WISELEAF SCIENTIFIC VENTURES



CHAPTER – 4
PHARMACOLOGY OF LACTATION AND THE POSTPARTUM PERIOD: MATERNAL THERAPY, BREAST MILK TRANSFER AND INFANT SAFETY

Dr. Sheryl Cecilia Pinto

Clinical Pharmacist, Department of Nephrology, Father Muller Medical College, Kankanady, Mangaluru.

Sherylcpinto@gmail.com

Abstract

The postpartum and breastfeeding periods involve distinct ethical and medical complications arising from the physiological changes in the mother's body, medication interaction with breast milk, and possible effects on infant health. It is imperative for health professionals to understand these factors in order to provide proper treatment for mothers and minimize the risks for infants. The postpartum period is characterized by physiological changes that might affect drug pharmacokinetics through changes in renal function, liver metabolism, hormonal levels, and body fluid distribution. Drug transfer into breast milk is influenced by such factors as drug molecular weight, the water solubility of the drug, tissue binding, and blood concentration of the drug. It is crucial to consider such factors as the amount of drug ingested by the infant relative to the threshold amount, the infant's age, breast feeding routine, and drug clearance in order to evaluate the safety of any medication for the baby. The medications that are frequently used include analgesics, antibiotics, antihypertensive medications, and antidepressant medications.

Keywords: Breastfeeding, Drug Transfer, Infant Safety, Lactation Pharmacology, Postpartum Period.

1. Introduction

The period following childbirth, also referred to as the postpartum phase, is an essential time in both maternal and infant health, and appropriate pharmacological therapy must be utilized

in treating maternal conditions without compromising infant safety. The postpartum phase starts just after delivery and calls for the changes within the maternal system that ensure the restoration to the pre-pregnancy state. During lactation, more pharmacological aspects need to be taken into consideration since any pharmacological agent might penetrate into the mother's milk and be ingested by the infant. Therefore, it is important to understand the processes of drug absorption during this time period if it is necessary to prescribe medications and avoid adverse effects. Although breastfeeding is associated with the provision of a number of benefits in regards to nutrition, immunology, and development, it is necessary to point out that some postpartum conditions such as high blood pressure, infections, diabetes, problems with the thyroid gland, pain, and psychiatric diseases may need pharmacological treatment [1].

Drug transport within breast milk can be influenced by a number of chemical and biological factors such as the size of the molecule, lipid-based solubility, ionization, protein adherence, and maternal blood concentration levels. However, the degree of drug transfer by itself is not enough to determine the risk for infants since some other factors play a significant role, for example: amount of milk consumed, infant's age and organs' maturity, and drugs' characteristics [2]. Milk-to-plasma (M/P) ratio and relative infant dose (RID) are very important parameters of pharmacology that allow understanding the amount of drug that was consumed in milk. M/P ratio shows the drug concentration in breast milk compared to the concentration of the drug in maternal blood while RID shows the amount of drug that the child takes in contrast to the amount of drug that the mother takes according to the weight. Even though these two parameters give valuable information about the infant exposure to drugs, the safety of the drugs should be evaluated based on their toxicity, therapeutic index, action metabolites, bioavailability, etc [3].

When selecting medications while lactating, individualized approaches need to be adopted especially in the case of mothers with premature infants, newborns, or infants with liver and kidney diseases. Clinical pharmacists are responsible for reviewing prescriptions, detecting drug interactions, assessing exposure on infants, suggesting safer alternatives, educating mothers about potential drug reactions. The decisions should be based on the current evidence-based references on lactation. The chapter focuses on postpartum changes in physiology,

pharmacokinetics, transferring of drugs to breast milk, M/P ratios, RID, medication safety, commonly used therapeutics, therapeutic drug monitoring, and baby exposure assessment [4].

2. Physiological Changes During the Postpartum Period

The postpartum stage involves multiple physiological, endocrine, metabolic, and anatomical changes of the body that take place after childbirth. These changes can contribute to the recovery of the mother, milk production, and influence her response to the actions of medications. In spite of the fact that many of the pregnancy-related changes begin to reverse after the delivery, the degree of recovery varies from one individual to another and from one organ system to another (**Figure 1)**. As a result, the dosages of medications which would be adequate during pregnancy should be evaluated at the postpartum stage. The physiological changes taking place in the postpartum period become important for the processes of elimination of drugs either through the kidneys or metabolization of drugs with the help of the liver. The changes in the blood volume, renal blood flow, plasma protein levels, and distribution of body fluids may lead to the alterations in drug concentration and its elimination. Hormonal shifts can interfere with practical insulin usage, thyroid changes, emotional condition, and metabolic processes [5].

2.1 Hormonal and Endocrine Changes

Once the placenta is delivered, the levels of estrogen and progesterone fall sharply in the bloodstream. The sharp drop in the hormones along with the elevated secretory activity of prolactin leads to voluminous milk production called secretory activation or lactogenesis II. While milk production is under the influence of prolactin, oxytocin is involved in milk ejection by stimulating mammary myoepithelial cells' contraction. Constant suckling promotes the secretion of both hormones and stimulates the production of milk. Changes occurring in the hormonal background postpartum have special implications for medication use. For instance, dopamine agonists can inhibit prolactin secretion and reduce the amount of milk, while dopamine antagonists can cause an increase in prolactin secretion. The same is true for contraceptives that contain estrogen, which can interfere with breastfeeding, especially when taken right after giving birth. Moreover, postpartum also leads to the disappearance of insulin resistance and therefore the adjustment of medications for lowering sugar that will be

particularly indicated for women suffering from diabetes. Thyroiditis after giving birth can manifest itself as hyperthyroidism followed by hypothyroidism and would need some treatment. Levothyroxine is normally safe for breastfeeding mothers [6].

2.2 Cardiovascular, Renal and Hepatic Changes

The cardiovascular systems adaptation process after childbirth includes a gradual return of blood volume, cardiac output, and vascular resistance to normal values. Movement of fluids into circulation together with greater excretion processes is a potential factor influencing blood pressure and cardiovascular pharmacotherapy. Postpartum hypertension, especially after pre-eclampsia or gestation-related hypertension development, requires monitoring and treatment. Labetalol, nifedipine, and enalapril can usually be considered as compatible with breastfeeding if necessary. Renal blood flow and glomerular filtration gradually return to pre-pregnancy level. Some complications, for instance, pre-eclampsia, bleeding, and acute kidney failure, can delay recovery and multipurpose drug elimination. Renally eliminated drugs, such as aminoglycosides and lithium, can require dose adjustment or medicinal product monitoring. Hepatic function also undergoes some transformations in the postpartum period. Liver perfusion, the activity of enzymes, and hormonoregulatory processes are altered. Women who have recovered from HELLP syndrome, severe pre-eclampsia, or acute fatty liver should necessarily be evaluated with respect to hepatic function prior to the prescription of drugs metabolized in the liver [7].

2.3 Changes in Body Fluid Distribution and Drug Response

The increase in plasma volume and body water during pregnancy is gradually reversed after delivery by excessive fluid loss. Changes in the volume of distribution of drugs can affect the plasma concentrations of many drugs, particularly hydrophilic drugs. The volume of distribution (VD) refers to the volume of distribution that reflects the concentration of drugs in the body and plasma. This volume of distribution affects the concentration of drugs after administration of the drug. Changes in the level of binding to plasma proteins, as well as the changes in albumin levels, affect the free fraction of drugs. Drugs that are highly bound to plasma proteins and have a narrow therapeutic index require special attention. The levels of albumin and renal function may alter the interpretation of phenytoin concentrations in blood

and in some patients, measuring free phenytoin is a more correct indicator. Fluid redistribution after delivery may also affect the action of diuretics and antihypertensives and drugs for treatment of heart diseases and, therefore, drug doses must be adjusted according to the clinical state, laboratory data, or organ function [8].

2.4 Physiological Adaptations During Lactation

Lactation occurs via the interaction of mammary epithelial cells with the hormones and local regulators. The mammary alveoli produce milk, transported via ductal systems to the nipple. Breastmilk is made up of water, carbohydrates, fats, proteins, vitamins, minerals, and immunoglobulins. Elements of the breastmilk can change during lactation, which influences the pharmacokinetics of drugs through altering pH of the breastmilk, fat content and protein composition. Lactation is mainly induced by the hormone prolactin and the hormone oxytocin functions to eject milk. Regular and effective removal of milk is crucial for ensuring its production. Medications can interfere with the hormone systems and affect lactation. Drug transfer to breastmilk depends on many factors such as timing of lactation and dose of medication absorbed in the bloodstream or the method of feeding. An equally important factor is the age of a child since babies have low metabolism and poor drug clearance systems. Therefore, drug choice should consider the state of the mother, ability to produce milk, conditions of the infant [9].

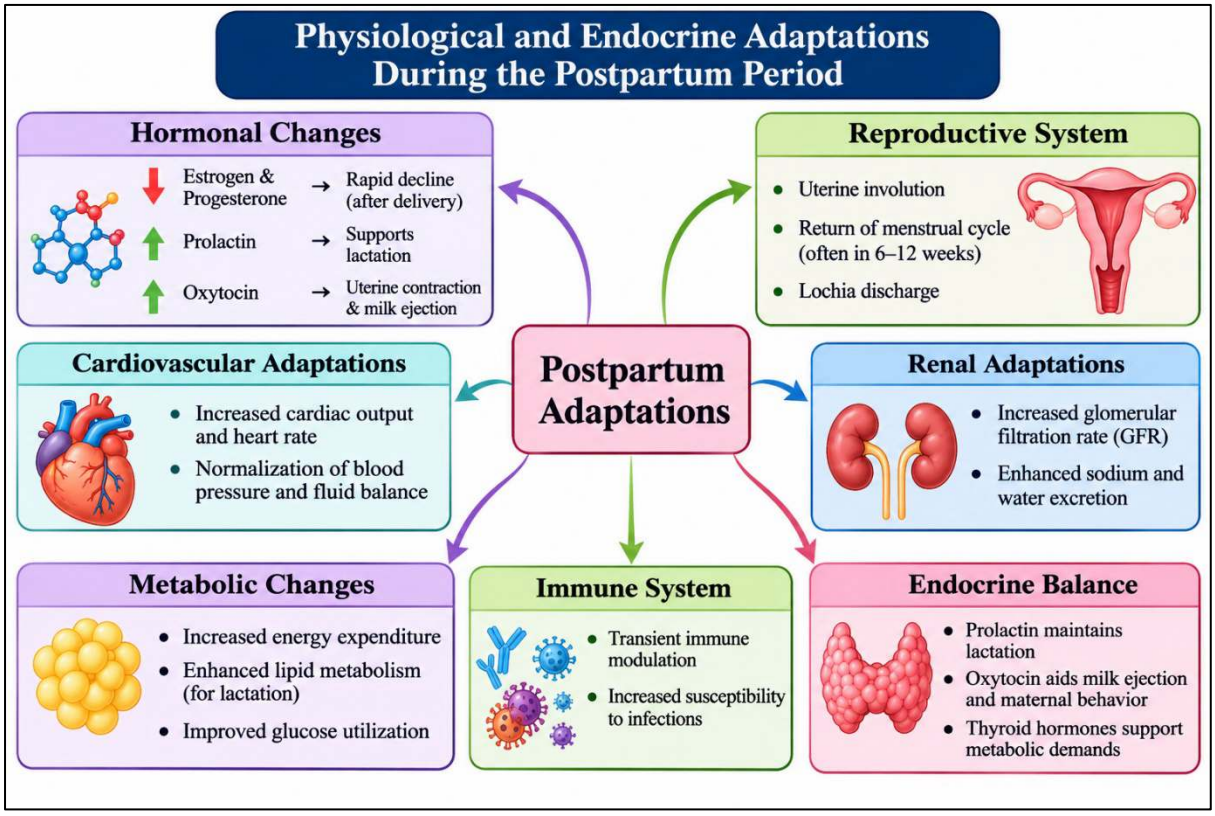

Figure 1. Physiological and Endocrine Adaptations During the Postpartum Period

3. Pharmacokinetics During the Postpartum Period

Pharmacokinetics is the study of the processes of absorption, distribution, metabolism, and excretion, which is abbreviated as ADME. The pharmacokinetics of the mother influence drug concentrations in circulation, which in turn impact the degree of the drug that gets into breast milk. Understanding pharmacokinetics postpartum is crucial for clinicians to know whether the previously used drug treatment needs to be readjusted. The postpartum period is not a homogeneous pharmacokinetic period. There are some physiological changes that resolve in some time while other changes take longer to resolve. The degree of the change depends on the organ system, the mother's medical background, the complications during delivery, and the drug involved in the treatment process. Thus, the dose must be determined based on the evidence and assessment of the individual patient [10].

3.1 Absorption and Bioavailability

The term drug absorption is used to denote the traveling of a drug from the place of administration into general circulation, while bioavailability refers to the amount of dosage entering circulation unchanged. Both processes are determined by the routes and nature of administration, the condition of intestines and liver. Postpartum pain relief drugs are administered for infected wounds, hypertension, chronic diseases, etc. Gastrointestinal capability might be affected by caesarean section delivery, anaesthesia employed, opioids used, nausea, constipation, and limited activity. The above-mentioned factors might influence the drug tolerance and absorption. Nevertheless, there are no significant changes to oral drug absorption in healthy women that suffered from uncomplicated labour. The intravenous administration guarantees total systemic bioavailability and is necessary whenever one needs the drug to be delivered quickly or steadily. Intramuscular and subcutaneous absorption depends on the perfusion and local conditions, while transdermal absorption takes place based on the integrity of the skin and the agent's characteristics. The bioavailability of a drug governs the concentration of the medicinal substance in the plasma. Hence, the concentration of the drug in the plasma allows pregnancy women and mothers breast-feeding to take certain medicines believed to be safe for breast-feeding [11].

3.2 Drug Distribution and Plasma Protein Binding

The term “drug distribution” is used to describe the transport of drugs from the bloodstream to the tissues of the body. Distribution is influenced by the blood flow, tissue permeability, molecular weight, lipid solubility, degree of ionization, and plasma protein binding of drugs. Also, postpartum changes in fluid balance and plasma protein levels may influence the distribution of drugs. Hydrophilic drugs distribute mainly with body water whereas lipophilic drugs will tend to accumulate in tissues with high lipid content. Hence, because of changes in body water and fat distribution the volume of distribution of certain drugs is affected. The binding of drugs to plasma proteins affects the amount of drug available for distribution, metabolism, and excretion. Unbound drugs readily permeate biological membranes; however, ability of the drugs to reach breast milk also depends on their physicochemical characteristics. Drugs having high binding are not completely prevented from entering breast milk. The

concentration of albumin might also affect the value of conventional measurements of plasma drugs. Hence, the drugs with narrow therapeutic indexes need to be evaluated accurately for free drug concentrations, clinical effects, and laboratory results, especially when any postpartum complications affect renal or liver functions [12].

3.3 Hepatic Metabolism and Renal Excretion

Hepatic metabolism of drugs occurs through the formation of metabolites. Hepatic metabolism consists of cytochrome P450 enzymes and conjugation pathways, but is affected by pregnancy, postpartum hormonal changes, degree of liver function, genetic differences, and drug interactions. After delivery, the effects of pregnancy on the enzymes begin to reverse; at different time intervals, different pathways recover. Thus, the assessment of drug metabolism should consider an individual situation rather than the postpartum time only. Some enzymes act as inhibitors leading to increased concentrations of drugs, or they act as inducers leading to reduced concentrations. Renal excretion consists of filtration, excretion, and reabsorption of substances in the kidney. The changes in the kidneys can affect drug clearance which leads to higher plasma concentrations especially in women with impaired renal function. Drugs like certain antibiotics or anticonvulsants sometimes need a dose adjustment based on renal function. Clinical and laboratory evaluations allow predicting drug toxicity or inactivity while using the drugs during the postpartum period [13].

3.4 Postpartum Changes in Drug Clearance and Dosage Requirements

Drug clearance means the amount of fully-cleared plasma of the specific drug in the blood within a certain period. Drug clearance together with Vd affects the duration of elimination half-life. Decreased clearance causes longer drug action, while increased clearance can lower plasma levels and influence the drug effect. Drug doses can vary greatly in the postpartum period. Pregnant women taking insulin usually require less insulin after giving birth, meaning that the insulin doses should be recalculated to prevent possible hypoglycemia. The same is true for kidneys and liver. Postpartum problems, such as acute kidney injury, liver impairment, infection, and bleeding, can interfere with drug clearance and lead to drug accumulation. Thus, it is extremely important to individualize drug dosing according to the patient's clinical condition, laboratory data, and treatments needed. In adjusting doses, it is essential to take into

account the efficiency of treatment and the possibility of exposure of the infant via milk. If the dose is not big enough, it means the treatment is ineffective, while if it is too high, it can result in toxicity [14].

4. Drug Transfer into Breast Milk

One of the most important concepts in lactation pharmacology is the transfer of drugs into breast milk. Once a drug is in the maternal systemic circulation, part of it can get from maternal blood into mammary tissue and then into milk. The amount transferred depends on the physicochemical characteristics of the drug, as well as on several other factors, such as maternal plasma concentrations, the composition of milk, mammary permeability, and the timing of feeds. Just because a drug is present in breast milk does not mean it will cause negative impact on the infant's health **(Figure 2)**. The clinical risk is determined by the amount of drug consumed by the infant, the proportion absorbed by the infant's gastrointestinal system, drug's pharmacological effects, and the infant's ability to metabolize and excrete it [15].

4.1 Mechanisms of Drug Transfer into Breast Milk

Most drugs enter the breast milk primarily through diffusion whereby the unbound concentration of the drug passes across the membranes. Transport of the drug depends on the lipophilicity, molecular size, ionization, protein binding, and membrane permeability of the drug. The lower the size of the molecules, the easier is the passage of biologically active substances through the membranes. Certain lipophilic drugs can easily get into the breast milk in some cases. However, even though these factors are relevant for the process, they cannot give enough information on the concentration of the drug in breast milk. Drug ionization depends on the pKa of the drug and the pH of the substance in the drug. Breast milk is slightly more acidic than the maternal plasma, so the weakly alkaline drugs can be found in the breast milk through ion trapping. In the breast milk, the drugs get more ionized thus preventing them from coming back in the blood of mothers. The extent of ion trapping also depends on the parameters of the drug itself and pH. At the same time, specific transporters can help with the transfer of the drug to breast milk [16].

4.2 Factors Affecting Drug Passage into Milk

Various physiochemical and physiological factors impact the transfer of a medication to the breast milk. The molecular weight is a determinant for the permeability of the membrane; smaller molecules are easily absorbed. The diffusion of drugs through membranes is enhanced by high lipid solubility, while the degree of drug binding to the plasma proteins decides how much free drug is available for the transfer. Drug distribution depends also on the ionization and pH values, as weakly basic drugs may be trapped in the milk. The maternal blood concentration is yet another contributing factor that regulates the total amount of the drug that enters the milk. Along with half-life and metabolites, the timing of the drug-related transfer into the milk must be known. Drugs with long half-lives will provide continuous exposure for the infant. The state of lactation will determine the milk composition. Lastly, the milk feeding frequency and volume will be determinant. All these factors must be assessed together with the infant's age and organ maturity and drug-specific safety evidence [17].

4.3 Maternal Plasma Concentration and Milk Drug Levels

Maternal plasma levels is a significant factor in drug passage to breast milk. Following the medication, plasma levels increase through absorption, peak, and decrease through distribution and elimination. Milk level is probably going to follow the same trend but at a different time and at a different level depending on the type of medication. Drug passage occurs with a different speed according to tissue distribution, elimination half-life, etc. Therefore, a single sample of milk does not reflect real exposure of the infant to the drug. It is necessary to sample milk multiple times to find the average level during the time. What infant intakes depends on milk level and amount of milk consumed. Other processes which take place in the body such as absorption through the gastrointestinal tract, first-pass metabolism, distribution, and elimination also influence the amount of the drug absorbed by the infant. Thus, it is important to consider maternal plasma and milk levels of the drug as well as the infant’s age, health condition, and pharmacological properties of the drug before deciding whether the medication is safe to use while breastfeeding [18].

4.4 Physicochemical Properties Influencing Drug Transfer

The physicochemical characteristics of a drug affect its movement through the mammary epithelial membrane and distribution from maternal plasma to breast milk. These

characteristics include molecular weight, lipid solubility, pKa, and ionization as well as protein binding. Lipid solubility means that lipophilic drugs cross the cellular membrane easily due to passive diffusion, however, the accumulation in different tissues prolongs drug exposure. pKa and ionization influence the degree of drug dissociation or unionization at certain pH. Unionized form crosses lipid membranes more effectively, and using mothers' and milk pH may influence drug distribution. Protein binding means that if the drug is highly bound to protein, its unbound fraction available for diffusion is lower. However, protein binding can't be the only factor in predicting the transfer to the milk. Molecular weight means that for lower molecular weight molecules, the chances for crossing the biological membranes is higher, and bigger molecules have limited transferring capabilities. Elimination half-life means the time of drug presence in the body and influences the time of drug transfer to the milk. For long-acting drugs, infant's exposure to the drug may be prolonged, especially in case of repeated administrations [19].

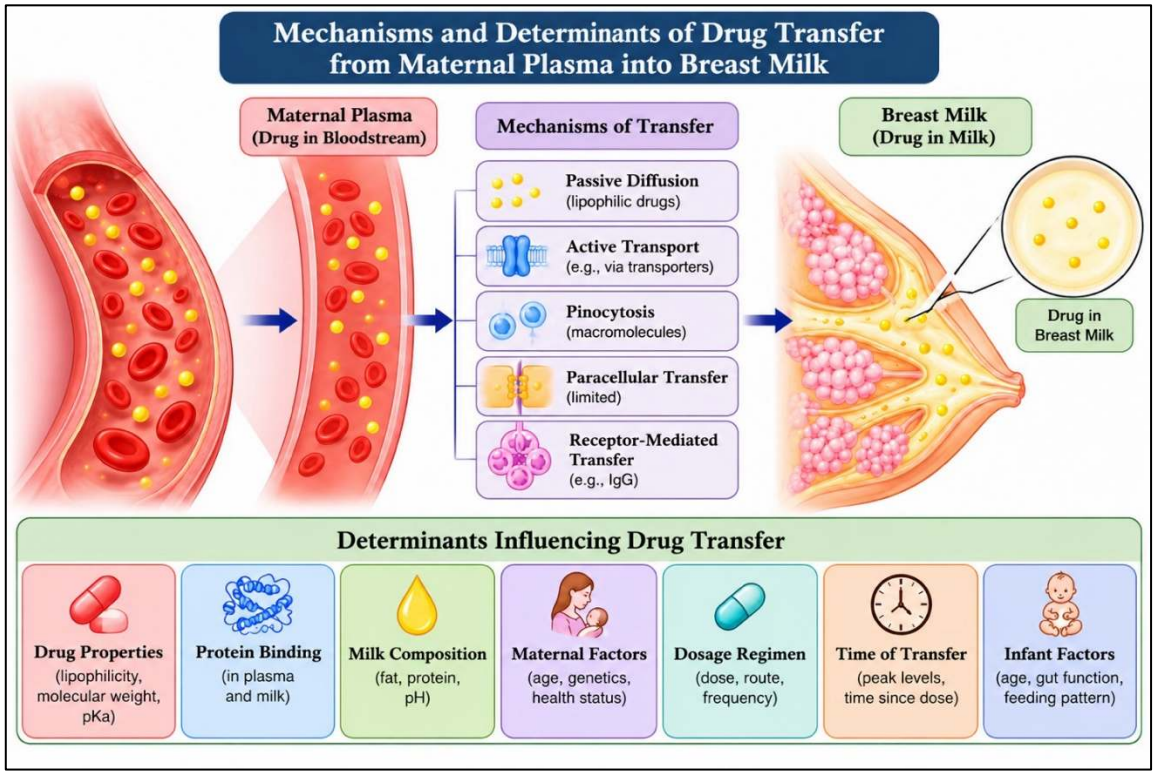

Figure 2. Mechanisms and Determinants of Drug Transfer from Maternal Plasma into Breast Milk

5. Milk-to-Plasma Ratio and Drug Distribution

The milk-to-plasma (M/P) ratio is a pharmacokinetic factor that explains the distribution of a drug in maternal plasma as well as breast milk. This calculation is done by dividing the amount of drug in milk by the amount of drug in plasma. The M/P ratio is influenced by various aspects such as protein binding, lipid solubility, ionization, maternal medication concentration, etc (**Table 1)**. High M/P ratio is not necessarily a result of elevated exposure of infants to a particular drug, since the real dose also depends on maternal plasma levels and infants' milk intake. Hence, when making decisions on the safety of breastfeeding, one should take into account the M/P ratio alongside the relative infant dose (RID), age of the child, oral bioavailability of the drug, and possible adverse reactions [20].

5.1 Definition and Pharmacological Significance

To find the milk to plasma ratio, researchers have to calculate breast milk concentration and divide it by plasma drug concentration.

$$\text{M/P ratio} = \frac{\text{Milk drug concentration}}{\text{Maternal plasma drug concentration}}$$

For instance, if the drug concentration in breast milk is 0.4 mg/L, while its concentration in maternal plasma is 0.8 mg/L, M/P ratio is determined to be 0.5. In general, a ratio smaller than 1 indicates lower breast milk concentration compared to plasma concentration, while the ratio larger than 1 indicates higher breast milk concentration. Thus, a ratio of 1 indicates equal concentrations in both breast milk and plasma. However, the M/P ratio is not sufficient to determine the safety of the drug for the infant. It may differ based on the maternal dose and when the breast milk sample has been obtained. Therefore, concentrations given at different times need to be thoroughly analyzed. In addition, measured averages might give an idea about drug delivery more representative than individual measurements [21].

5.2 Factors Affecting the Milk-to-Plasma Ratio

Multiple pharmacokinetic and physiologic aspects influence the milk to plasma (M/P) ratio.

Lipid solubility: Drug with high lipid solubility crosses the mammary epithelium more easily but is influenced by tissue distribution as well as the composition of milk.

Plasma protein binding: Drugs bound by plasma proteins have less amount of free drug to get passed to lactating mother's milk.

Ionization and the effect of pH: Differences in the pH of plasma and milk can influence the distribution of drugs. Basic drugs accumulate in the milk through ion trapping.

Maternal plasma concentration: Changes in the drug levels in maternal plasma can alter the dynamic between plasma and milk concentration.

Time of sampling: The concentration of milk and plasma can be higher and different points of time leading to different M/P ratios.

Lactation stage: Changes in the permeability of the mammary gland and composition of milk can influence transfer of drugs.

Consequently, the data provides insight on the differences in the M/P ratios for different drugs. Thus, benchmarking has to consider the dosage of the drug, timing of the sampling, lactation stage, and assessment methods [22].

5.3 Interpretation and Limitations of the Milk-to-Plasma Ratio

In spite of the value of the milk-to-plasma ratio (M/P) (M/P) for pharmacokinetics analysis, certain constraints still exist. The ratio does not provide the total quantity of the drug taken by infant and total drug quantity depends on both the volume of feeding and milk concentration. The M/P ratio also does not take into consideration the absorption, metabolism or elimination of the drug by the infant. As a result, the measurable drug transfer does not necessarily mean significant systemic exposure. Further, the M/P ratio is inadequate for predicting drug safety or toxicity. Specifically, a low M/P ratio is not an indication of safety of the drug especially when it comes to drugs with narrow therapeutic indices or serious possible side effects. Likewise, a high M/P ratio does not necessarily mean that breastfeeding needs to be interrupted. Moreover, sampling time, low plasma levels and active metabolites may make calculations difficult. Thus, it is recognized that the M/P ratio needs to be used in tandem with relative infant dose (RID), the drug's toxicity, infant's maturity and available clinical evidence [23].

5.4 Clinical Applications in Medication Safety Assessment

The ratio of milk-to-plasma (M/P) can be used in the analysis of drug transport into the breast milk. Moreover, the M/P ratio offers an opportunity to make correct clinical decisions regarding

the use of pharmaceuticals while breastfeeding. The M/P ratio opens the windows for understanding the degree of distribution of particular drugs between breast milk and plasma and determining whether any medications can be used with caution. The M/P ratio needs to be integrated with the relative infant dose (RID), maternal dose, half-life of the drug, oral bioavailability of the medication, and any potential drug toxicity. If drugs have a narrow therapeutic window and active metabolites, special attention needs to be paid to them. Clinical pharmacists can use this information to recommend alternative medication options and adjust drug dosage and regimen. The infant's age, premature delivery, feeding, liver and kidney functionality are the parameters that need to be considered when selecting medications. Summarizing, the use of M/P ratios in conjunction with clinical judgement helps to achieve the best possible pharmacotherapy results [24].

Table 1. Factors Influencing Milk-to-Plasma Ratio and Their Pharmacological Significance

Factor	Pharmacological influence	Effect on drug transfer into breast milk
Molecular weight	Determines the ability of a drug to cross biological membranes.	Low-molecular-weight drugs generally transfer more readily.
Lipid solubility	Influences diffusion through mammary epithelial cell membranes.	Highly lipid-soluble drugs may enter milk more easily.
Plasma protein binding	Only the unbound fraction is readily available for membrane transfer.	Highly protein-bound drugs generally show lower milk transfer.
Degree of ionization	Depends on drug pKa and the pH difference between plasma and milk.	Weak bases may become ion-trapped in relatively acidic breast milk.

Milk pH	Influences the ionization and distribution of drugs between plasma and milk.	Acid–base differences may promote accumulation of certain drugs in milk.
Maternal plasma concentration	Determines the concentration gradient driving drug transfer.	Higher maternal plasma concentrations may increase milk drug concentrations.

6. Relative Infant Dose and Lactation Risk Assessment

The relative infant dose (RID) is vital in pharmacokinetics as it gives insight into the infants' exposure to certain medications. RID indicates the weight-adjusted dose of drugs delivered to the nursing infant through breast milk as a fraction of the weight-adjusted dose of the mother. RID plays an important part in making it possible to find out the amount of the drug that reaches the infant in the respective milk drink and draws comparisons between the use of different medications; however, it does not provide an accurate estimation of the drug concentration level in the blood of the infant (**Table 2)**. Low RID suggests less exposure of the infant to the medication, which is not equal to higher safety of the drug meaning that RID should be compared to the indices of drug toxicity. It should be noted that a high RID number does not automatically make drugs unsafe for use while breastfeeding [25].

6.1 Definition and Calculation of Relative Infant Dose

The relative infant dose can be calculated by taking the baby's dose from the breast milk and dividing it by the maternal adjusted dose after which you multiply the result by 100.

RID (%) = (Estimated infant dose through milk in mg/kg/day / Maternal dose in mg/kg/day) × 100

The baby dose is obtained from average milk concentration, daily milk intake, and weight of the baby.

Estimated infant dose (mg/kg/day) = Average milk concentration (mg/L) × Daily milk intake (L/day) / Infant body weight (kg)

As an example, let's say that for a certain drug and there is an average drug concentration in the milk of 0.2 mg/L; the baby drinks 0.15 liters of milk in a day and weighs 5 kg. The adjusted dosage for the mother is 0.5 mg/kg/day.

Estimated infant dose = (0.2 × 0.15) / 5

Estimated infant dose = 0.006 mg/kg/day.

If the maternal weight-adjusted dose is 0.5 mg/kg/day, the RID is:

RID = (0.006 / 0.5) × 100

RID = 1.2%.

This would mean that the dose received by the infant represents only 1.2% of the adjusted maternal dose. However, it should be noted that it is not possible to evaluate the safety of the drug only on the basis of RID [26].

6.2 Factors Influencing Relative Infant Dose

Some maternal, pharmacokinetic, and infant-based factors impact the estimated relative infant dose (RID).

Maternal dose and frequency: Higher doses are associated with higher drug concentrations in the milk, while repeated doses may cause drug accumulation.

Concentration in milk: The concentration of the drug in the mother's milk also impacts the estimated dose the infant gets from drinking milk.

Volume of drink: The amount of milk taken has a profound impact on the infant's dose but this is influenced by the age of the infant and feeding habits.

Body weight of infant: The smaller the baby, the dose adjusted for body weight will be greater for the same absolute dose of medication.

Maternal pharmacokinetics: The process of drug uptake, distribution, metabolism, and elimination impacts the concentrations of the drug in the mother's blood and in turn in milk.

Breastfeeding stage: The stage of breastfeeding may also make a difference for the infant exposure.

Formulation of drug: It is possible that the drug is available in both immediate or modified release formulations, causing different release patterns [27].

6.3 Interpretation of Relative Infant Dose Thresholds

Typically used as a benchmark for the assessment in lactation pharmacology, the RID of less than 10% is often considered as an indication of the safety of the drug in question. However, just like the RID threshold itself, this benchmark does not serve as a universal standard for safety. For some medications, the RID of under 10% may mean that the medication can be used due to the fact that it is not associated with any undesirable effects. At the same time, some medications require caution even at significantly lower RID values due to the fact that they can have an adverse effect on the growing infant.

The clinical interpretation of RID includes the following factors to take into account:

1. Drug toxicity and therapeutic range.
2. The presence of active metabolites and possible accumulation.
3. The information concerning the adverse effects of the drug found in infants.
4. The effects of the mother's untreatable condition and advantages of breastfeeding.

Therefore, it is incorrect to use the RID threshold independently from other factors [28].

6.4 Limitations of Relative Infant Dose in Predicting Infant Safety

Despite that the relative infant dose (RID) is relevant in estimating exposure to medication, there are deficiencies. Firstly, it does not measure the amount of drug absorbed; the figures reported indicate the amount of medication reaching the systemic circulation. Thus, the actual exposure of the infant is influenced by the metabolic process as well as absorption in the digestive system. Secondly, the RID does not measure the effect or concentration of the drug in the blood plasma of the baby directly. Even a low value of the RID can lead to harmful effects due to the narrow therapeutic range of the drug. Thirdly, inaccurate measurements of the milk concentration and fluctuations throughout the day may generate inaccuracies in the calculations. Assumed feeding volumes could not correspond to the amount of breastfeeding by a particular baby. Additionally, RID fails to take into account age-related differences in drug metabolism and elimination. This means that newborns and preterm babies might present with immature hepatic and renal functions which would increase the likelihood of drug accumulation. Finally, the lack of history concerning some drugs can lessen the relevance of the calculations performed. Consequently, RID should be used in combination with other information available [29].

Table 2. Classification and Interpretation of Relative Infant Dose in Breastfeeding

Relative Infant Dose (RID)	General interpretation	Clinical significance
Less than 1%	Very low estimated infant exposure	Generally, indicates low exposure, although drug-specific risks must be considered.
1–5%	Low estimated infant exposure	Usually associated with limited exposure; individual drug characteristics remain important.
5–10%	Moderate estimated infant exposure	Requires assessment of drug properties, infant age and potential adverse effects.
Greater than 10%	Higher estimated infant exposure	Warrants careful evaluation and consideration of safer alternatives when appropriate.

7. Maternal Medication Safety During Lactation

Maternal medication safety during breastfeeding is aimed at keeping the mother healthy while minimizing the exposure of the baby to drugs. Several factors should be taken into account when selecting drugs, which include severity of the maternal illness, effectiveness of the treatment, characteristics of the drugs, and risks for the baby **(Figure 3)**. It must also be noted that breastfeeding should not prevent a mother from receiving the required therapy in cases when a lack of treatment may present a danger to the mother and the child. A proper assessment is very important in this case because medication safety is influenced by factors such as the prescribed dose of the medicine, its properties, infant's age, degree of infant maturity, feeding quantity, and infant's health condition [30].

7.1 Principles of Safe Prescribing During Breastfeeding

The concept of safe prescribing while breastfeeding starts with determining the clinical reason for initiation of the treatment with drugs and the need for medication. If medication is needed, it is up to clinicians to pick a drug with effective pharmacological properties. The use of drugs

with proven safety in lactation is generally preferable to the use of their equivalents unless there are reservations regarding treatment efficacy.

The following principles support the logic for drug prescribing:

1) Only when indicated by the clinical case;

2) The use of effective drugs with established safety profile is preferred;

3) The dose applied must be effective but as low as possible;

4) The half-life and dosing interval of the prescribed drug as well as its route of administration should be taken into account;

5) Maternal renal and hepatic function should be assessed if needed;

6) Infant age and health condition including degree of prematurity must be taken into account;

7) Drug interactions, prescription medication, and supplementation must be checked;

8) Monitor the effectiveness of the therapy applied to the mother and infant.

These principles should be taken into account in the light of clinically accepted standards and drug-specific lactation materials [31].

7.2 Benefit–Risk Assessment of Maternal Pharmacotherapy

Benefit/risk assessment requires that the therapeutic benefits of drug therapy to the mother be compared against the risks to the child via breast milk. The assessment must also take into account the repercussions of not treating maternal illness as well as the advantages of breast-feeding. Important parameters to be considered in the evaluation include severity of disease, duration of treatment, toxicity of drugs used, availability of alternative therapies, as well as estimating exposure to drugs by infants. Hence, breastfeeding alone is not a justification for withholding drug therapy. For instance, if the maternal bacterial infection is not treated, it will progress and pose significant danger for the mother. Antibiotics should be selected depending on the disease and microbiological findings though lactation safety. Likewise, if left untreated, postpartum depression may lead to negative consequences in functioning of the mother, her emotional state as well as mother-child relationship. Proper psychological treatment and pharmacotherapy should be initiated. It is also vital that doctors involve patients in decision-making regarding their treatment [32].

7.3 Drug Interactions and Polypharmacy

Polypharmacy is defined as the concurrent use of multiple medications that might apply to lactating women with chronic illness, postpartum problems, infections, or psychological illnesses. Although the treatment may be warranted clinically, use of numerous medications has a potential for causing negative effects, interactions, and mistakes in medication. Interaction can influence absorption, distribution, metabolism, or elimination of drugs. Inverse relationship between enzyme inhibitors and concentrations of drugs can be established, and enzyme inducers can reduce efficacy of drugs in the body. An additive effect may also be obtained when similar types of drugs are used. For instance, the use of sedatives may contribute to increased sleepiness in mothers and cause worries regarding the baby's exposure to drugs. The use of antihypertensive drugs may also lead to increased reduction of blood pressure or interactions related to anticoagulants and bleeding problems. Therefore, medication reconciliation is of paramount importance to identify duplicate medication, unnecessary medication, and dangerous medication. All healthcare workers should check the drugs prescribed, drugs purchased without prescription, herbs, vitamins, and diet supplements. The interactions affecting the concentration of drugs should also be analyzed based on the relevant evidence instead of relying on guesswork [33].

7.4 Contraindicated and Cautionary Medications

Some drugs cannot be used during breastfeeding because of possible severe toxicity, high infant exposure to the drug, and insufficient safety margin. The decision on their use is made after careful assessment of the need for treatment, vulnerability of the infant, and availability of alternative drugs. There may be some anticancer drugs, radiopharmaceuticals, or some other medicine that requires discontinuation of breastfeeding during treatment. Recommendations are based on the specific drug and its use. Lithium deserves special attention due to the fact that it can be transferred to breast milk putting infants at risk of serious concentration. Each case should be carefully evaluated and monitored. Opioids are also of concern because some ones may make infants sleepy or have respiratory depression especially in case of a high dose or long-term use. Codeine is usually not recommended as it cannot be reliably metabolized and may lead to high concentrations of morphine. Many sedatives, antiepileptics, and

immunosuppressants should also be evaluated individually. The lack of safety data does not mean that the drug cannot be used [34].

7.5 Evidence-Based Medication Selection and Breastfeeding Recommendations

Selecting medications for breastfeeding mothers is based on the pharmacokinetics of the drug, research findings, case studies, and opinions of specialists, as well as characteristics of an individual patient. Reliable sources provide information about the drug's transfer to breast milk and potential consequences of breastfeeding it, alternate treatment options, and monitoring recommendations which are important because mothers who are breastfeeding are often less represented in clinical trials. The decision about the drug choice should also take into account its safety profile, the infant's expected drug exposure as well as the presence of active metabolites in the drug and possible adverse reactions. It is necessary to prioritize the efficacy of the therapy used by the mother. Physicians should provide information about the proper methods of taking medications in addition to signs of possible infant reactions. Depending on the selected medicine, monitoring may include child feeding habits, alertness, weight, development of gastrointestinal symptoms, etc. Laboratory tests may be necessary only for some high-risk medicines [35].

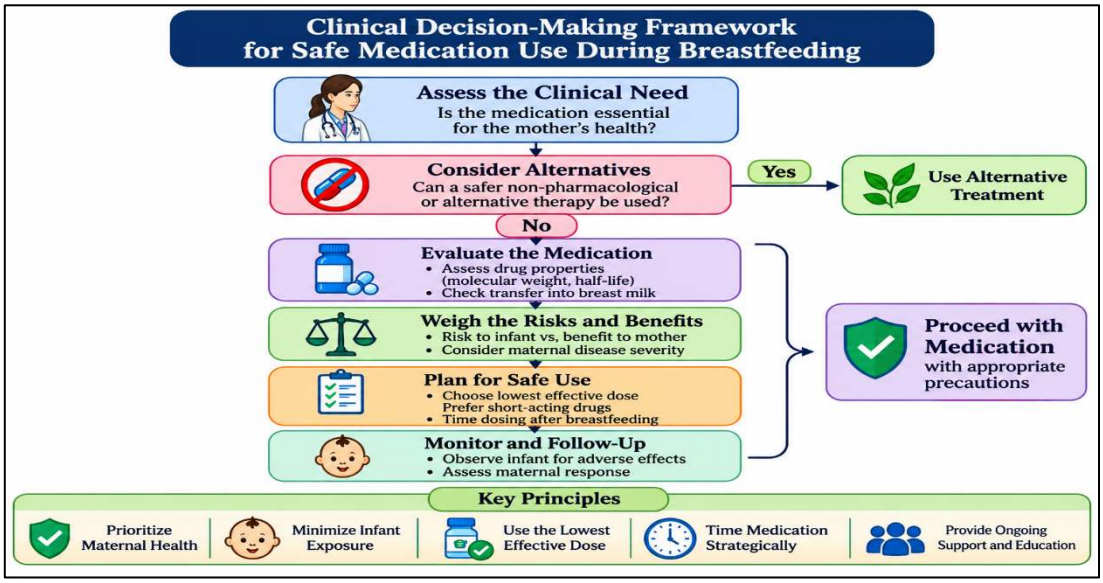

Figure 3. Clinical Decision-Making Framework for Safe Medication Use During Breastfeeding

8. Central Nervous System Drugs During Lactation

Drugs that are part of the central nervous system are prescribed for the treatment of various disorders, including depression, anxiety, bipolar disorder, epilepsy, psychosis, insomnia, and severe pain. Some of these conditions may necessitate continued treatment postpartum when stabilization of maternal mental and neurological function is necessary for recovery and infant care. However, some central nervous system medications may pass into breast milk and result in infant sedation, feeding problems, irritability, or other neurotoxic effects in the infant. The level of risk depends on the medication utilized, the frequency and dose and the pharmacokinetics in breast milk and the infant. It is essential to weigh the risks of treatment and potential exposure to the drug in the infant (**Table 3)**. Hence, it is imperative to provide medication on an individualized basis and not to abandon breastfeeding automatically [36].

8.1 Antidepressants and Anxiolytics

Postpartum depression as well as anxiety is a severe issue which the new mothers may face and, therefore, some psychological help and/or social treatment may be necessary. In general, SSRIs are prescribed to patients. Sertraline is a less-transferred medication during lactation period among others. Some other drugs, like paroxetine, might be prescribed as well, but paroxetine does not transfer much in some cases as well. Nevertheless, deciding which antidepressant to prescribe to the new mother should depend on her treatment history and symptom severity. Those mothers who had been on successful medications before having a baby might not switch to a new drug just for the sake of breastfeeding, as such a decision may lead to relapse. Some drugs might have half-lives longer than usual and active metabolites, which makes prescribing them a more delicate matter. Benzodiazepines might be prescribed to manage anxiety in the new mothers, but prolonged use of those drugs could lead to undesirable effects on the baby. Hence, the prescriber should be careful regarding these drugs and monitor the baby and the mother accordingly [37].

8.2 Antipsychotics and Mood Stabilizers

There might be a necessity of antipsychotics as well as mood stabilizers while treating schizophrenia, bipolar disorder, severe mood disorders and postpartum psychosis. Postpartum psychosis is an emergency of psychiatric nature, and it requires urgent evaluation and treatment since it can have symptoms such as confusion, hallucinations, delusions, abnormal moods and

impaired judgment. Moreover, the choice of antipsychotic drug when breastfeeding should take into consideration the treatment response of the mother, how quickly treatment is needed, pharmacokinetics of the drug regarding milk transfer and the available data about the safety of the drug concerning infants. Certain substances are more easily passed into milk, while some of them have insufficient safety information regarding their use among infants or could lead to sedation of infants. Clozapine should be paid special attention to because of the possible adverse effects on the infant, such as sedation and hematological toxicity. Lithium may also be transferred into breast milk and reach effective infant concentration and thus requires special specialists' assessment. If the treatment involves breastfeeding, it is important to monitor such factors as the amount of lithium in infant blood, kidney and thyroid function of infants, hydration, feeding and weight gain [38].

8.3 Antiepileptic Drugs

Continued treatment and follow-up of epilepsy in the postpartum phase can be critical for safety of mother and child. Seizures need to be controlled fairly well during this time, as sleep deprivation, missing doses of medication, physiological changes, and changes in drug clearance can influence seizure incidence and management. Different antiepileptic medications vary in their transfer to breast milk, protein binding, metabolism, and elimination, and this means that the exposure of the newborn and its possible effects are quite different between medications. Some medications are likely to require additional control due to possible side effects. Lamotrigine clearance in body may rise while pregnant, leading to the decrease of the drug concentration. After delivery clearance returns back to pre-pregnancy level of Lamotrigine clearance, leading to the increase of drug concentrations unless dose adjustment is made. The reassessment of postpartum dosage and drug testing may be needed to ensure effectiveness. Levetiracetam gets into breast milk, too, and a mother may have to assess psychomotor activity of her infant. Valproate, as well as carbamazepine, are appropriate for postpartum treatment in some cases, although the effectiveness of these medications should also be evaluated taking into consideration different factors [39].

8.4 Sedatives, Hypnotics and Opioids

Sedatives and hypnotics can aid in severe insomnia and other disorders while opioids will only be used for serious post-surgical pains and important pain diseases. Such medications should be closely examined rigorously since their central nervous system depressor properties tend to decrease maternal responsiveness with a risk of endangering the baby. Benzodiazepines have different half-life periods, active metabolite types and accumulation ability. Short-term usage of selected drugs is acceptable during breastfeeding but long usage or mixing sedatives causes concern. Babies must be monitored for behavioral changes like time spent sleeping, feeding habits, and reacting to situations. Some opioids provide pain medication along with sedative effects and difficulty in breathing. In every case, proper medication should be chosen and minimum possible doses prescribed. Codeine has to be avoided since gene variation can lead to very fast morphine producing resulting in considerable doses presented to the baby. Tramadol should also be applied with caution. Morphine can also be used if done carefully [40].

8.5 Infant Monitoring and Neurodevelopmental Considerations

Monitoring in infants whose mothers are taking CNS medications should depend on the drug and exposure risk, as well as infant clinical condition. Monitoring should be based on factors including alertness, feeding efficacy, sleep patterns, weight gain, and development progress. Excessive sleepiness and poor feeding indicate negative side effects, while irritability, abnormal muscle tone, odd behavior, and responsiveness changes may require assessment. Still, these symptoms need to be evaluated looking on other circumstances. Long-term neurodevelopmental outcomes are difficult to assess due to impact of maternal illness, genetics, and environmental factors. Furthermore, the report on side effects for various CNS drugs vary substantially, and therefore, limited reporting should not lead to making the conclusion that the drug is safe. If the drug has serious toxicity or little evidence about safety in lactation, clinicians need to figure out if there are drugs available that would be better drug options. Nonetheless, changing stable mother's treatment can provide the risk of relapse. At the same time, coordinated effort of mother, prescribing physician, pharmacist, and pediatrician makes monitoring possible [41].

Table 3. Commonly Used Central Nervous System Drugs During Lactation and Their Potential Infant Effects

Drug class	Examples	Potential infant effects	Monitoring considerations
Antidepressants	Sertraline, paroxetine, fluoxetine	Irritability, poor feeding or sleep disturbances in some cases.	Monitor feeding, sleep patterns, weight gain and behavioural changes.
Anxiolytics	Lorazepam, oxazepam, diazepam	Sedation, drowsiness and impaired feeding.	Observe alertness, feeding efficiency and respiratory status.
Antipsychotics	Quetiapine, olanzapine, risperidone	Sedation, poor feeding and possible extrapyramidal symptoms.	Monitor alertness, feeding, weight gain and abnormal movements.
Mood stabilizers	Lithium, lamotrigine	Lithium may cause toxicity; lamotrigine may occasionally cause sedation or rash.	Drug-specific infant monitoring, including renal and thyroid function for lithium when indicated.
Antiepileptic drugs	Carbamazepine, valproate, levetiracetam	Sedation, poor feeding or other drug-specific adverse effects.	Monitor feeding, alertness, weight gain and relevant laboratory parameters.

Sedatives and hypnotics	Zolpidem, temazepam	Excessive sleepiness and reduced feeding activity.	Monitor infant alertness and feeding behaviour.
Opioid analgesics	Morphine, codeine, tramadol	Sedation, respiratory depression and poor feeding; risks vary by drug.	Monitor respiratory status, feeding and unusual sleepiness; avoid codeine and tramadol during breastfeeding.

9. Antimicrobial Therapy During Lactation

Postpartum women frequently require the use of antimicrobials to treat infections such as endometritis, mastitis, urinary tract infections, and other infections. This treatment is crucial to prevent complications and aid in recovery. During lactation, antibiotic choice will take into account the type of infection, the severity of the illness and allergies of the mother. Most antibiotics pass into breast milk in small quantities making most of them compatible with breastfeeding (**Table 4)**. Nevertheless, some drugs can have an effect on the infant's gastrointestinal system causing outcomes like diarrhea or thrush. So, treatment should be personalized in order to avoid unnecessary exposure in newborns. This underlines the importance of proper care and education of the mother [42].

9.1 Penicillins, Cephalosporins and Other Antibiotics

Breastfeeding mothers can safely use antibiotics like penicillins and cephalosporins in case their babies are not allergic. These antibiotics include amoxicillin, ampicillin, or various city of cephalosporins. Although all antibiotics might end up in the breast milk, the amount is usually too low. However, some infants may experience side effects after exposure, such as gastrointestinal problems, diarrhea, skin rashes, and oral thrush. Antibiotic selection has to be based on the pathogen identified, possible location of infection, and whether bacteria are resistant to medicines. For example, bacterial mastitis requires antibiotics that would be able to kill the bacteria causing the infection. Other types of antibiotics, such as macrolides, tetracyclines, fluoroquinolones, and aminoglycosides, require separate evaluation due to their distinct characteristics. In general, aminoglycosides have low absorption in infants, therefore

the exposure to the drug when breastfed is low. Nevertheless, aminoglycoside use should be based on clinical considerations and the baby's condition [43].

9.2 Macrolides, Tetracyclines and Fluoroquinolones

Macrolides, tetracyclines, and fluoroquinolones are classes of antibiotics that are used in the treatment of various bacterial infections. Macrolides such as azithromycin and erythromycin are regarded as safe drugs to use while nursing, although in some instances an infant may have gastrointestinal disturbances. Tetracyclines have traditionally raised worries about their negative effects on the teeth and bones of the baby. Nevertheless, it has been generally accepted that short-term treatment with doxycycline is unlikely to cause harm because concentrations of the drug in milk and absorption through it are very low. On the other hand, longer treatment with doxycycline or repeated treatments require more caution. Fluoroquinolones, such as ciprofloxacin, may be prescribed for certain infections when clinically indicated. Although there were some concerns regarding cartilage formation in infants, evidence shows that the exposure to the drug through breast milk is not high with certain drugs. The choice of a particular antibiotic should be influenced by the severity of the infection and other therapies available, as well as recommendations regarding breastfeeding or lactation at present. Furthermore, considerations of antimicrobial resistance should play an important role in the choice of the antibiotic [44].

9.3 Antifungal and Antiviral Agents

It is essential to administer antifungal and antiviral medications during breastfeeding in order to treat infections which pose risks to maternal health. Antifungals can be used to treat candidiasis and other fungal infections based on the type of drug, method of administration, systemic absorption and the possibility that the drug may be transferred into breast milk. Generally, topical antifungal therapy provides a lower explanation than orally administered drugs or systemic treatment. The direct contact of infants with the treated areas should be taken into account when deciding on the administration method of antifungal agents. Antivirals may be used for the treatment of infections including influenza, herpes and other viral illnesses. The administration of acyclovir and valacyclovir is usually considered safe for breastfeeding

mothers. The decision on treatment of the lactating mother should depend on the severity of the infection and the condition of the mother [45].

9.4 Drug-Specific Risks and Effects on Infant Gastrointestinal Health

Breast milk provides antimicrobial agents to infants that might influence the development of their gut microbiota. Intensive use of antibiotics disrupts the composition of gut microorganisms and may lead to diarrhea, abnormal bowel movements, and oral and diaper candidiasis. Whether such effects occur depends on the medication, its concentration in the milk, its amount of exposure in infants, and other aspects. Most infants do not present with major conditions after taking antibiotics that are thought to be safe for breastfeeding. Nevertheless, a great amount of vigilance should be exercised by doctors in clinical practice. Some medications can trigger sensitivity reactions in infants. Symptoms of possible complications, such as rashes, diarrhea or blood in the stool should be investigated. Research is still ongoing regarding the effects of maternal antimicrobial treatment on the development of the infant microbiome and the significance of the changes. Hence, the clinicians must not rely on the wrong premise that each change in the infant microbiome leads to harmful effects. Proper antimicrobial treatment, including correct diagnosis, treatment selection, and dosage, might lessen the risks of unnecessary exposure [46].

9.5 Selection of Appropriate Antimicrobial Therapy

When choosing an antimicrobial in the peri-partum period, one ought to assess carefully the maternal infection, severity of clinical condition and potential exposure of the infant to the drug. When applicable, microbiological studies and culture susceptibility tests can help clarify the infectious agent and give directions for completing the treatment. In cases when immediate therapy is needed it may be required to use empirical therapy. Receiving the prescription for the treatment, one has to take into account maternal allergic history, renal and hepatic functionality, previous drug response, drug interactions, and possible antimicrobial resistance. The issue of lactation must also be dealt with in this context. When the drug has equal treatment efficacy, the one which works better in the course of breastfeeding must be chosen. However, efficacy of the treatment must be the priority. Mothers must be well taught about the dosage

and the mode of taking drugs in order to avoid the self-discontinuation of therapies due to breastfeeding concerns [47].

Table 4. Safety Profile of Common Antimicrobial Agents During Breastfeeding

Antimicrobial class	Examples	Potential infant effects	Breastfeeding considerations
Penicillins	Amoxicillin, ampicillin	Diarrhoea, rash and alteration of intestinal flora.	Generally compatible with breastfeeding.
Cephalosporins	Cephalexin, cefuroxime	Loose stools, diarrhoea and occasional candidiasis.	Generally considered compatible with breastfeeding.
Macrolides	Azithromycin, erythromycin	Diarrhoea, vomiting and gastrointestinal disturbances.	Usually compatible; consider clinical context and infant monitoring.
Tetracyclines	Doxycycline	Theoretical concerns regarding effects on developing teeth and bones with prolonged exposure.	Short-term doxycycline use is generally considered acceptable; prolonged or repeated courses require assessment.
Fluoroquinolones	Ciprofloxacin, levofloxacin	Possible gastrointestinal disturbances and alteration of intestinal flora.	Ciprofloxacin is generally considered acceptable when clinically indicated; assess alternatives and infant factors.

Antifungal agents	Fluconazole, nystatin	Occasional gastrointestinal disturbances.	Generally compatible with breastfeeding at usual therapeutic doses.
Antiviral agents	Acyclovir, valacyclovir	Significant adverse effects are not generally expected from milk exposure at usual doses.	Generally considered compatible with breastfeeding.

10. Analgesics and Anti-Inflammatory Drugs

Managing pain is an important component of postpartum care since a mother could suffer from pain after a normal delivery or C-section or either a perineal injury or the procedures done during childbirth. Adequate pain relief improves a mother's recovery, movement, sleeping pattern, and her care for a newborn. Nevertheless, while choosing medications during breastfeeding, a physician has to consider not only the transfer of the medications into the milk but also the possible effect of medicine on the baby. Treatment depends on the degree of pain, the health status of the woman, and the level of functioning of her organs, other medicines administered to her, and the age of a newborn. Non-opioid painkillers should be used whenever possible because they are safer, and pain can be dealt with without them. Multimodal approach of combining different analgesics and non-pharmacological means can promote better pain control with a smaller number of opioids [48].

10.1 Paracetamol and Non-Steroidal Anti-Inflammatory Drugs

Paracetamol (or acetaminophen) is one of the most commonly used drugs for the relief of moderate pain and fever. The activity of this drug is based on its action on the nervous system as part of pain modulation and thermoregulation. Paracetamol is generally believed to be safe for breastfeeding, provided that the drug is used in the recommended doses, since only a small quantity is excreted into breast milk. However, care must be taken by mothers with hepatic disease and those taking paracetamol in various formulations in order to avoid adverse effects of acute overdose. Nonsteroidal anti-inflammatory drugs (NSAIDs) are drugs used for symptomatic pain and inflammation relief by inhibiting cyclooxygenase and decreasing the amount of prostaglandin synthesized. Among NSAIDs, ibuprofen is often preferred by

lactating mothers due to its short duration of action and low quantity excreted into breast milk. This drug is useful in pain relief in the perineal region, uterus, musculoskeletal pain, and post-operative inflammation. The use of other NSAIDs depends on their safety profile. However, when prescribing NSAIDs to lactating mothers, general caution should be applied in the presence of renal insufficiency, gastrointestinal ulcers, bleeding disorders, cardiovascular problems, etc [49].

10.2 Opioid Analgesics and Associated Infant Risks

Opioid painkillers are used for the treatment of moderate to critical pain when other medications are not capable to help. These medicines have analgesic effects acting on the opioid receptors present in the central nervous system which help in pain recognition in the body. The most common medications include morphine, oxycodone and hydromorphone. It should be pointed out that some medications can be transmitted through breast milk and have negative effects on the infants, including sedation, poor appetite and respiratory depression. Newborns and premature babies are especially sensitive to opioids because of their underdeveloped systems of drug metabolism and elimination. It is vital for the medical specialists to prescribe the treatment meeting the achieved medicine, lowest dose of the medication and minimum period of its usage. Morphine is often considered to be a better choice than other types of opioids in the process of treatment, though monitoring of the infant remains important. Codeine should be avoided because of genetic polymorphisms of its metabolism and unpredictable outcomes of usage. Tramadol should be used with care and according to modern recommendations. The signs of unusual sleepiness, difficulty in waking up, refusal to eat and respiratory complications should not be ignored [50].

10.3 Local Anaesthetics and Postoperative Pain Management

Local anesthetics are used for effective pain management during labor and delivery, as well as in perineal procedures and cesarean sections. Their mechanism is characterized by blocking voltage-gated sodium channels in the nerves, thus preventing the passing of pain signals. The most popular anesthetics used for this purpose are lidocaine and bupivacaine. In most cases, the use of local anesthesia does not lead to significant systemic action and is safe for breastfeeding if administered properly. Spinal and epidural anesthesia is conventional for

obstetrics and provides reliable pain relief during and after childbirth. Medical approach for pain control may include anesthetics and painkillers as well as short-term use of opioid drugs when necessary. Regional analgesia decreases the need for opioids and thus prevents the appeared adverse effects. The choice of anaesthesia depends on the type of surgery and on mother's health state, contraindications, and clinical picture. The mother's alertness level must be monitored after the surgery and her ability to take care of the child should be defined [51].

10.4 Multimodal Pain Management During Breastfeeding

The multimodal pain management technique incorporates medications and non-medical methods which operate through different mechanisms to effectively relieve pain. By this strategy, one can decrease reliance on separate analgesics, especially opioids and improve comfort and recovery of women in labor. For instance, a woman after cesarean could have paracetamol and NSAID taken if needed and may receive an additional medication for breakthrough pain. Regional anesthesia and local anesthetic methods should decline the need for systemic medications as well. Non-medical methods which usually include correct position of the body, proper care of wounds and little mobility, and also comfort intervention can also help. Particularly it is necessary for women who are nursing as they should feed the baby in a way that the injury would not be affected, thus making the recovery process go smoother. Regular assessment of pain helps medical staff to evaluate treatment effectiveness and to implement any changes. Poorly controlled pain can disturb mobility, sleep, breastfeeding, and general condition of a woman. On the other hand, too much painkiller sedative can cause danger for a baby. Thus, individualized multimodal treatment provides mothers with recover while helping babies to stay safe [52].

11. Pharmacotherapy for Chronic Diseases During Lactation

Certain chronic illnesses like hypertension, diabetes, thyroid diseases, asthma, epilepsy, and heart diseases may require treatment persistently in postpartum period. The effectiveness of treating of the above diseases is important for mother’s recovery and general health. It is important to note that the physiological changes after delivery may change the effectiveness of drugs used during the period of pregnancy. For instance, a person may need less insulin after delivery. Hence, postpartum drug review is very important as well. When treating the above

diseases, it should be considered how the drugs may get inside the mother's milk. Though many chronic diseases are treated with breastfeeding compatible drugs, it is important to understand the peculiarities in the use and necessity of proper medication to ensure the health of mothers and their babies.

11.1 Antihypertensive and Cardiovascular Drugs

After giving birth, some women may find that they continue to have high blood pressure or develop the condition. A woman suffering from uncontrolled high blood pressure may encounter complications like stroke, which increases the need for the diagnosis and treatment of the health issue. Treatment options consist of medications such as labetalol and enalapril, which may be considered safe in those who are breastfeeding. The choice of medication will depend on a woman's blood pressure, kidney function, pre-existing medical conditions, and contraindications. Diuretics also need to be considered in particular conditions, such as cardiac disease, though the fact that some diuretics can reduce the rate of milk production should be kept in mind. Cardiac disorders such as cardiomyopathy and arrhythmias might need a treatment with beta-blockers or anticoagulants. The decision about the intake of the medication depends on more factors apart from simply having cardiovascular conditions.

11.2 Antidiabetic Agents and Insulin Therapy

The postpartum period presents dramatic alterations in maternal carbohydrate metabolism, as the secretion of pregnancy-associated placental hormones ceases and the insulin requirement systematically declines. For this reason, the treatment has to be reassessed to avoid the occurrence of maternal hypoglycaemia. Lactation leads to the increase in maternal energy expenditure and the change in the blood glucose values of the women who use insulin and any other medications intended for glucose regulation. Hence, it is vital to provide women with specific recommendations regarding glucose monitoring, nutrition, meal schedules, and modifications of therapy. While insulin is generally considered lactation-friendly being a peptide digested in the intestines of the baby and hence limiting the overall absorption of it, metformin is also safe in most cases although special consideration has to be given to the maternal renal function and the condition of the infant. As for other antidiabetic drugs,

assessment of their safety during lactation is required as each drug might be specific in this regard.

11.3 Thyroid Disorders and Hormonal Therapy

Management of these thyroid disorders while breastfeeding is of utmost importance in terms of maintaining the health of mothers and proper functioning of the body. Levothyroxine is the most commonly prescribed medicine for hypothyroid patients, and it is safe for breastfeeding mothers provided the dosage is adequate. In women, postpartum thyroiditis may appear, which means they will go through the hyperthyroid phase at first and then the hypothyroidism stage. The signs of hyperthyroidism include heart palpitations, anxiety, tiredness, weight fluctuations, and others. At times, it can be difficult to differentiate this condition from ordinary postpartum issues, which is why it is important to monitor thyroid function. Antithyroid drugs may also be given to mothers, if necessary, provided the right dosage has been used. As far as contraceptive methods are concerned, it should be noted that progestin-based forms of contraception do not pose any risks for breastfeeding mothers, while contraceptive methods with estrogen may present some challenges associated with low amount of milk produced and higher risk of thromboembolic complications. Contraceptive options are to be selected based on the health of the mother, aspirations, preferences and possible contraindications.

11.4 Asthma and Respiratory Disease Medications

Asthma and other lung diseases may need ongoing treatment during the postpartum period. The control of asthma disease is crucial since uncontrolled lung disease could endanger the health of the mother and her everyday abilities. Inhaled medications such as short-acting bronchodilators and inhaled corticosteroids are thought to be compatible with breast-feeding, as these medications produce very little systemic exposure when used properly. Following proper inhaler technique through diligence is critical for maintaining care of asthma. If an asthma attack is severe, systemic corticosteroids may be used in the treatment. Their use during breast-feeding depends on the individual characteristics of the medication, dosage, length of treatment, and the guidance related to a particular drug. Some respiratory drugs may need more caution to use depending on their pharmacological characteristics. Clinicians need to consider

the severity of the condition, how well the patient responded to the treatment, and alternative drugs before changing the treatment method accordingly.

11.5 Renal, Hepatic and Other Chronic Disease Management

Women suffering from chronic kidney disease, liver diseases, and autoimmune conditions might need the subsequent usage of medications while breastfeeding. The listed medical conditions can have an impact on the processes of drug metabolism, protein binding, and elimination, what necessitates the individualization of medications, aside from the fact that renal impairment is characterized by the accumulation of drugs that are mostly excreted via kidneys in the body. Such drugs may need to be dosed according to the characteristics of the drug and renal function. Hepatic impairment, on the other hand, can also interfere with drug metabolism. In this regard, the regularity of the laboratory checkup must be defined. Immunosuppressive and immunomodulatory drugs might be required for women suffering from autoimmune diseases with the corresponding difference in compatibility of different kinds of drugs with breastfeeding. It is necessary to take into account the characteristics of drugs and the severity of the maternal medical condition while coming up with the appropriate treatment during breastfeeding [53].

12. Therapeutic Drug Monitoring During Lactation

The practice of therapeutic drug monitoring, or TDM, is the process of obtaining biological measurement of drug levels, typically in blood, for the purpose of individualized medication dosing. Therapeutic drug monitoring can be helpful in the case of a medication that has a narrow therapeutic index and variable pharmacokinetics or toxicity related to drug concentrations **(Figure 4)**. During the period of postpartum recovery, some of the physiological changes in renal function, hepatic metabolism, and extent of plasma protein binding may lead to altered drug levels. Thus, the dose that was already prescribed may need to be reconsidered after delivery. Therapeutic drug monitoring may not be used for each drug but is applicable only in cases when measurement of certain drug concentrations is helpful in making the right decisions in treatment.

12.1 Principles and Clinical Importance of Therapeutic Drug Monitoring

Therapeutic drug monitoring may be defined as the process whereby concentrations of drugs in maternal blood are measured at appropriate time intervals with a view to determining how best to maintain effective therapy while minimizing toxicity. Usually, blood samples are taken according to a schedule relative to medication dosing, such as trough concentrations-the lowest concentration before the subsequent dose is administered. Nevertheless, sampling requirements vary depending on the drug and the clinical indication. Result interpretation should consider the dose, dosing interval, adherence to treatment, time elapsed since the last dose, renal and hepatic function, and possible interactions with other drugs. During lactation, this is particularly pertinent when there is a post-partum physiological change affecting drug elimination or when maternal concentrations may be elevated, thus augmenting nursing infant exposure. However, the level of drug in mother's plasma is not in itself an indication of how much drug is transferred into breast milk. Wings have been clipped, except in certain clinical or research situations for which the measurement was indicated. Monitoring should be reevaluated following a dose change, an alteration of organ function, the introduction of interacting agents, or in response to suspected adverse drug effects.

12.2 Drugs Requiring Concentration Monitoring

Some prescriptions of the status of being postpartum may demand monitoring due to their pharmacokinetics and possible side effects.

- Lithium: Lithium has a low therapeutic window and is mainly excreted through kidneys. Changes in renal function, hydration, and medications after the delivery may affect its concentration. It is necessary to constantly monitor the mother, including during breastfeeding.
- Lamotrigine: The clearance of this drug is higher during pregnancy but may drop quickly after the labor. As a result, it is important to monitor its concentration in the blood of the patient.
- Phenytoin: The drug is known to have nonlinear pharmacokinetics and strong protein binding. Given the fact that its concentration may change due to alterations in the albumin level, it may become useful to monitor only free drug concentration in some cases.
- Carbamazepine: This drug needs monitoring only when some changes in seizure control occur, side effects manifest, or during some interactions.

- Digoxin: The careful concentration measuring may be necessary in case of suspicion of toxicity or renal function modifications.

The determination of whether someone needs to be monitored depends on the medication used by them, the health condition, response to the treatment, and the available data.

12.3 Maternal Plasma and Breast Milk Drug Concentrations

Both maternal plasma and breast milk levels of drugs offer different insights regarding drug exposure during breastfeeding. Plasma levels indicate the total drug exposure in the body and thus help in the process of therapeutic dosing. The drug concentration present in breast milk shows the amount of drug in the milk and estimates the degree of possible exposure in the infant. The milk-to-plasma ratio signifies the relationship between drug levels measured in the milk and maternal plasma. However, the milk-to-plasma ratio cannot effectively show the overall amount the infant has consumed. To determine infant exposure, it is important to know milk intake, drug concentration, and infant weight. After this it is possible to derive the relative infant dose rather than know the milk-to-plasma ratio. However, even this process takes into account the need for absorption, metabolism, and elimination of substances after ingestion. Thus, the two processes under discussion should be compared.

12.4 Dose Adjustment and Individualized Pharmacotherapy

Individualized pharmacotherapy means appropriate choice of drugs and adjusting their dosages depending on maternal health condition, pharmacokinetic characteristics, drug response, and sick child exposure. It is known that pregnancy changes in physiology reverse gradually during the postpartum period and this may influence the metabolism of drugs. This leads to the necessity of reconsidering drugs which were previously used in larger doses during pregnancy. Dose adjustment may be needed when renal and liver functions change or new co-administered drugs make their appearance. However, the process of dose reduction shall in no way focus exclusively on lowering the child contamination but also include adequate treatment of the mother. In the case of drugs that are narrow therapeutic index, TDM. In cases of drugs having narrow therapeutic index, the necessity for monitoring them and dosing them individually is more pronounced. Abrupt stopping taking drugs or taking an uncontrolled dosage is to be avoided, especially in order to treat such diseases as epilepsy or bipolar disorder. Decisions on

the treatment have to cope with mothers' needs and safety for the child as well as success of breastfeeding.

12.5 Role of Clinical Pharmacists in Monitoring and Counselling

Clinical pharmacists play a critical role in ensuring the safety of drugs used during lactation by performing medication reviews, therapeutic drug monitoring, and patient counselling. They help in recognizing drug interactions, determining the dosage of drugs depending on renal and liver functions of the patient, and evaluating drug concentrations in the patient's serum. The pharmacists are also able to guide physicians about the medications to be used based on the requirements of the mother and the lactation safety available. They are responsible for educating mothers about the use of drugs, adhering to prescribed medications, monitoring any side effects, and following up with the mothers. The factors that should be considered during medication assessment are the conditions related to both the mother and the newborn. The assessment of the mother consists of drug history, drug dosage, outcome of treatment, functions of organs, and toxicity of the drug. The factors considered during the assessment of a newborn may include age, maturity level, feeding method, and other symptoms related to clinical conditions [54].

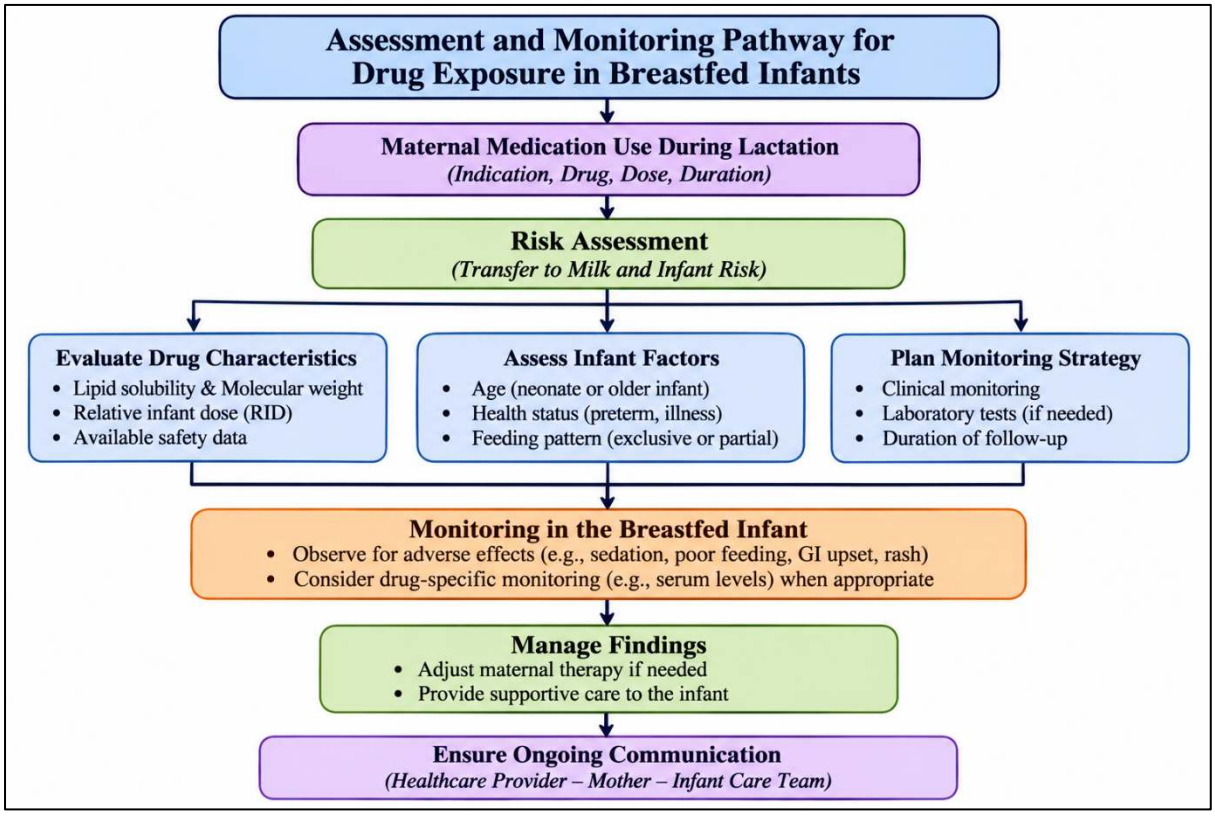

Figure 4. Assessment and Monitoring Pathway for Drug Exposure in Breastfed Infants

13. Infant Drug Exposure Assessment and Safety Monitoring

Assessing drug exposure in infants is a crucial part of prescribing medications to breastfeeding women. This process includes estimating the quantity of drugs present in breast milk, assessing whether or not they are absorbed in babies' bodies, and determine whether any negative effects may appear. Finding a drug in breast milk may not necessarily mean that it will cause harm to an infant. The degree of risk varies depending on the amount of medication that an infant receives, the extent to which it is absorbed, pharmacological features of the drug, and infants' ability to metabolize and get rid of the medication. The age of the infant, gestational age, and health status are also important factors that determine susceptibility to drugs. Making a detailed assessment enables health care providers to identify low-risk exposure levels and decide whether they need further monitoring and treatment alternatives.

13.1 Estimation of Infant Drug Exposure Through Breast Milk

The estimation of infant drug exposure via breast milk follows an average concentration of the drug in milk multiplied by the quantity of milk taken. The estimated infant dose is usually measured in mg/kg/day. For instance, if the average concentration of milk happens to be 0.1 mg/L and if an infant drinks 0.75L of milk daily, the total intake comes to 0.075 mg/day which gives the infant dosage by weight of 0.015 mg/kg/day for a baby weighing 5 kg. It is worth mentioning that this is just an example as it does not represent the exposure brought about by a concrete medication. The estimated infant dose can be compared along a maternal weight-adjusted dose so as to get a relative infant dose (RID). However, while estimating the exposure, other factors such as oral bioavailability, active metabolites, therapeutic index, and the power of drug elimination must be considered. In reference to the particular types of medicines, there may also be measurement of plasma content in the infant which gives a different picture about the exposure from drug intake. Collection of blood is generally considered unnecessary for most breastfeeding infants unless very serious cases of toxicity or symptoms emerge.

13.2 Infant Age, Maturity and Drug Elimination Capacity

The age of the infant and their maturity in development plays a major role in how sensitive they are to effects from medication while breastfeeding. Newborns, especially those born too early, have underdeveloped systems for filtering blood and for metabolizing drugs. These factors might mean the drug stays in the system longer than it would in an older child. The level of development of an infant depends on the time, period, and illness suffered. The process of development in babies takes time. As newborns grow, like everything else, the effectiveness of the drugs improves. However, the time of effectiveness of drugs is different from one another. As such, what is okay for older infants can be dangerous for younger babies. Infants with liver defects might also be more vulnerable to drug effects. Therefore, if a medication is prescribed, a physician needs to take into consideration the age, state of health of the infant, and the drug action.

13.3 Assessment of Short-Term and Long-Term Adverse Effects

It is important to evaluate the short- and long-term effects of drug exposure in breastfeeding babies. The short-term impact of drug exposure can manifest right away, and can involve excessive drowsiness, inability to feed properly, vomiting, diarrhea, agitation, skin rashes and

abnormal respiratory patterns. These symptoms depend on the pharmacological properties of the drugs that were taken but can also depend on the vulnerability of the baby to the drug taken. Nevertheless, these symptoms do not always indicate the influence of the drug since they can be caused by infections, problems with feeding and other factors. Long-term effects should be carefully evaluated since they can affect the baby growth, neurological development, behavior and other developmental parameters. However, the assessment of the long-term effects is complicated due to the possibility of the mother's pathology, the effect of drugs taken during pregnancy, genetic predispositions and environmental factors. In addition, the availability of information regarding long-term safety is quite variable for different medicines. Hence, health professionals need to take into consideration the available clinical data, the necessity for the treatment of the mother and the possibilities for following the baby after birth.

13.4 Clinical Signs of Drug Toxicity in Breastfed Infants

Monitoring is critical in the process of recognizing drug-related complications in infants who are breast-fed. The signs of drug toxicity vary based on the nature of the drug, dosage size, and maturity level of the newborn. General signs of toxicity involve excessive drowsiness, inability to wake up, inability to feed normally, poor weight gain, continuous vomiting, diarrhoea, skin rashes, as well as altered behaviour. Furthermore, neurological manifestation, change in muscle tone, decreased reactivity, and respiratory depression could take place in certain cases as well. Such symptoms are not exclusive to drug toxicity and could relate to other medical problems. Therefore, an appropriate clinical assessment is crucial before establishing a link to drug exposure. Serious breathing problems, extreme unresponsiveness, and inability to feed need immediate care. Mothers should be given the necessary information on what symptoms to be concerned about and what to do in such situations. Individual monitoring needs to take place according to the medication's known adverse effect profile, and the condition of the infant in order to be able to recognize any complications at an early stage and not to put the mother under unnecessary stress.

13.5 Infant Monitoring and Follow-Up Strategies

Monitoring and follow-ups for infants should be specific to the particular properties of the medications given, the expected exposure levels, and the level of maturity of the infant. In the

case of currently known safe drugs used in breastfeeding, monitoring with paediatric follow-ups will be adequate. On the other hand, certain medications may need additional monitoring, which may include laboratory tests, liver and kidney examinations, or measurements of the infant's drug levels. In infants born prematurely or with diseases that predispose them to the adverse effects of the treatment monitoring must be performed more frequently. Monitoring intervals and duration will depend on exposure time frames and characteristics associated with drug release mechanisms and possible toxicology outcomes of the licensed drugs. Good communication among the maternal healthcare provider, pharmacist, and paediatrician is critical for medication with narrow therapeutic index or unknown safety during lactation. The lactating mothers must be informed of the symptoms requiring monitoring [55].

14. Clinical Challenges and Special Considerations

There are various difficulties encountered in the approach to managing medications when nursing mothers consider taking medicine. Numerous medications have been declared compatible for use with lactation; however, some should be assessed cautiously due to the adverse effects of pharmacologic agents that may potentially harm the newborn. The clinician has to decide on the treatment approach to be followed, which is usually a compromise between the need of the mother for therapy and potential adverse effects of the medication on the child. Many parameters impact the medication selection for a nursing mother, including her health condition, treatment dose, age of the infant, and how well baby's body metabolizes drugs. The health workers are responsible for providing evidence-based recommendations, evaluating the pros and cons of individual therapy, and facilitating exchange of opinions among the professionals.

14.1 Medication Use in Premature and Neonatal Infants

Premature and newborn infants are especially vulnerable to exposure to medications via milk lactation due to immature metabolic pathways, liver function, and renal processes. Therefore, even small doses of certain drugs may cause adverse effects in those age groups where the drugs are relatively safe for infants older than one month of age due to narrow therapeutic index or strong respiratory, nervous, or cardiovascular effects. Risks are associated with multiple factors including gestational and postnatal age, organ function, volume of milk ingested, and

infant condition. Medications recognized as safe for breastfeeding older infants require special attention when given to mothers of premature or unstable babies. It is essential for healthcare people to analyse drug properties, available data on potential adverse effects, and possible substitutes before giving recommendations. In case of pregnancies with potentially high-risk medications, the monitoring of infants' state and consulting specialists may be required. Decisions regarding breastfeeding suspension should be taken on a case-by-case basis.

14.2 Maternal Mental Health and Medication Adherence

The role of maternal mental health is crucial for postpartum care because the consequences of mental conditions on a mother's intellectual functioning, sleep quality, caring for an infant, and nursing activities can be considerable. Fears of drug transmission through the milk may motivate some mothers to seek no treatment at all or to reduce the prescribed dosages to dangerously low rates or even give up on the use of medicines contrary to medical advice. These actions may lead only to the increased risk of relapses, progression of diseases, and disruption of motherhood. Doctors should provide information about the risks and benefits of psychotropic medications used during the breastfeeding period. Choice of medication should be dependent on the results of the previous use of medicines, severity of disease, clinical picture, and preferences of a woman. Many psychotropic drugs may be applied during lactation provided that they are chosen properly and monitored regularly. Compliance might be improved with the help of information provided in a clear manner, simple prescriptions, keeping in touch with patients regularly, and cooperation among mental health professionals and maternal healthcare specialists.

14.3 Limited Evidence and Uncertainty in Lactation Safety Data

There is limited information related to medication safety in breastfeeding regarding many drugs. Some medications have well-studied pharmacokinetics and well-established clinical experience, but many medications have insufficient evidence with respect to breast milk concentrations, exposure of the infant, and long-term effects. Performing randomized controlled trials with breastfeeding mothers is often difficult due to ethical and practical issues. As a result, the current state of knowledge is based on observational studies, case series, pharmacokinetic studies, and clinical experience. However, such evidence can be associated

with many limitations, such as small sample size, lack of follow up, inconsistency of reporting, and confounding factors. These limitations mean that the choice of medications proves to be difficult, especially with respect to new medications or those that can cause serious side effects. Therefore, healthcare providers should take time to evaluate the quality of evidence available rather than jump to conclusions about safety or harm with respect to the lack of available information. Various options regarding treatment are also possible, depending on the mother's needs, risks associated with infant treatment, and availability of alternatives.

14.4 Balancing Maternal Treatment and Breastfeeding Continuation

In lactation pharmacotherapy, it is crucial to balance the needs regarding maternal treatment and the need for continuing breastfeeding. Decisions made should take into consideration the extent to which a certain medicine could be passed into breast milk, whether there are any adverse effects for infants, how serious the disease is in an individual, and whether breastfeeding has been proven to be beneficial in respective cases. Many medicines can be taken without ceasing breastfeeding while others can bring up the need to use other medications or to watch over the infant closely. In some cases where toxicity is considerable, breastfeeding needs to be interrupted. If it is recommended to stop breastfeeding, doctors have to explain the reason and time of interruption and whether the expressing and keeping breast milk or discarding it will keep its production active. The moment when breastfeeding is to be resumed should depend on the properties of the respective drug and the exact clinical guidelines [56].

15. Emerging Approaches and Future Perspectives

Recent developments in pharmacokinetic modelling, artificial intelligence, clinical data integration and personalised medicine open up exciting opportunities for improving safety of drugs in lactation. These models allow predicting drug transmission into breast milk, evaluating drug exposure in infants and making the most appropriate decisions regarding the treatment processes **(Figure 5)**. In addition, innovative technologies which have emerged may allow medical workers to foresee possible issues in the process of selection of the right drugs for lactating women. However, the efficiency of these technologies relies heavily on the available clinical data upfront. Therefore, clinical trials with the technologies under examination will

need to be conducted to validate them. It is important that the information gained should supplement the existing pharmacological evidence, guidelines and practitioner's decisions.

15.1 Advances in Lactation Pharmacokinetic Modelling

Pharmacokinetic modelling entails the application of mathematical techniques to forecast the absorption, distribution, metabolism, and elimination of medications. During lactation, pharmacokinetic modelling aids in estimating maternal plasma levels, the concentration of drugs in milk as well as potential drug exposure to the neonate. In particular, PBPK models include physiological characteristics such as the size of the organs of the body, blood volume changes, activity of enzymes, composition of the milk, as well as the metabolism of drugs in the neonate's body system. The models specific for lactation enable the evaluation of drugs for which direct clinical information is lacking. Moreover, these models make it possible to predict the impact of maternal dosage and intervals, physiological changes in the body, and the age of the infant on drug exposure. Such modelling can help clinicians in determining the safety of drugs and selection of treatment. Nevertheless, the application of pharmacokinetic modelling is contingent on the quality of data and formulation of assumptions. As such, the predictions provided by PBPK models need to be corroborated with clinical results.

15.2 Population-Based and Individualized Risk Assessment

By doing population studies, important information is gathered about the effects of drugs and safety patterns of lactating women as well as children. Analyzing large data sets allows to find commonly used drugs, rare negative effects, and differences in reactions to medicines of different groups of patients. Risk assessment for every case can improve the results of studies because specialists take into consideration individual factors, such as the work of the mother’s organs, dosage, the infant’s age, and other health complications. Combining general evidence with individual assessments can help doctors determine which babies need monitoring and which drugs can be taken while breastfeeding. In addition to that, this will allow making safer prescriptions and avoiding unnecessary interruptions in breastfeeding. Nevertheless, it is important to conduct observational studies correctly as their results depend on factors like data distortion and incomplete data.

15.3 Artificial Intelligence in Lactation Pharmacology

Artificial intelligence (AI) is able to boost lactation pharmacology due to integration of information received from drug databases and drug pharmacokinetics studies, clinical data, and scientific literature. Machine learning methods may be useful in discovering patterns linked to drug transfer into human milk, estimating the extent of exposure of infants, and identifying drugs for further analysis. AI-driven clinical decision support system can allow medical professionals to obtain information on drug compatibility, relative infant dosage, potential negative interactions, and infant's drug concentration monitoring. Natural Processing Language methods can also be applied in extraction and systemization of relevant information from scientific papers. On the other hand, despite many advantages AI systems can provide inaccurate results due to unrepresentative nature of training datasets. Algorithmic bias can further disrupt the reliability of AI-generated recommendations. Consequently, careful verification of AI-generated advice with an authoritative lactation reference and also with the clinical guidelines is required.

15.4 Clinical Validation and Future Research Directions

In upcoming studies, it is essential to concentrate on the improvement of evidence related to drug transfer to breast milk, the level of exposure of infants to drugs, and the possible outcomes in terms of health in both short- and long-term perspectives. In order t ensure reaching reliable results in research, it is necessary to implement standardized sampling methods, to make reliable measurements of drugs' concentration, and to employ uniform custom of reporting practices. Moreover, there should be more focus on under-represented populations, such as women suffering from chronic diseases, mothers who take various drugs, and mothers with preterm babies because there may be several differences regarding exposure to drugs in these populations. Long-term studies should be able to help with understanding the long-term effects of the given drug on babies' growth and development. More work should be completed in terms of developing and clinically validating PBPK model, AI prediction tools, and risk assessment procedures in the areas where there is no opportunity to receive evidence to guide us in making decisions regarding the usage of drugs [57].

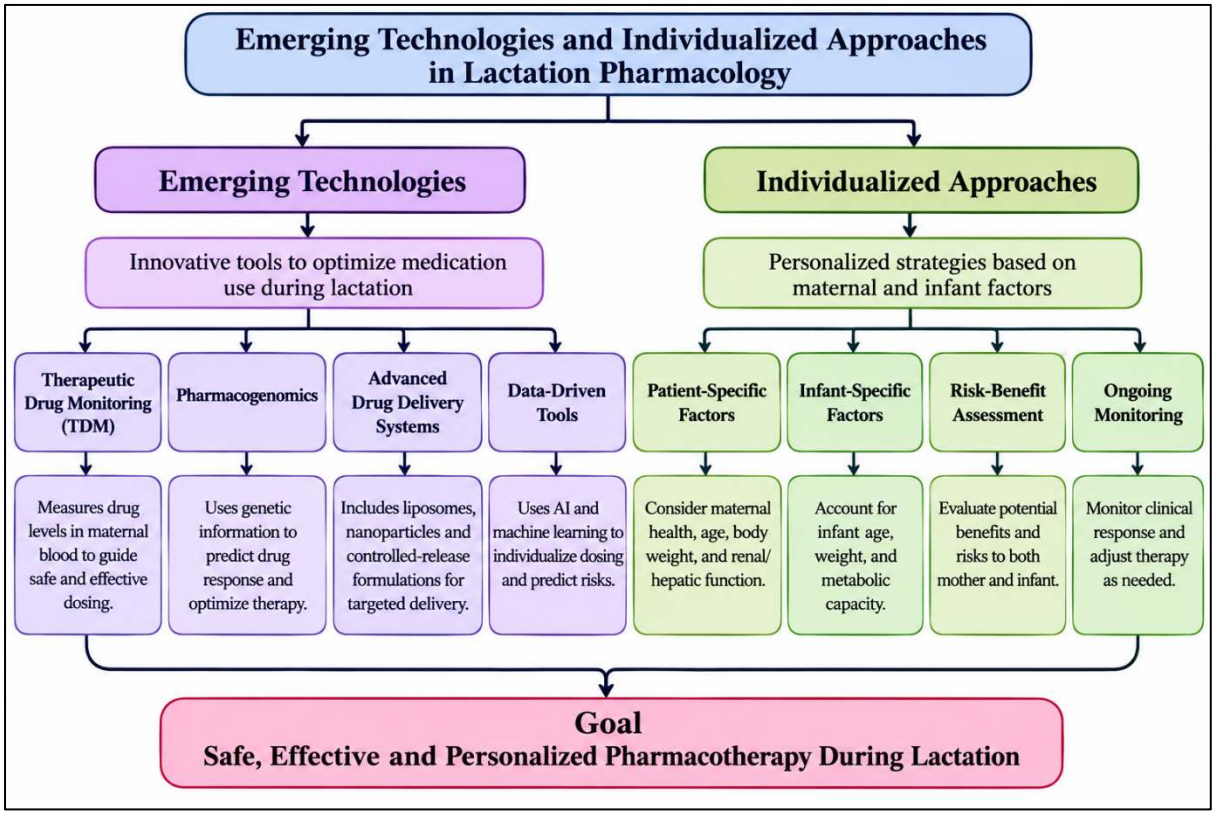

Figure 5. Emerging Technologies and Individualized Approaches in Lactation Pharmacology

16. Conclusion

The process of using medication during the postpartum phase and the breastfeeding period necessitates evaluation of various factors including the physiological systems of the mother, pharmacokinetics of drugs, the extent to which such medicines are transferred to the environment, and how the infant in question can absorb the medications. The effect of childbirth on medication dependency in the mother shows how crucial it is to consider the treatment regimens. The milk-to-plasma ration and the amount of the drug absorbed by the infant are excellent measures of communion of medicine when the mother is breastfeeding. However, these factors on their own do not guarantee the safety of any medication prescribed. Proper therapy in case of maternal medical conditions such as infections, pain, high blood pressure, diabetes, mental problems, and chronic diseases is vital. There are numerous drugs available for breastfeeding women if evidence and safety concerning their use have been

evaluated. Unjustified stop of maternal therapy or cessation of breastfeeding may create new risks. Clinical pharmacists as well as other specialists in the sphere of health care will help to optimize the treatment process by performing medication review and therapeutic drug monitoring. Furthermore, treatment plans should be developed taking into consideration the health condition of the mother, the condition of the infant, and the benefits of breastfeeding. Innovative techniques like physiologically-based pharmacokinetic modelling, personalized exposure analysis and the use of artificial intelligence can enhance the decision-making process in the future; nevertheless, their application must be validated properly and monitored clinically. In general, employing a multidisciplinary and evidence-based approach is important for assuring effective pharmacotherapy for mothers in a manner of minimizing the likelihood of avoidable risks for infants. The primary aim is to enhance mothers' health, ensure a healthy life for infants, and promote breastfeeding when possible.

References

1. Hale TW, Krutsch K. Hale's medications & mothers' milk 2025-2026: a manual of lactational pharmacology. Springer Publishing Company; 2024 Jul 26.
2. Berwick MA, Heuberger AJ, Martin JV, Hale TW, Louis-Jacques AF. Drugs in lactation. In Seminars in Perinatology 2025 Jun 1 (Vol. 49, No. 4, p. 152077). WB Saunders.
3. Otieno D, Ojara FW, Richardson N, Waitt C, Zhao P, Hartman D. Treating pregnant and lactating women: insights from clinical pharmacology. Annual Review of Pharmacology and Toxicology. 2026 Jan 23;66(1):191-210.
4. Kepley JM, Bates K, Mohiuddin SS. Physiology, maternal changes. InStatPearls 2023 Mar 12. StatPearls Publishing.
5. Wu X, Jin R. Effects of postpartum hormonal changes on the immune system and their role in recovery. Acta Biochimica Polonica. 2025 Jun 11;72:14241.
6. Melaku L. Physiological changes in the pregnancy and anesthetic implication during labor, delivery, and postpartum. The Open Anesthesia Journal. 2022 Sep 19;16(1).
7. Edinoff AN, Williams B, Landry L, Cornett EM, Kaye AD. Physiological maternal adaptive changes during pregnancy, eg, alterations of endometrium and decidua, menstruation, placenta, fetal membranes, placental hormones, morphological and

functional fetal development. InPharmacology, Physiology, and Practice in Obstetric Anesthesia 2025 Jan 1 (pp. 3-14). Academic Press.

8. Cattaneo L, Piccioli-Cappelli F, Minuti A, Trevisi E. Metabolic and physiological adaptations to first and second lactation in Holstein dairy cows. Journal of Dairy Science. 2023 May 1;106(5):3559-75.
9. Deferm N, Dinh J, Pansari A, Jamei M, Abduljalil K. Postpartum changes in maternal physiology and milk composition: a comprehensive database for developing lactation physiologically-based pharmacokinetic models. Frontiers in Pharmacology. 2025 Feb 3;16:1517069.
10. Li Y, Liu Z, Chen Y, Wang W, Chen T, Li S, Wu Y, Xie H. Physiologically based pharmacokinetic coupled model of zonisamide to predict the exposure and dose exploration in maternal, fetal, and neonatal populations during pregnancy and postpartum. Journal of Pharmaceutical Sciences. 2025 Jul 23:103912.
11. Cardoso E, Monfort A, Ferreira E, Nordeng H, Winterfeld U, Allegaert K, Gandia P, Guidi M, Panchaud A. Maternal drugs and breastfeeding: risk assessment from pharmacokinetics to safety evidence-a contribution from the ConcePTION project. Therapies. 2023 Mar 1;78(2):149-56.
12. Vassiliou D, Sardh E. Acute hepatic porphyria and maternal health: clinical and biochemical follow-up of 44 pregnancies. Journal of Internal Medicine. 2022 Jan;291(1):81-94.
13. Ryu R, Hebert MF. Impact of pregnancy on maternal pharmacokinetics of medications. InClinical Pharmacology During Pregnancy 2022 Jan 1 (pp. 19-46). Academic Press.
14. Muller DR, Stenvers DJ, Malekzadeh A, Holleman F, Painter RC, Siegelaar SE. Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes: a systematic review of the evidence. Frontiers in endocrinology. 2023 Oct 10;14:1215356.
15. Gong C, Bertagnolli LN, Boulton DW, Coppola P. A literature review of drug transport mechanisms during lactation. CPT: Pharmacometrics & Systems Pharmacology. 2024 Nov;13(11):1870-80.

16. Tardiveau J, LeRoux-Pullen L, Gehring R, Touchais G, Chotard-Soutif MP, Mirfendereski H, Paraud C, Jacobs M, Magnier R, Laurentie M, Couet W. A physiologically based pharmacokinetic (PBPK) model exploring the blood-milk barrier in lactating species-a case study with oxytetracycline administered to dairy cows and goats. Food and Chemical Toxicology. 2022 Mar 1;161:112848.

17. Nauwelaerts N, Macente J, Deferm N, Bonan RH, Huang MC, Van Neste M, Bibi D, Badee J, Martins FS, Smits A, Allegaert K. Generic workflow to predict medicine concentrations in human milk using physiologically-based pharmacokinetic (PBPK) modelling—a contribution from the ConcePTION project. Pharmaceutics. 2023 May 11;15(5):1469.

18. Biswas R, Mondal S, Ansari MA, Sarkar T, Condiuc IP, Trifas G, Atanase LI. Chitosan and its derivatives as nanocarriers for drug delivery. Molecules. 2025 Mar 13;30(6):1297.

19. Byerley EM, Perryman DC, Dykhuizen SN, Haak JR, Grindeland CJ, Williamson JD. Breastfeeding and the pharmacist's role in maternal medication management: identifying barriers and the need for continuing education. The Journal of Pediatric Pharmacology and Therapeutics. 2022 Feb 1;27(2):102-8.

20. Abduljalil K, Faisal M. Impact of Milk pH and Fat Content on the Prediction of Milk-to-Plasma Ratio: Knowledge Gap and Considerations for Lactation Study Design and Interpretation: K. Abduljalil et al. Clinical Pharmacokinetics. 2024 Nov;63(11):1561-72.

21. Dodeja P, Chaphekar N, Laffey T, Albukhaytan H, Caritis S, Shaik I, Venkataramanan R. Clinical study design and modeling approaches to study secretion of drugs in human milk. Frontiers in Pediatrics. 2026 Jun 17;14:1843294.

22. Stratigakis A, Paty D, Zou P, Zhao Z, Li Y, Zhang T. A regression approach for assessing large molecular drug concentration in breast milk. Reproduction and Breeding. 2023 Dec 1;3(4):199-207.

23. Gasparyan J, Anderson PO, Lewis T, Yeung CH. Rules of thumb for estimating drug levels in breast milk: how well do they work?. Clinical Pharmacology & Therapeutics. 2026 Jan;119(1):101-8.

24. Huang D, Luo Z, Gong X, Zou K, Peng Y, Zeng S. Post marketing safety assessment of the novel postpartum depression drug, Zuranolone: evidence from real-world pharmacovigilance analysis based on the FDA adverse event reporting system. Frontiers in Psychiatry. 2025 Aug 15;16:1517773.

25. Cardoso E, Monfort A, Ferreira E, Nordeng H, Winterfeld U, Allegaert K, Gandia P, Guidi M, Panchaud A. Maternal drugs and breastfeeding: risk assessment from pharmacokinetics to safety evidence-a contribution from the ConcePTION project. Therapies. 2023 Mar 1;78(2):149-56.

26. Bereda G. Pediatrics pharmacokinetics and dose calculation. J Pediatr Neonatal Cares. 2022;12(2):96-102.

27. Dinleyici M, Barbieur J, Dinleyici EC, Vandenplas Y. Functional effects of human milk oligosaccharides (HMOs). Gut Microbes. 2023 Dec 31;15(1):2186115.

28. Ziesenitz VC, Welzel T, van Dyk M, Saur P, Gorenflo M, van den Anker JN. Efficacy and Safety of NSAIDs in Infants: A Comprehensive Review of the Literature of the Past 20 Years: VC Ziesenitz et al. Pediatric Drugs. 2022 Nov;24(6):603-55.

29. Verstegen RH, Anderson PO, Ito S. Infant drug exposure via breast milk. British Journal of Clinical Pharmacology. 2022 Oct;88(10):4311-27.

30. Spencer JP, Thomas S, Pawlowski RH. Medication safety in breastfeeding. American family physician. 2022 Dec;106(6):638-44.

31. Crescioli G, Cacini C, Bonaiuti R, Vannacci A. Medication Safety in Maternal Care: Addressing Inappropriate Prescribing during Pregnancy and Lactation.

32. Hale TW, Krutsch K. Hale's medications & mothers' milk 2025-2026: a manual of lactational pharmacology. Springer Publishing Company; 2024 Jul 26.

33. Bettonte S, Berton M, Marzolini C. Magnitude of drug–drug interactions in special populations. Pharmaceutics. 2022 Apr 4;14(4):789.

34. Vannacci A. Prescribing during Pregnancy and. Polypharmacy and Inappropriate Medication Use. 2026 Jun 10:59.

35. Meek JY, Noble L, Section on Breastfeeding. Policy statement: breastfeeding and the use of human milk. Pediatrics. 2022 Jul 1;150(1):e2022057988.

36. Freiría-Martínez L, Iglesias-Martínez-Almeida M, Rodríguez-Jamardo C, Rivera-Baltanás T, Comís-Tuche M, Rodrígues-Amorím D, Fernández-Palleiro P, Blanco-Formoso M, Diz-Chaves Y, González-Freiria N, Suárez-Albo M. Human breast milk microRNAs, potential players in the regulation of nervous system. Nutrients. 2023 Jul 24;15(14):3284.

37. Kamińska-Sobczak A, Gawlik-Kotelnicka O, Strzelecki D. Use of psychotropic medications during lactation-practical guidelines for psychiatrists. Psychiatr Pol. 2022 Jun 30;56(3):493-508.

38. Kokras N, Poulogiannopoulou E, Sotiropoulos MG, Dalla C. Maternal and infant pharmacokinetics of psychotropic medications during pregnancy and lactation. InPerinatal Psychopharmacology 2025 Aug 31 (pp. 21-44). Cham: Springer Nature Switzerland.

39. Heinonen EW. Psychotropic drug treatment during pregnancy and lactation: effects on mother and child. Karolinska Institutet (Sweden); 2022.

40. Browne G. Central Nervous System Drugs. InPharmacologyPro: A Practical Guide for Anaesthesiology Exams 2025 Nov 8 (pp. 91-113). Cham: Springer Nature Switzerland.

41. Breadon C, Kulkarni J. Antipsychotics in Pregnancy. InPerinatal Psychopharmacology 2025 Aug 31 (pp. 167-235). Cham: Springer Nature Switzerland.

42. Al-Beltagi M. Human milk oligosaccharide secretion dynamics during breastfeeding and its antimicrobial role: A systematic review. World Journal of Clinical Pediatrics. 2025 Jun 9;14(2):104797.

43. Hardefeldt LY, Prescott JF. Beta-lactam Antibiotics: Penam Penicillins. Antimicrobial Therapy in Veterinary Medicine. 2024 Dec 30:119-42.

44. Baymenov BM, Bulashev AK, Chuzhebayeva GD, Aliyeva GK, Beishova IS, Kokanov SK, Raketsky VA. Phenotypic and genotypic resistance to antibiotics in Staphylococcus

aureus strains isolated from cattle milk in Northern Kazakhstan. Veterinary world. 2023 Sep 14;16(9):1815.

45. Ragi SD, Garelick E, Hocevar MW, Cheng J, Murase JE. Safety of Dermatological Drugs in Pregnancy and in Lactation. Skin and Pregnancy. 2024 Nov 26:172-95.

46. Costa B, Ferreira-da-Silva R, Ribeiro I, Vale N. Post-Marketing Surveillance and Precision Pharmacovigilance in Pregnant, Postpartum and Breastfeeding Patients: Mapping Outcomes to Enhance Drug Safety. Pharmaceuticals. 2026 Nov.

47. Laudy-Wiaderny H, Nitsch-Osuch A. Antimicrobial resistance in the practice of primary care physicians: antimicrobial therapy. Family Medicine & Primary Care Review. 2025 Oct 1;27(4):469-72.

48. Schreiber K, Frishman M, Russell MD, Dey M, Flint J, Allen A, Crossley A, Gayed M, Hodson K, Khamashta M, Moore L. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: comorbidity medications used in rheumatology practice. Rheumatology. 2023 Apr 1;62(4):e89-104.

49. Pain N. Nociception and Analgesic Action Sites. Drain's PeriAnesthesia Nursing–E-Book: A Critical Care Approach; Elsevier: Amsterdam, The Netherlands. 2022 Dec 27:353.

50. Archer V. *Intravenous Acetaminophen for Postoperative Pain in Neonates: A Multi-Methods Approach* (Doctoral dissertation).

51. Mozzachio K. Illness and Disease. Potbellied Pig Veterinary Medicine-E-Book: Potbellied Pig Veterinary Medicine-E-Book. 2022 Mar 3:129.

52. Fonseca ML, Cossi MS, Dantas AC, de Souza Bezerra H, de Araújo MG. STRATEGIES FOR MANAGING PAIN RELATED TO BREASTFEEDING: AN INTEGRATIVE LITERATURE REVIEW. Revista de Pesquisa, Cuidado é Fundamental Online. 2025;17:1-1.

53. Baltaci MA, Pamukcu M. Targeted Treatment Strategies and Medication Management for Rheumatic Diseases During Pregnancy and Lactation: A Comprehensive Review: Rheumatic Diseases in Pregnancy and Lactation. Journal of European Internal Medicine Professionals. 2024 Oct 20;2(4):130-8.

54. Thurin NH, Pajouheshnia R, Roberto G, Dodd C, Hyeraci G, Bartolini C, Paoletti O, Nordeng H, Wallach-Kildemoes H, Ehrenstein V, Dudukina E. From inception to ConcePTION: genesis of a network to support better monitoring and communication of medication safety during pregnancy and breastfeeding. Clinical Pharmacology & Therapeutics. 2022 Jan;111(1):321-31.

55. Simões EA, Madhi SA, Muller WJ, Atanasova V, Bosheva M, Cabañas F, Cots MB, Domachowske JB, Garcia-Garcia ML, Grantina I, Nguyen KA. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. The Lancet Child & Adolescent Health. 2023 Mar 1;7(3):180-9.

56. Graziottin A, Di Simone N, Guarano A. Postpartum care: Clinical considerations for improving genital and sexual health. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2024 May 1; 296:250-7.

57. Patterson R, Balan I, Morrow AL, Meltzer-Brody S. Novel neurosteroid therapeutics for post-partum depression: perspectives on clinical trials, program development, active research, and future directions. Neuropsychopharmacology. 2024 Jan;49(1):67-72.