance or hospital billing data to observe drug use patterns and outcomes.
- Patient-reported Outcome Platforms: Apps or portals where pregnant women can report symptoms, medication use, and experiences in real-time.

Longitudinal Cohort Studies: Long-term tracking of pregnant women and infants to assess developmental outcomes.

Another significant advancement is in the field of **pharmacogenomics**. Genetic differences can greatly influence how a drug is metabolized and how effective or harmful it might be. During pregnancy, understanding these variations becomes even more important, as the body undergoes many physiological changes that can alter drug kinetics. Studying maternal and fetal genotypes can help tailor drug therapies to minimize risks and improve outcomes.[51]

In vitro and in silico modeling are also transforming the way we study drug safety. Placental perfusion models and mammary gland cell lines allow scientists to simulate how drugs cross into the fetus or breast milk, without the need for invasive testing. Physiologically Based Pharmacokinetic (PBPK) models offer computer simulations that mimic drug behavior in the body, taking into account pregnancy-specific changes such as increased blood volume or altered enzyme activity.[52]

Pharmacogenomics & Personalized Medicine

Genetic differences can influence how drugs are absorbed, distributed, metabolized, and excreted.

Types

- Genotyping of Pregnant Women: Understanding how genetic variants affect drug metabolism (e.g., CYP450 enzymes) to adjust dosing.
- Fetal Pharmacogenomics: Studying how fetal genes may impact susceptibility to drug effects.
- Tailored Therapy: Designing drug regimens based on the mother's and fetus's genetic profile to minimize toxicity.

Global collaboration is key to expanding this knowledge base. Initiatives such as multinational registries and data-sharing platforms have made it easier for researchers to access larger and more diverse datasets. This collective approach not only improves statistical power but also helps detect rare adverse effects that might not appear in smaller studies.[53]

Lastly, as scientific methods evolve, so too must our ethical and regulatory frameworks. There's a growing movement to safely include pregnant women in research under carefully monitored conditions.[54] Regulatory bodies are also updating drug labelling requirements to provide clearer, more relevant information about pregnancy and lactation risks.

Together, these innovations hold the promise of a future where decisions around drug use in pregnancy and breastfeeding are guided by robust data, personalized risk assessments, and real-world insights—ultimately leading to better care for both mothers and their babies.[55]

International Collaboration & Data Sharing

Global cooperation enhances research quality and improves safety evaluations.

Types

- Multinational Databases: Shared platforms like the WHO Uppsala Monitoring Centre or EU Pharmacovigilance Databases.
- Public-Private Partnerships: Governments, academia, and pharma companies working together (e.g., IMI ConcePTION project).
- Open-access Repositories: Making pregnancy safety data publicly available for research and meta-analysis.[56]

After the FDAAA was passed in 2007 and the PLLR was passed in 2015, there was a noticeable rise in PMRs connected to pregnancy and breastfeeding. It is helpful to characterize PMRs and PMCs that the FDA requests for pregnancy and lactation in order to pinpoint areas that require more study.[57] Research studies addressing significant issues regarding the safety and effectiveness of medications during pregnancy and lactation can be guided by data from pregnancy and lactation-based PMRs and PMCs.[58]

Post marketing pregnancy and breastfeeding safety studies are crucial in producing vital information to direct the safe use of medication in this group, since interventional clinical trials usually do not allow pregnant and nursing women to participate. Although there are now more regulations requiring these post-marketing safety studies, the difficulties in conducting pregnancy safety studies are exacerbated by the ambiguities and lack of uniformity among international regulations, which ultimately causes a delay in getting this information on medication labels. Therefore, there is still a need for improving pharmacological benefit-risk decisions for women who are pregnant or nursing. Some of these issues are being addressed; for instance, the FDA is required by the recently passed Prescription Drug User Fee Act (PDUFA) VII in the United States to "develop guidance and propose a framework for determining [the] necessity and type of pregnancy post marketing studies, encompassing [post marketing requirements]"[32] Together with the knowledge gained from the COVID-19 pandemic, these initiatives may mark the beginning of a new era in pharmacovigilance research related to pregnancy and breastfeeding. To achieve more harmonization of worldwide rules, regulators, industry, and special interest groups must collaborate. This includes developing creative solutions that may quickly and effectively provide important information on the safe use of medications in pregnant and lactating women.[59]

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