WISELEAF SCIENTIFIC VENTURES



CHAPTER-3
CLINICAL PHARMACOLOGY OF PREGNANCY: MATERNAL–FETAL DRUG EXPOSURE, PLACENTAL TRANSFER AND PRECISION DOSING

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Abstract
Pregnancy leads to important physiological changes affecting medication absorption, distribution, metabolism, and elimination, which influences the amount of drug present in the mother's body and the safety of the foetus. Pharmaco-therapy in pregnancy aims to obtain knowledge regarding these changes in order to enhance drug effectiveness while minimizing possible dangers for the developing foetus. One of the main principles of the fetal drug past is placental transfer which determines the amount of drug available for fetal organisms. Placental transfer depends on some factors such as molecular weight, lipophilicity, protein binding, placentary transporters and gestational age. Maternal physiological changes such as increase of plasma volume and changes in kidney clearance and hepatic metabolism could lead to alterations of pharmacokinetics of the drug in pregnant women. As a result of those factors, traditional dosing schemes cannot result in enough concentrations of the drug in the pregnant female organism and, unfortunately, will not achieve efficiency. The audience can benefit from using precision approaches to pharmacotherapy involving therapeutic drug monitoring, pharmacogenomics, physiological modelling and risk assessment. Knowing the possible interconnections between drugs and mother's organism is essential for using correct medications, adjusting their dosage and preventing negative outcomes of pregnancy.

Keywords: Fetal Drug Exposure, Maternal Pharmacokinetics, Placental Transfer, Precision Dosing, Pregnancy.

1. Introduction

Pregnancy is a complicated physiological state that involves multiple changes in how mother's organ's function, hormonal regulation, and metabolism, which can significantly affect pharmacokinetics and pharmacodynamics of medicines. Treating patients with medicines during pregnancy is often unavoidable due to the requirement to resolve pre-existing medical conditions, to cure pregnancy-related disorders, and to avoid complications concerning health of mother and child. The importance of the phenomenon consists not only in the fact that physiological adaptations that happen during pregnancy can change drug absorption, distribution, metabolism, and excretion (ADME) which might result in variations in effect and adverse reactions of the medicine being applied. Hence, following principles of clinical pharmacology during pregnancy is vital for successful and safe pharmacotherapy with the least exposure of the foetus to medicines [1][2].

The transfer of drugs across the placenta plays a vital role in determining the fetal amount of drug exposure. The transfer relies on factors such as molecular weight, solubility in lipids, binding capacity, ionization, activity of transporters in the placenta, and gestational age. Despite the fact that the placenta selectively shields the fetus being developed, it does not completely prevent the transfer of drugs and their metabolites into the fetal bloodstream. The fetal results from drug exposure depend on the drug, amount ingested, how long it has been taken, and what stage of development is the fetus. Hence, some drugs can interfere with organogenesis, growth, or development of functioning organs, which is a reason why it is important to assess the possible teratogenic effects and trimester-specific risks [3][4].

The advancements in pharmacokinetic modelling, therapeutic drug monitoring, pharmacogenomics and artificial intelligence offer new avenues to enhance medication management in pregnancy. The physiologically based pharmacokinetic (PBPK) model can be used to anticipate changes in drug concentrations in the maternal organism and estimate the exposure in the fetus under the specific physiological conditions of the pregnancy. In the same manner, dosing powered by artificial intelligence might provide valuable information for

individualizing the dosing by integrating clinical characteristics with laboratory data, genetic information, and pharmacokinetic information. [5] All these approaches will facilitate the development of precision pharmacotherapy which has the aim to improve efficacy of therapy while minimizing the risks of the mother and foetus. The incorporation of pregnancy-specific data on pharmacology, pharmacovigilance and new computational technologies is crucial for their application in personalized maternal medicine and improvement of pregnancy results.

2. Physiological Changes During Pregnancy

Pregnancy is associated with profound physiological changes that are required to allow fetal development and prepare the maternal body for delivery. These physiological adaptations affect cardiovascular functioning, kidney filtration, liver enzyme activity, hormonal control, and body fluids. Increased blood volume, alterations in protein binding, enhanced renal excretion, and changes in enzymes metabolizing drugs may influence the absorption, distribution, metabolism and excretion of drugs (**Figure 1)**. As a consequence, during pregnancy the pharmacokinetics of drugs is likely to differ considerably from that in patients who are not pregnant. Therefore, knowledge of the physiological changes and the changes in pharmacokinetics is essential for proper drug choice, optimization of drug dosage and therapeutic monitoring. The choice of therapy should be made with regard to maternal health, fetal development as well as possible drug-related complications [6].

2.1 Cardiovascular and Hemodynamic Changes

The cardiovascular system changes dramatically during pregnancy in terms of how much work that needs to be done in order to meet the metabolic needs of the new mother and the fetus inside her body. One of the most important developments is the increase in the blood volume. The heart stroke volume and output go up; the resistance of blood vessels drops due to hormonal mechanisms and development of the uteroplacental circulation. These changes can result in alterations in the way drugs are distributed and their concentration in the blood plasma of a woman. Increased blood volume and cardiac output can lead to the changes in the way the drugs are distributed, especially when we talk about those drugs that are distributed widely into tissues of the body. Reduced systemic vascular resistance can also have some impact on the blood pressure of the mother and her sensitivity to cardiovascular drugs. Furthermore, changes

in uteroplacental blood flow can affect the absorption of drugs by the placenta and fetal exposure. Hence, it is very important to be especially careful when using drugs in the process of treatment for chronic diseases such as hypertension and cardiovascular disease [7].

2.2 Renal and Hepatic Adaptations

The changes in renal function are very noticeable in pregnancy as they involve the increased renal blood supply and glomerular filtration rate (GFR). Due to these changes, various medications that are eliminated through the kidneys will get excreted much faster and consequently, their levels will be lower in the blood and their half-lives will be shorter. Therefore, medications like antibiotics may have to be reassessed in order to provide the necessary therapeutic effect. However, the change in the dosages should be based on the type of medication, clinical reasoning, phases of Pregnancy, and pharmacological studies. The metabolic process in the liver may be affected as pregnancy increases the activity of many drug-metabolizing enzymes. For example, the activity of cytochrome P450 enzymes may change in pregnancy; in some cases, it may be increased (for example, CYP3A4) and in other cases, decreased (for example CYP1A2). Therefore, based on these changes, one may see the rapid or slow metabolism of the drug, depending on the type of drug. The degree of such changes varies based on the individual [8].

2.3 Hormonal Changes and Plasma Volume Expansion

One of the defining features of pregnancy is a rise in the quantity of hormones such as estrogen, progesterone, and human placental hormone which are responsible for the modulation of physiological changes in mothers and fetus development. Hormonal fluctuations affect gastrointestinal peristalsis, hepatic enzyme activity, the expression of drug transporters, and renal function which may disrupt the process of absorption, metabolism, and elimination of drugs during the pregnancy. An increase in the volume of maternal plasma leads to an increase in the apparent volume of distribution of some hydrophilic substances. Moreover, albumin content in the blood generally decreases because of haemodilution which may result in an increase in the free fraction of highly protein-bound drugs. The increase in the free drug concentration would affect the processes of tissue distribution, action, and elimination of the compound. However, the drug effect depends on some pharmacokinetic properties and drug

clearance. Moreover, pregnancy-associated changes of protein binding may affect the interpretation of the therapeutic drug monitoring results thus the estimation of both total and free drug concentrations is necessary to eliminate the therapeutic effect of medication and minimize potential risks for mother and fetus during pregnancy [9].

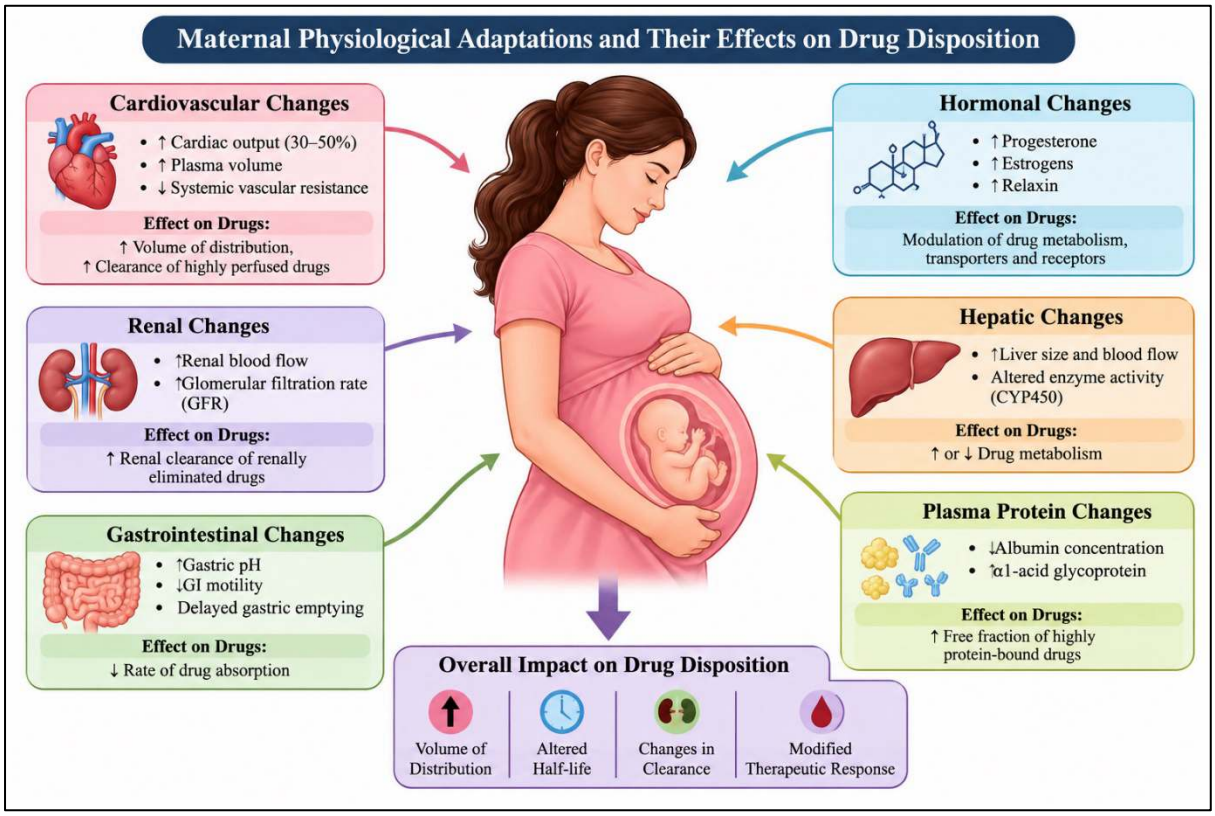

Figure 1. Maternal Physiological Adaptations and Their Effects on Drug Disposition

3. Pregnancy-Associated Alterations in ADME

ADME or Absorption, distribution, metabolism, and excretion are some of the pharmacokinetic processes related to the drug concentrations, efficacy and safety of the drug. Pregnancy brings about several changes in the ADME process due to physiological, anatomical and hormonal changes that happen in body for the development of the fetus. Changes in the gastrointestinal activities can also lead to change in absorption of drugs while the increase in plasma volume will affect their distribution. Similarly, different hepatic enzyme activities will change the metabolism of the drug while the increased renal blood flow and different glomerular filtration rate will have an effect on the elimination of drugs (**Table 1)**. The extent of changes may vary

with the type of drug used, stage of pregnancy, health condition of women and physiological characteristics of women. Due to these changes, it can be seen that drug exposure needs to monitored carefully. Thus, understanding the processes mentioned above becomes important for carrying out necessary changes in medications being prescribed [10].

3.1 Changes in Drug Absorption and Distribution

The process of drug absorption can be hindered by the changes in gastrointestinal tract, such as the motility and the disruption of gastric emptying and acidity. The alteration of the gastric emptying process and the gastrointestinal motility can affect the time taken for the drug administered through the mouth to enter the systemic circulation. The level of absorption may differ with medicines used since the changes will not be the same for all drug classes. Moreover, drug distribution is affected by the increase in the volume of the plasma, the body water, and the body fat. As many changes in the volume of distribution occur, the hydrophilic and lipophilic drugs will be affected differently. The decrease in the quantity of albumin concentration can also change the way proteins bind and increase the amount of the unbound drugs in the blood. Thus, it is crucial to understand that the quantity of the drug in the blood plasma can also decrease while still being active in the bloodstream [11].

3.2 Alterations in Drug Metabolism

Changes in the activity and expression of enzyme used in drug metabolism can lead to alteration in drug metabolism in pregnancy. Some substrates display increased metabolic activity through enzymes such as CYP3A4, CYP2D6, and CYP2C9, while CYP1A2 activity usually decreases. As a result, this could have an effect on drug clearance, where some drugs may be cleared faster or have lower concentration post administration corresponding to higher metabolic activity, while slower metabolism is likely to lead to drug accumulation. Enzyme modifications can also be responsible for changes in the production of active metabolites and the ratio between active and harmful products. The importance of an alteration in metabolism basically depends on the metabolic pathway, therapeutic index, and the role of an enzyme in the metabolism of a drug. Besides, genetic variation and other factors such as other drugs taken by a patient, or diseases that he/she suffers from can play a significant role in this process [12].

3.3 Changes in Drug Excretion

Renal excretion is a significant factor affecting the drug elimination process in pregnant women. Due to the increased renal blood flow and glomerular filtration, drug clearance in the body may speed up where renal excretion is the principal route of drug elimination. Thus, drug concentration in plasma might become lower, decreasing the effectiveness of some medicines in the context of standard doses. This issue is of particular relevance when it comes to the medications with narrow therapeutic indices or those requiring constant concentration in the patient's bloodstream for reaching their effect. The changes in renal functions associated with pregnancy may also affect the elimination of the metabolites of drugs and endogenous substances utilized in the assessment of the condition of kidney functions. The levels of creatinine in the blood tend to decrease during uncomplicated pregnancy due to the increased glomerular filtration. As a result, renal function must be stated with regard to the specifics of pregnancy development rather than relying on the general information used for the non-pregnant population [13].

Table 1. Pregnancy-Related Changes in Absorption, Distribution, Metabolism and Excretion (ADME)

Pharmacokinetic process	Physiological changes during pregnancy	Pharmacokinetic implications
Absorption	Increased gastric pH, delayed gastric emptying and reduced gastrointestinal motility	May alter the rate and extent of drug absorption
Distribution	Increased plasma volume, total body water and body fat	Increased volume of distribution of hydrophilic and lipophilic drugs
Plasma protein binding	Reduced albumin concentration and altered binding of certain drugs	Increased unbound fraction of highly protein-bound drugs

Hepatic metabolism	Altered activity of drug-metabolizing enzymes, including CYP3A4, CYP2D6, CYP2C9 and CYP1A2	Increased or decreased metabolism depending on the enzyme and drug
Renal excretion	Increased renal blood flow and glomerular filtration rate	Enhanced clearance of drugs primarily eliminated through the kidneys
Drug elimination	Changes in hepatic metabolism and renal clearance	Altered elimination half-life and maternal systemic drug exposure

4. Maternal Drug Exposure

Maternal drug exposure refers to the concentration and the time duration when a medicine is present in maternal circulation and tissues after administration. It is generally characterized by pharmacokinetics parameters such as maximum plasma concentration, area under the plasma concentration curve, clearance, and half-life. Physiological changes during pregnancy can alter these parameters and, therefore, the efficacy and safety of a treatment. Clinical importance of maternal drug exposure is that it may again affect the amount of the drug available to cross the placenta and subsequently become available to the fetus [14].

4.1 Determinants of Maternal Drug Exposure

The degree of exposure of drugs taken by a mother to her fetus appears to depend on factors including route of administration, concentration of a drug given, interval of dosing, bioavailability, distribution, metabolic process, and elimination pathway. Changes in plasma volume and binding to proteins, liver and kidney function have also been seen to modify drug concentrations in the blood stream. Time of giving drugs is important too because the physiological adaptations could take place in the mother's body as the pregnancies progress, and the pharmacokinetics of drugs could completely change from one trimester to another, having been influenced by factors including age of the mother, body composition, nutritional

status, genetic differences, kidney and liver function, and concurrent medication. Thus, chronic diseases before pregnancy as well as pregnancy-related complications may have an impact on drug disposition. For example, in the case of kidney-clearance drug, clearance may increase during an uncomplicated pregnancy, but clearance rate may decrease in patients suffering from renal failure [15].

4.2 Maternal Plasma Concentrations and Therapeutic Response

Drug levels in the maternal blood can give information on systematic exposure, and can predict treatment success if it is possible to demonstrate the association between drug levels and treatment outcomes. However, because of the changes in the pharmacokinetics affecting the drug metabolism during pregnancy, levels of some drugs in pregnant patients may decrease too much, resulting in insufficient control of the disease being treated. On the other hand, if the clearance decreases or there is a change in the amount of free drug, it may lead to increased effects of medications and/or risk of overdose. Monitoring of the patients treated with the drugs with narrow therapeutic ranges can be very effective. The timing of the sample collection, gestational age, clinical status, and the type of analysis performed should be taken into account when interpreting the results of drug levels. Importantly, decrease of the total concentration does not mean that treatment was unsuccessful, especially for drugs which are highly protein-bound [16].

4.3 Maternal Drug Exposure and Pregnancy Outcomes

Maternal drug exposure causes many impacts on pregnancy outcomes due to the effect of the drug on the mother along with its influence through the placenta and exposure to fetal tissues during the development. The drug and the timing of exposure are considered to determine the potential effects of exposures such as congenital disorders, increased fetal toxicity, impaired fetal development, preterm birth along with complications that can occur in newborns. The stage of fetal development is of much importance as some harmful drugs can affect the process during early pregnancy while other medicines can interfere with fetal growth and development later. The seriousness of the disease of the expectant mother also matters because the influence of untreated disease can harm both the mother and the child. Therefore, in order to manage the particular condition at hand, one should take into account the necessity and effects of the

treatment, consequences of the absence of treatment, potential alternative methods, and the probability of fetal exposure [17].

5. Placental Drug Transfer

Placenta is a special organ that allows the fetus to grow by providing for the exchange of oxygen and nutrition between the maternal and fetal circulations. While being a selective barrier, the placenta does not stop medications from penetrating into the fetus (**Figure 2)**. The degree of drug transfer through the placenta depends on many factors, such as chemical structure of the drug itself, concentrations of the drug in the maternal and fetus blood, placental drug transporters' activity, and the period of pregnancy. Placenta drug transfer must be well understood to evaluate reptilian exposure to drugs, to choose the medicines, and to limit the potential risk for the development of the fetus [18].

5.1 Structure and Transport Functions of the Placenta

The placenta is formed during the course of pregnancy and is responsible for acting as the main site for the interface of fetal circulation with the mother. Its functional parts include the chorionic villi, trophoblast layers, fetal capillary endothelium, and related transport systems. The syncytiotrophoblast creates a major cellular barrier separating the maternal blood from the fetal tissues and controlling the transport of substances through the placenta. Normally, maternal and fetal blood are kept apart but close proximity allows them to exchange important substances and some drugs. The functions of the placenta include transport of nutrients, respiration of gases, elimination of waste, production of hormones, and immunological control. It also expresses different membrane transporters having effects on movement of drugs and endogenous compounds. The efflux transporters, for example, P-glycoprotein and breast cancer resistance protein (BCRP) transfer certain substances from fetal circulation thus helping limit fetal exposure. Even though such protection is in place, it can vary from drug to drug, and from the activity of transporters and the period of pregnancy [19].

5.2 Mechanisms of Placental Drug Transfer

Different mechanisms allow drugs to pass through the placenta. One of them is passive diffusion; this mechanism has a major role in transporting low molecular weight drugs. Passive diffusion takes place due to concentration difference between mother and baby blood, but other

factors influence it too, including the size of molecules, their ability to dissolve in lipids, whether they are ionized or not, and their ability to bind proteins. In general, lipid-soluble non-ionized drugs penetrate biological membranes better than substances that are strongly ionized and/or poorly soluble. At the same time, the fact that drug consists of certain molecules described above does not guarantee fetal exposure. Facilitated diffusion, active transport, and some other processes can also take place. Facilitated diffusion implies the use of transport proteins that assist the transport of substances down the concentration gradient without a need for the consumption of energy; active transport means that substances can move against the concentration gradient with the active transport system being quite successful in delivering drugs to foetuses [20].

5.3 Factors Influencing Placental Permeability

Several factors determine placental permeability, including properties of the drug such as molecular size, lipid solubility, degree of ionization, protein binding, and chemical structure. Generally, small, lipid-soluble, non-ionized molecules cross the placenta more easily than large molecules and drugs with significant protein binding. However, the actual permeability of certain drugs to the placenta can be modified by various specialized transporters. Thus, the extent of placental transfer should always be assessed based on drug specific information when it is available. Another important aspect of the issue is gestational age, as placental structures and morphology change throughout pregnancy. Maternal drug concentration, placental health status, fetal circulation, and physiological state also affect the level of fetal exposure to the drugs. The differences in the mother's and fetal's pH can alter the distribution of weakly basic drugs and can cause the accumulation of drugs in the fetal blood. Moreover, placental insufficiency and other complications during pregnancy may also influence drug activity [21].

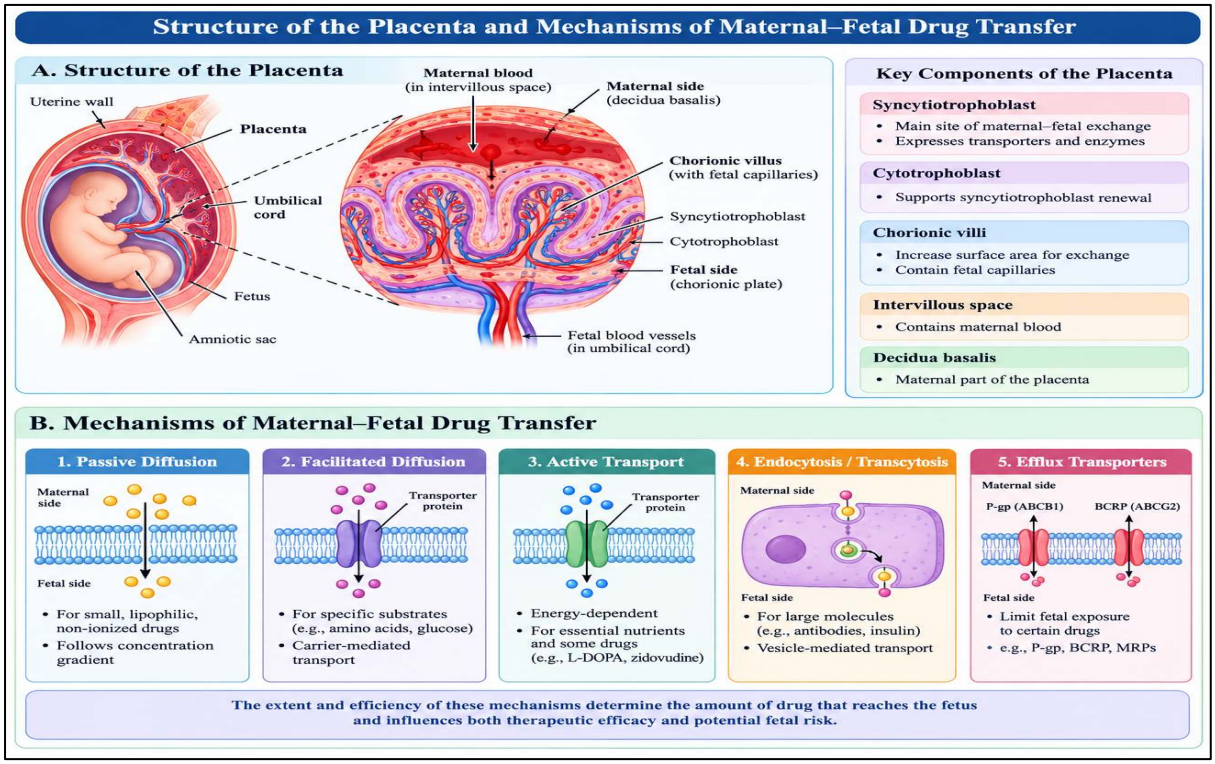

Figure 2. Structure of the Placenta and Mechanisms of Maternal–Fetal Drug Transfer

6. Maternal–Fetal Pharmacokinetics

Maternal–fetal pharmacokinetics assesses the transfer and distribution of drugs across the pregnant woman's body, placenta, and fetal organs. After being administered to an expectant mother, a drug enters her circulation, travels throughout her body, and is eliminated from her system. The drug then moves across the placenta into the fetal circulation and organs and undergoes metabolism or elimination from the fetal system (**Figure 3)**. The relationship between maternal and fetal drug concentrations is complicated because it is dependent on the type of the drug, the process involved in transporting it through the placenta, the woman's gestational age, and the development of the fetus [22].

6.1 Maternal and Fetal Drug Concentrations

The concentration of drugs in both maternal and fetal systems is the result of drug delivery, systemic clearance, transport across the placenta, and fetal distribution. Maternal blood concentration of the drug is a good indicator of systemic exposure of the drug in the body, but it does not always give the accurate prediction of fetal exposure. For example, drugs that are

able to cross the placenta easily will produce fetal exposure, while medications that have limited permeability or are actively eliminated by the transport system will not affect fetal concentrations. The relationship of maternal and fetal drug concentrations greatly depends on various factors, including the type of the drug and the point of time when it is detected. Some drugs will show similar concentrations in mother and fetus after some time, while other medications will very wide concentration difference due to the low transferability of the drug and active transport. Also, repeated administration may have an effect on the amount of drug in the fetal system, especially, in cases where transport is prolonged or slow elimination [23].

6.2 Fetal Drug Distribution and Elimination

Once drugs permeate through the placenta, they will circulate in the total fetal blood volume, arriving to the organs depending on their physicochemical characteristics, tissue affinity, and binding modes. Fetal body makeup is different from the adult one in terms of body water, fat content, and protein binding. These factors might affect both the volume of distribution and concentration of the drug in the fetal body. Also, different drugs will be distributed differently as the fetal organs mature while the pregnancy progresses. Fetal drug elimination is dependent on the maturation degree of liver and kidneys of the fetus. Hepatic cytochrome systems are at an early stage of development and many pathways might not achieve the level of hepatic activity characteristic of adults. Additionally, kidneys of the fetus are immature as for filtration and tubular functions. Therefore, it is possible for certain drugs or their metabolites to stay in fetal circulation longer than what would be predicted based on maternal pharmacokinetics data. Some of them can even be back transported to the maternal circulation through the placenta, which allows maternal metabolism to reduce their concentration [24].

6.3 Amniotic Fluid and Fetal Drug Accumulation

Amniotic fluid creates the safe environment that surrounds the fetus as it grows, and it plays a part in fetal movement, thermoregulation, and proper development. Some the medications taken by the pregnant woman can reach the amniotic fluid due to transfer from the maternal blood, fetal urination, or other mechanisms of transfer. The degree of the drug presence in the amniotic fluid depends on how permeable the placenta is, how well the kidneys of the fetus function, whether the fetus swallows the amniotic fluid, the characteristics of the membranes,

and the physicochemical properties of the compound. Fetal exposure to the drug may last longer, as the substance may go into the amniotic fluid and then be swallowed by the fetus. It may then enter the tissues again after being absorbed by the fetus. This mechanism may contribute to prolonged exposure to some substances, but the clinical significance may differ from one drug to another. Accumulation can be also connected with how many times the pregnant woman was dosed with the drug or how well the fetal organs function in metabolization depending on the substance. These mechanisms should be known when dealing with drugs that may potentially cause toxicity in the fetus [25].

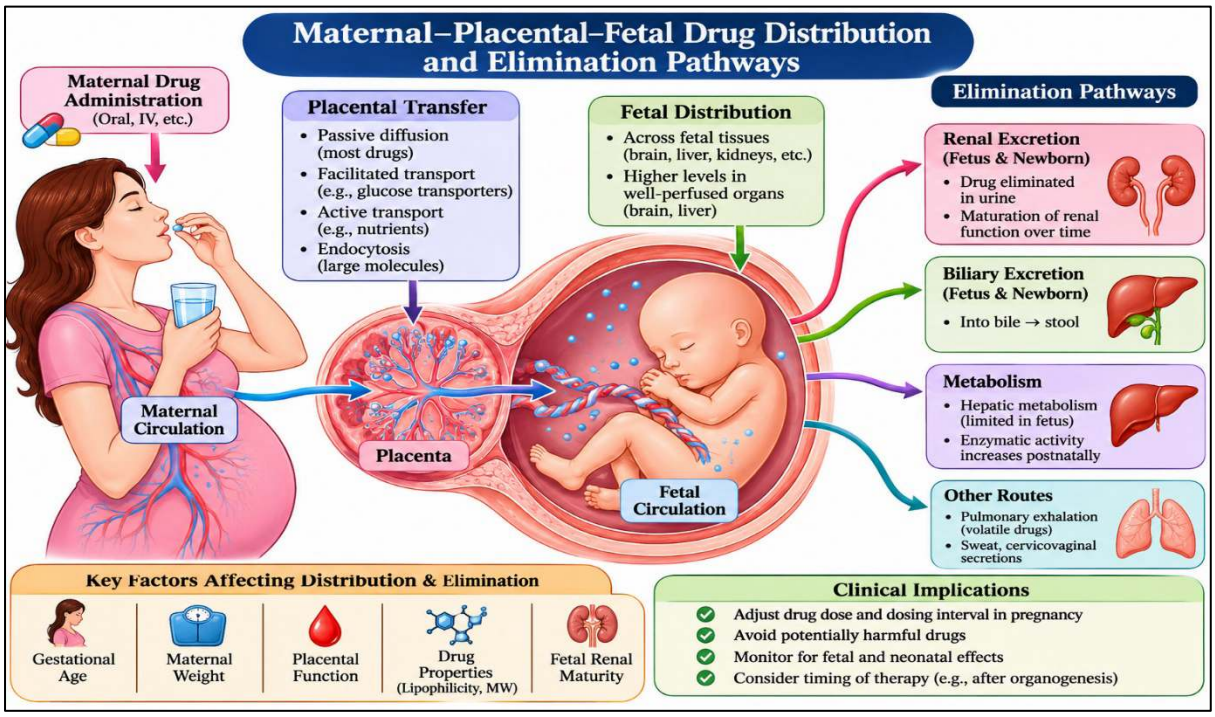

Figure 3. Maternal–Placental–Fetal Drug Distribution and Elimination Pathways

7. Teratogenicity and Fetal Drug Safety

Teratogenicity refers to the ability of certain substances, including specific medications, to interrupt embryonic or fetal development, causing defects in their structure and function. The use of medications during pregnancy should be examined closely due to variations in fetal susceptibility impacted by the drug type, dose, duration of exposure, and the stage of development (**Table 2**). However, not all medications can cross the placenta to the same extent and therefore crossing the placenta does not necessarily mean that a drug will cause any

damage. Thus, fetal drug safety assessment should be based on pharmacology data, developmental biology science evidence, severity of maternal diseases and anticipated positive effects of treatment [26].

7.1 Mechanisms of Drug-Induced Teratogenicity

Teratogenicity related to the use of drugs can be caused by a variety of mechanisms, such as disruption of cell proliferation, interference with DNA synthesis, change of gene expression, stress induced by oxygen, and disruption in fundamental signaling pathways vital for development. A few medications can intervene with the process of folate metabolism, the process of signaling of hormones, vasculogenesis, or organogenesis of a particular organ. Depending on the mechanism of action and time of exposure, these processes can result in formation of anatomical abnormalities, disturbance of growth, or dysfunction of the developing CNS and other organs. In addition, the severity of teratogenic effects depends on the type of a drug, the amount of drug that reaches the fetal tissue, the duration of the exposure, and the vulnerability of the developing organ. Gene composition and health of the mother play a role in fetal response too. Additionally, some drugs can induce fetotoxic effects without classical structural deformities forming [27].

7.2 Critical Periods of Fetal Development

The timing of exposure to medications is a very important factor in determining how they might affect development. In fact, immediately after conception, severe exposures can lead to the death of the embryo. Surviving foetuses have the potential to develop normally. This phenomenon can be dubbed the approximate all-or-none period, although it is not absolute. The formation of organs primarily occurs during the first trimester of pregnancy and affects embryos in a more intense manner as they are particularly vulnerable to possible disturbing agents. Certain medications, when used in the first trimester, may thus be said to increase the chance of anomalies appearing. During the second and third trimesters, organ growth and maturation as well as neurological development occur. Certain groups of drugs may have a negative impact on the fetus' growth, kidney, endocrine and central nervous system development during this period. Some drugs may lead to complications in newborns, such as respiratory problems, withdrawal or failure in physiological adaptation. The exact range and

frequency of both of these disorders depend on the medication prescribed. Hence, it is important to consider teratogenic effects and the stage of the pregnancy [28].

7.3 Assessment and Prevention of Fetal Drug Risks

Fetal risk assessment for drugs begins with a detailed understanding of the drug's known safety profile, human pregnancy data available, animal testing results, pharmacokinetic characteristics, and the clinical conditions the drug is required to target. The healthcare professional should weigh the indication, available alternatives, dosage, route of administration, duration of exposure, and gestational age. They must also weigh the likely consequences of untreated maternal disease since poor disease control itself can threaten the lives of the mother and fetus. Risk prevention entails the choice of the best medication supported by evidence, in appropriate dosage, with no unnecessary drug exposure, and with maternal and fetal health monitored when necessary. Preconception counseling is particularly important for patients on drugs with recognized fetal risks, so that modifications are allowed before the initiation of pregnancy. During pregnancy, medication regimens should be routinely reviewed and not suspended abruptly in absence of proper clinical advice. Ultrasound, laboratory assessments, and further fetal monitoring interventions may be done depending on the particular medication and the clinical situation. Collaboration between patient and healthcare team in making decisions helps enhance informed choice and a fair compromise between the mother's therapeutic needs and fetal safety [29].

Table 2. Classification of Drug-Induced Fetal Risks According to Developmental Outcomes

Type of fetal risk	Description	Potential developmental outcomes
Structural abnormalities	Interference with normal organ formation during embryonic development	Congenital cardiac, neural tube and limb abnormalities
Growth restriction	Disruption of normal fetal cellular growth and development	Low birth weight and intrauterine growth restriction

Functional impairment	Alteration of fetal neurological, endocrine or physiological development	Neurodevelopmental and functional abnormalities
Fetotoxicity	Direct toxic effects on fetal organs and tissues	Fetal renal impairment, reduced organ function and toxicity
Pregnancy loss	Severe interference with embryonic or fetal development	Spontaneous abortion or fetal death
Neonatal toxicity	Drug exposure close to delivery resulting in persistent pharmacological effects	Respiratory depression, withdrawal symptoms and neonatal adaptation problems

8. Trimester-Specific Pharmacotherapy

Pharmacotherapy that pertains to specific trimesters refers to choosing and modifying drug regimens based on the trimester of pregnancy, the mother's health requirements, the baby's development, and the associated risks of drug treatment. Changes in physiological processes during pregnancy can alter the absorption, distribution, metabolism, and elimination of drugs and the response to pharmacotherapy. Moreover, the fetus has different vulnerabilities to medication during gestation (**Figure 4)**. Adequate pharmacological therapy requires an assessment of the prospective benefits of therapy vs. potential side effects and the effects of untreated maternal condition in each individual case. Regular assessment of medication and prescribing medication based on the available evidence are crucial for maximizing the health of the mother and ensuring the fetus's normal development [30].

8.1 Pharmacotherapy During the First Trimester

The first trimester of pregnancy is an important period in which embryonic development and formation of organs occur. Some teratogenic drugs can be harmful in this process and result in congenital malformations. Accordingly, choice of medications during early pregnancy requires thorough assessment of the safety profile of the drug, the alternatives available and dose and duration of administration. At the same time, maternal treatment cannot be avoided if the

balance between risks and benefits of treatment is positive. The medications prescribed during this period should be chosen according to the already established recommendations and safety data. To illustrate, the use of folic acid is recommended for avoiding the risk of developing neural tube defects and the appropriate medications need to be used for the treatment of infections, epilepsy, hypertension, etc. Certain medications, including isotretinoin and valproate, should be carefully avoided due to their strong association with fetal adverse effects. Use of medical reconciliation, preconception counselling, and early antenatal assessment can help find potential exposures that can harm the fetus and choose safer treatment option [31].

8.2 Pharmacotherapy During the Second Trimester

The second trimester is marked with advancing fetal development, maturation of organs, along with alterations in maternal physiology which may affect the requirements of the medications. Although the chance of congenital malformations caused by organogenesis decreases after trimester one, this does not mean that this period comes without the risks of medications. Certain substances may have a negative impact on fetal growth, brain development, kidneys, or other physiological processes. Thus, medical decisions should be based on the evidence related to specific medications instead of assuming that all medications are harmless at this time. In the second trimester, pharmacological therapy may include the treatment of gestational diabetes, hypertension, infectious processes, thyroid diseases, etc. Insulin can be used to control blood sugar levels where it is necessary while certain antihypertensive medications can be prescribed according to the overall guidelines. The physiology may also change during this period, such as increased clearance from kidneys or altered metabolism in the liver, all of which may affect the concentration of some medications in the blood [32].

8.3 Pharmacotherapy During the Third Trimester

In the third trimester fetal growth is fast, maturity of faculties, and preparation for birth takes place. Here, the balance must be struck while using the medicine between fetal effects and possible complications in newborns. Drugs can affect either fetal cardiovascular or renal function, whereas others cause respiratory depression, withdrawal symptoms, bleeding complications, or altered adaptation after the newborn is born. Whether or not an outcome occurs typically depends on the type of medicine used, the dose, the duration of exposure, and

the time of exposure during pregnancy. Treatment in the late stages of pregnancy may involve the administration of medications for treating hypertension, diabetes, infections, pain, or any other clinically significant conditions. However, drug selection must take into consideration how close delivery may be and neonatal effects. For example, NSAIDs are generally avoided starting at about 20 weeks of pregnancy, unless absolutely indicated, along with other considerations limited to almost all later pregnancies due to fetal renal and cardiovascular risks. Further, medications with neonatal adaptation risks required meticulous evaluation prior to delivery. An effective collaboration among obstetricians, pharmacologists, and other health professionals will support active treatment planning and postpartum monitoring [33].

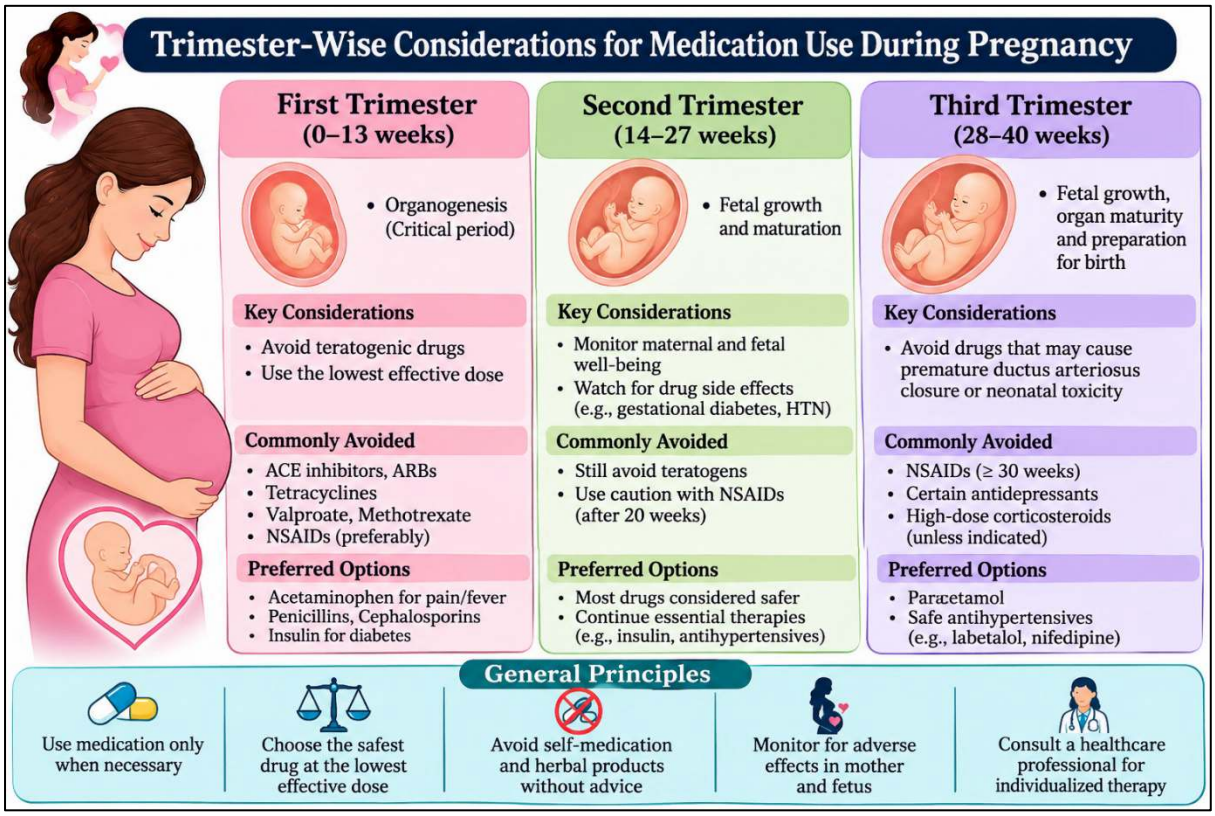

Figure 4. Trimester-Wise Considerations for Medication Use During Pregnancy

9. Pharmacotherapy of Maternal Diseases

The purpose of pharmacological treatment of health problems associated with pregnancy is to guarantee the good state of health of a pregnant woman while limiting dangers for the fetus. Such disorders as high blood pressure, diabetes, seizures, mental disorders, infections, and

thyroid diseases require treatment during pregnancy (**Table 3)**. Uncontrolled health issues of pregnant women may lead to serious consequences, and thus proper treatment is vitally important in pregnancy care. When deciding upon the treatment, the specialists have to take into account the seriousness of the disorder, the safety data specifically aimed at pregnant women, pharmacokinetic alterations, and the availability of medicines with similar efficacy [34].

9.1 Management of Hypertension and Diabetes

When managing hypertension during pregnancy, it is necessary to keep an eye on the possibility for development of complications in the mother, including serious hypertension, stroke, and any issues caused by preeclampsia. Drugs used to treat hypertension include labetalol and nifedipine in extended form, while methyldopa can be a suitable option in some situations. The action of inhibitors of angiotensin and blockers of angiotensin II is not performed during pregnancy because of fetal consequences, particularly regarding the development of kidneys and functioning. When choosing treatment, it is important to follow guiding principles in obstetrics and take into account the severity of hypertension and the clinical facts of the case. Diabetes and gestational diabetes need to be treated correctly to avoid complications with the baby. One of the methods used can be changing the lifestyle and nutrition. If the pharmacological treatment is required insulin is usually prescribed. Metformin can be prescribed in some cases, although it is able to cross the placenta. Mother's blood sugar control and continuous observation of the baby provide for the effectiveness of the treatment [35].

9.2 Pharmacotherapy of Neurological and Psychiatric Disorders

Many neurologic and psychiatric illnesses like epilepsy, migraine, depression, anxiety disorder, or bipolar disorder may require the application of drug-based therapy during the period of pregnancy. The process of the selection of drugs involves many difficulties due to the fact that while drugs may affect the fetus, uncontrolled illness can result in serious problems, e.g. maternal injuries due to seizures or fetal deficiency in oxygen. The main distinctive feature of anticonvulsants is the significantly different levels of safety of their usage during the development of the fetus. It seems that valproate may lead to higher risks of congenital malformations and is supposed to be avoided during pregnancy unless there is no other

effective medication. Lamotrigine or levetiracetam can be prescribed only to the selected groups of patients depending on the type of seizures that require treatment. Psychotropic drugs include some selective serotonin inhibitors that may be prescribed in justified cases. The process of therapy should take into account the severity of the disease of the mother, the previous experience of drug usage, the possible effects on the newborn child, and the likelihood of changes in the concentrations of the drug [36].

9.3 Treatment of Infectious and Endocrine Diseases

Prompt evaluation and proper antimicrobial treatment should be provided if a pregnant woman gets an infection to avoid any complications for the mother and the baby. Selection of antibiotics can depend on the infected organism, organs affected, and the severity of the disease and the period of pregnancy. Penicillins and cephalosporins are often applied due to good experience with their use during pregnancy but any other medications might be used as well depending on the infection types. Untreated infections might lead to increased occurrence of maternal illness and preterm births. Endocrine disorders such as hyperthyroidism and hypothyroidism should also be treated carefully. The treatment for hypothyroidism is levothyroxine; the doses might vary during the pregnancy. Thyroid functions has to be monitored with the help of special techniques based on pregnancy demands. In case of hyperthyroidism, it is recommended to use propylthiouracil in the first trimester and methimazole later. Medical decisions have to be made only with the help of doctors as the negative influence of uncontrolled disease or overtreatment can be dangerous [37].

Table 3. Common Maternal Disorders During Pregnancy and Their Pharmacological Management

Maternal disorder	Common pharmacological agents	Therapeutic objective	Important considerations
Hypertension	Labetalol, nifedipine and methyldopa	Control maternal blood pressure and	ACE inhibitors and ARBs are generally

		reduce complications	avoided during pregnancy
Gestational diabetes	Insulin and metformin	Maintain appropriate maternal blood glucose levels	Monitor maternal glucose and fetal growth
Epilepsy	Lamotrigine and levetiracetam	Prevent maternal seizures	Individualized dose adjustment and therapeutic drug monitoring may be required
Depression	Sertraline and other appropriately selected antidepressants	Maintain maternal mental health and prevent relapse	Assess maternal benefits and potential neonatal risks
Bacterial infections	Penicillins and cephalosporins	Eliminate bacterial infection	Select antibiotics according to infection type and pregnancy safety
Hypothyroidism	Levothyroxine	Maintain appropriate thyroid hormone concentrations	Monitor thyroid function throughout pregnancy

10. Pregnancy Pharmacovigilance

Pharmacovigilance in pregnancy means the systematic identification, assessment, comprehension, and prevention of harmful effects resulting from medications used during pregnancy and lactation when applicable. This process is especially important because

pregnant women have been historically excluded from medical tests, thus leading to a lack of necessary information about medication safety, maternal pharmacokinetics, and fetal outcomes. Pharmacovigilance helps combine clinical observations, spontaneous reports of harmful events, pregnancy registries, observational studies, and real-world data, enabling the enhanced understanding of medication-related risks. Such actions facilitate the emergence of evidence-based prescriptions, along with sound regulatory decisions [38].

10.1 Monitoring Maternal and Fetal Adverse Drug Reactions

Monitoring adverse drug reactions during pregnancy includes detecting and assessing negative experiences that arise during the course of drug therapy. Possible maternal adverse reactions include damage to one of the organs, allergic reactions, metabolic disorders, etc. Possible adverse outcomes for the fetus and the newborns include various congenital malformations, slowed growth, fetal toxicity, premature birth, etc. The assessment process takes into account the suspected drug, its dose, length of exposure, and other relevant aspects of the patient's medical history, including information about her diseases and other possible causes of the conditioned outcome. For monitoring purposes, all medical professionals, including obstetricians, pharmacists, medical assistants, and nurses, must coordinate their actions. The medical history must be recorded precisely, including prescription drugs, OTC medications, herbal remedies, and dietary supplements. The suspected adverse drug reactions must be examined by means of pharmacovigilance systems. If needed, laboratory tests of the mother, ultrasonography of the fetus, and assessment of the newborn may be performed for the purpose of detecting any complications in time [39].

10.2 Pregnancy Registries and Drug Safety Surveillance

Pregnancy registries are observational systems that gather information on drug exposures during pregnancies and the maternal, fetal, and child-related outcomes. These registries allow researchers to look for likely links between drug exposure and adverse outcomes whenever randomized controlled trials are not possible or are considered unethical. The data may indicate drug exposure dates and types, the drug dose, diseases in the mother, pregnancy results, congenital malformations, and infant development indices. Comparison of the patients who took the drugs and appropriate control groups may help find the safety signals. Drug safety

monitoring also involves spontaneous report systems and post-marketing studies, health care database analyses, etc. All these methods complement each other because each method provides different types of evidence. Spontaneous reports are useful for finding unexpected events but do not allow to establish their frequency or the causative link. At the same time, an adequately conducted observational study can provide more precise estimates. However, pregnancy registries have their problems such as missing data, sample size issues, and complications caused by diseases in the mother. Combining data from different sources is useful for assessment of drug safety [40].

10.3 Real-World Evidence in Pregnancy Pharmacovigilance

Real-world evidence is produced when information collected through normal health care practice is analysed. Such information is obtained from electronic health dossiers, insurance reports, medicament supply systems, records of births and data from clinical follow-up systems. Therefore, it can provide information about the use of medicaments by various populations of pregnant women and be used for outcomes evaluation that is not available from clinical trials. The real-world analysis is important for issues related to rare adverse reactions, long-term effects of drugs and drug utilization trends during the various stages of pregnancy. Nevertheless, real-world evidence has some restrictions since observational data may be characterised by deficient records of exposure, incorrect recording of outcomes, and absence of important clinical data and confounding factors. For instance, the disease of the mother may play a role in the outcome of pregnancy making it difficult to calculate the effect of the drug as well as the disease. By incorporating the right study design, validated definition of outcomes, the investor will enhance the accuracy of data. One of such methods is linking the real-world with registry data and prospective studies [41].

11. Physiologically Based Pharmacokinetic (PBPK) Modelling

Physiological-based pharmacokinetics (PBPK) refers to the use of mathematical models in terms of physiologic, chemical, or other drug-specific data parameters involved in the absorption, distribution, metabolism, and excretion of drugs (**Table 4)**. Various significant changes happen in the body of a pregnant woman that affect her drug disposition depending on organ function, body composition, kidney functions, and physiological functions of the

placenta. In general, the established models for PBPK during pregnancy account for all those factors that help evaluate drug concentrations in maternal blood and its variations in the fetus, provided sufficient data and model structure is available. Thus, PBPK models provide useful insights into the peculiarities of drug metabolism in pregnancy [42].

11.1 Principles of Pregnancy-Specific PBPK Modelling

Pregnancy PBPK modelling views the human body as a series of interlinked functional units like the liver, kidneys, intestines, adipose tissue, and other organs. These compartments are identified using parameters such as volume, blood flow, drug permeability, enzymatic activity, and transport activity. The movement of the drugs can be expressed through the help of mathematical equations in terms of the concentration of the drug at the end of the studied period. While traditional models use simplified compartments, PBPK models involve detailed biological processes for drug distribution. Pregnancy PBPK modelling takes into account the physiological changes that happen during pregnancy such as maternal plasma volume, total body fluid, total body fat, cardiac output, glomerular filtration rate, and enzymatic activity of the liver. The models can be developed basing on the information about the physiochemical properties of the drugs and the physiological properties due to pregnancy. In order for the models to be effective, it is necessary to validate them against clinical data [43].

11.2 Prediction of Maternal and Fetal Drug Exposure

PBPK models can forecast maternal drug levels depending on the stage of pregnancy by considering changes in absorption, distribution, metabolism, and excretion. The predictions of these models can clarify the reasons for the reduced plasma levels and higher clearance of certain drugs during pregnancy. Additionally, PBPK models allow for predicting some parameters of exposure based on the simulating the administration of different doses and time intervals. All this can be done in order to establish whether the drug is given at the correct dose. Modern pregnancy-specific PBPK models take into account transport through placenta, fetal blood circulation, distribution to fetal tissues, and development of function metabolism and kidney. Thus, the calculations can provide information about fetal exposure on different maternal doses. However, predictions for fetuses are generally more uncertain than those made for mothers because of the limited information about the fetal concentrations and possible

unspecified mechanisms occurring in placenta. The use of PK modeling is more useful when its findings are correlated with clinical data and other types of pharmacological information [44].

11.3 Clinical Applications and Limitations of PBPK Models

PBPK modelling specific to pregnancy is helpful in making drug dose calculation, drug interaction assessments, clearance alterations evaluations, and predictions of exposure to both mother and child. This type of modelling could be especially helpful in case of drugs that undergo significant pregnancy-mediated changes in their pharmacokinetic characteristics and for drugs for which clinical dosing data are insufficient. These models can simulate various pregnancy stages enabling determination of the presence of the situation where standard doses lead to either too much or too little exposure. In addition, they can provide assistance in clinical trial operation since it is possible to check the timing of sampling and estimate drug concentration occurrence range using these modelling techniques. However, it should be noted that PBPK modelling has certain limitations. The success of this technique depends on the data quality regarding physiology, drug properties and assumptions regarding pregnancy changes. Also, each such model may not include the differences between people, diseases of the mother, placental disorders, genetic variations, and so forth. Such problems produced difficulties in model validation due to insufficient preciseness of information on fetal concentrations. Moreover, predictions cannot be treated as evidence in terms of safety and efficacy of the clinical dosing decisions [45].

Table 4. Applications of Pregnancy-Specific PBPK Modelling in Drug Exposure Prediction

PBPK model component	Pregnancy-associated physiological parameter	Application in drug exposure prediction
Cardiovascular system	Increased cardiac output and blood volume	Predicts changes in systemic drug distribution
Gastrointestinal system	Altered gastric pH and gastrointestinal motility	Evaluates changes in oral drug absorption

Hepatic system	Changes in liver blood flow and enzyme activity	Predicts alterations in hepatic drug metabolism
Renal system	Increased glomerular filtration rate and renal blood flow	Estimates changes in renal drug clearance
Plasma protein binding	Altered albumin and binding protein concentrations	Predicts changes in unbound drug concentrations
Placental compartment	Placental permeability and transporter activity	Estimates maternal-to-fetal drug transfer
Fetal compartment	Fetal blood flow, tissue distribution and metabolic capacity	Predicts fetal drug concentrations and potential accumulation
Amniotic fluid compartment	Drug exchange between fetal circulation and amniotic fluid	Evaluates potential drug accumulation in amniotic fluid

12. Artificial Intelligence-Assisted Dosing

The investigation of artificial intelligence (AI) as an adjunct to clinical decision-making, predictions of pharmacokinetic variability, and enhancement of medication dosing has become an increasing focus of research. Such an approach may help resolve the intricacies of maternal physiology, gestational age, disease particulars, lab results, other concomitant medications, and fetal safety during pregnancy, especially when a machine-learning algorithm recognizes patterns out of vast datasets and estimates associations between a patient's characteristics, drug exposure, and therapeutic outcomes. Moreover, when combined with validated pharmacological knowledge, AI may facilitate achieving more individualized medication management (**Figure 5)**. That said, however, careful validation is needed for its clinical use as there are still many medications with limited pregnancy-specific pharmacokinetic and pharmacodynamic information [46].

12.1 Machine Learning for Pharmacokinetic Prediction

Machine learning is based on algorithms used for analysis of data and prediction of new outcomes. In the field of clinical pharmacology, machine learning can process various parameters, including maternal age, body mass, term of pregnancy, kidney and liver functions, genetic information, drug dose, and concentration of the drug in the blood. Based on the data quality and quantity, machine learning methods can be used to predict drug clearance, concentration-time curve, therapeutic effect, and adverse response. In pregnant women, machine learning can be applied to detect those patients whose pharmacokinetic parameters deviate from general population norms. A possible case of application of machine learning is related to the need for predicting drug concentrations in time when renal clearance and hepatic enzyme activity change in pregnancy. Moreover, machine learning methods can be employed in PBPK modeling, allowing indicating certain processes missing in regular assumptions. However, accuracy of predictions assumes development of representative databases that comprise different pregnant people and important clinical outcomes [47].

12.2 AI-Based Dose Optimization and Clinical Decision Support

Dose optimization using artificial intelligence identifies dosing regimens that allow achieving therapeutic targets while reducing the risk of toxicity. These systems can make use of pharmacokinetic monitoring data, clinical laboratory tests results, patient characteristics, and proven dosing therapies in order to make personalized recommendations. If there is enough evidence, then the AI has the potential to help identify the patients who require additional monitoring, reveal possible drug interactions, and highlight dosing regimens that might contradict the established pregnancy recommendations. Integrating electronic health records might give decision-support systems an opportunity to take into account gestational age, maternal diagnoses, current medications, and relevant laboratory parameters while prescribing medications. AI can also help determine the changes in the clinical situation which require reviewing the medications used. At the same time, recommendations made should be explainable and clinically justified and approved by qualified specialists. Automated forecasts must not substitute for established clinical guidelines [48].

12.3 Challenges in AI-Assisted Pregnancy Dosing

AI-assisted pregnancy dosing faces many different challenges, one of the most significant being the lack of sufficient accurate and relevant data. Clinical data on pregnant patients have been lacking historically, while many observational studies do not provide adequate information regarding gestational age, exposure to medications, paediatric outcomes, or long-term child development. Because of this, the models created based on these kinds of datasets may be biased and, therefore, ineffective when transferring them to other groups of patients. The challenges that AI-assisted pregnancy dosing may face may also include issues with data privacy, transparency of algorithms, reproducibility of results, cooperation between different health care facilities, and regulatory control. Furthermore, the AI models may discover statistical correlations without finding also biological mechanisms or causal relationships. The wrong recommendations would lead to the wrong treatment and would expose the foetuses, so AI systems should undergo careful validation and bias testing. In order to make sure these systems are safe and effective, cooperation between pharmacologists, obstetrician-gynaecologists, pharmacists, data scientists, and authorities is needed [49].

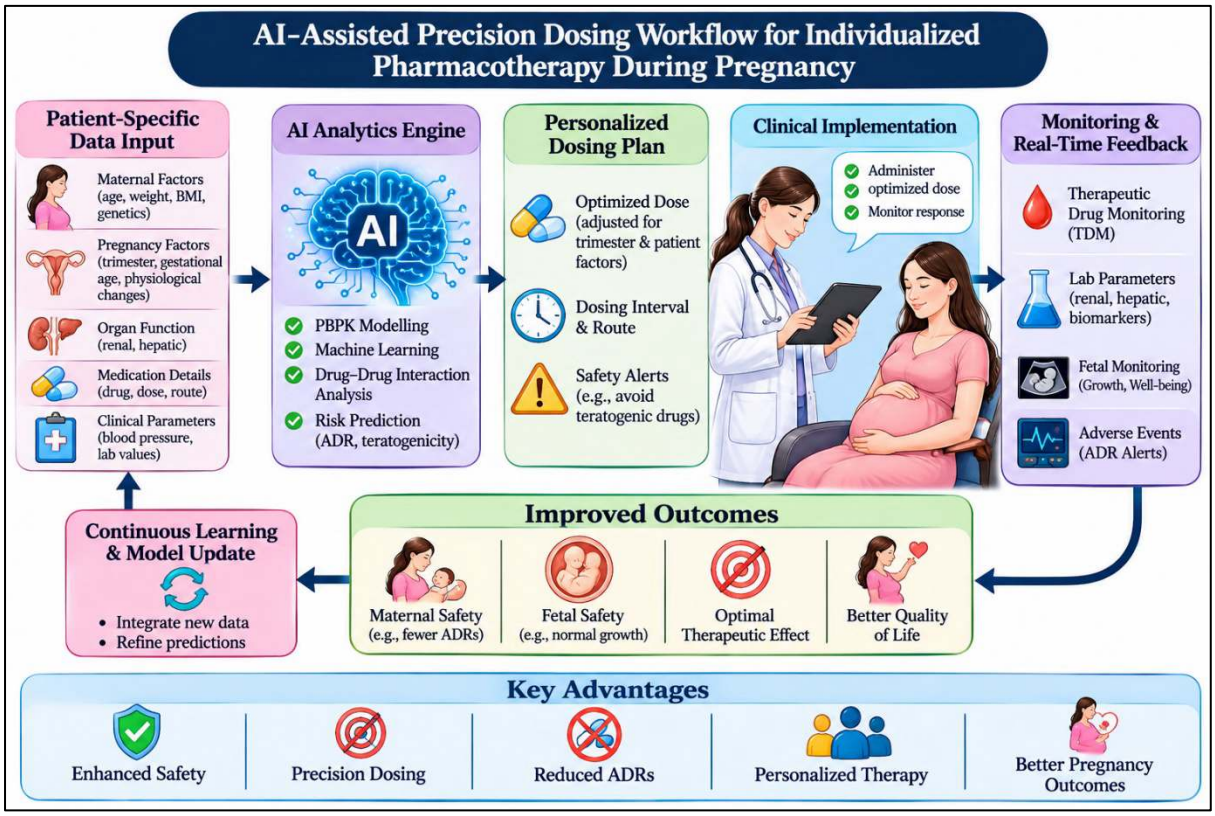

Figure 5. AI-Assisted Precision Dosing Workflow for Individualized Pharmacotherapy During Pregnancy

13. Precision Pharmacotherapy During Pregnancy

Precision pharmacotherapy seeks to customize drug therapy and dosage to suit individual characteristics of a patient instead of opting for general treatment methods that are generally suited for the population as a whole. The relevance of the approach grows even larger in the case of pregnancy, since maternal physiology changes during the nine months of gestation, drug responses vary from one woman to another, and treatment methods may have an influence on both maternal and fetal health. The approach presupposes that the combination of clinical characteristics, pharmacographic data, genetic data, and biological markers will allow for more efficient therapy and fewer risks that could have been avoided [50].

13.1 Individualized Medication Selection and Dose Adjustment

Personalized medicine means considering in the selection of the required medicines the condition of the mother, the severity of the illness being treated, the gestational age, the experience with treatments in the past, and the safety of the medications in question. The best pharmaceutical options are those that give substantial therapeutic advantages and at the same time that create the smallest risk levels for the fetus. One has to consider such parameters as the state of the kidney and liver functions, body mass indexes, concomitant drugs, and receptor polymorphism in making recommendations on medications. Dosing plans should depend on the drug's pharmacokinetics, therapeutic target, result of the treatment administered and available information about pregnancy. Certain medications need higher or more frequent doses because of their higher clearance. Other drugs should be given in smaller doses or not at all because of the potential risks they pose to mothers and foetuses. In the case of drugs with low therapeutic index, testing for the plasma concentration makes adjustments which are necessary. Changes to the dose should not be based on one particular laboratory test or physiological factor [51].

13.2 Therapeutic Drug Monitoring and Pharmacogenomics

Therapeutic drug monitoring (TDM) refers to the assessment of drug concentration levels in biological specimens and can be utilized to optimize the dosage of patients whenever the

efficacy of the drug is related to the drug levels. During pregnancy, TDM can be helpful for certain drugs whose dosage changes greatly in relation to the state of pregnancy and for which the therapeutic range is defined. However, for the TDM results to be accurate, it is important to take into consideration when blood was taken, what dosage was administered, what gestational period is ongoing, whether the drug binds to serum proteins, and what effects does it produce. The origin of pharmacogenomics lies in its ability to show how genetics determine drug absorption and metabolism. Some genetic variations might play a role in drug metabolism and effect in pregnant women. According to the current recommendations, pharmacogenomics can help select drugs and select their dosages. However, pharmacogenomics data must be interpreted taking into account all the physiological changes that occur in pregnant women and the physiological state of the mother [52].

13.3 Personalized Maternal–Fetal Risk–Benefit Assessment

In conducting personalized maternal-fetal risk-benefit analysis, one must assess patients regarding the benefits from therapy against possible negative consequences for both the mother and the fetus/newborn. Factors influencing risk-benefit evaluation include the severity of the mother's illness, possible outcome if the disease is not treated, the ability of the drug to be transferred across the placenta, as well as the duration and timing of the therapy. Since the vulnerability of the fetus differs as the pregnancy progresses, risk assessment should be adjusted accordingly. Decision-making in the clinic should take into consideration in what way the information available is integrated, incl. patients' previous history of successful therapy. In case there is no definitive answer for a specific case, health specialists should explain the client possible risks, limitations of data available, as well as what consequences may have different alternatives. A collaborative work of obstetricians, clinical pharmacists, appropriate specialists and patient is considered to be helpful in making reasonable decisions [53].

14. Current Challenges and Future Perspectives

Although progress in the field of clinical pharmacology has been made, it continues to be hampered by many challenges regarding drug metabolism and drug safety. The absence of pregnant subjects in clinical drug trials, lack of knowledge on pharmacokinetics, and inability to assess fetal drug exposure reduce the evidence for various drugs. Besides, there are

differences between mothers in terms of physiology, type of disease, genetics, and access to healthcare, making it harder to develop personalized medicine. Nowadays, innovative technologies such as PBPK modelling, artificial intelligence, pharmacogenetic analysis, and modern monitoring technologies can help tackle some of these challenges [54].

14.1 Evidence Gaps in Pregnancy Drug Research

A large evidence gap in pregnancy pharmacology is the lack of prospective studies assessing drug pharmacokinetics, efficacy, and safety over various stages of pregnancy. Most conventional drugs have dosing guidelines derived from studies done on non-pregnant adults, ignoring the major physiological differences during pregnancy. Also, fetal drug concentration cannot be directly measured, and long-term developmental effects are likely to remain unidentified. It has also been noticed that there is a scarcity of data on drug-drug interactions, maternal comorbid conditions, variation in placental transporters, and diversity of drug response among different population groups. Observational studies still suffer from confounding factors, incomplete exposure information, and a small number of participants. In the future, more reliable studies on pregnancy pharmacokinetics, pregnancy registries, standardized outcome definitions, and long-term follow-up of mother and child would be needed. Collaboration between institutes and healthcare systems would greatly improve the quality of the obtained data [55].

14.2 Ethical and Regulatory Considerations

The research process that involves pregnant persons requires consideration of maternal agency, fetal welfare, scientific accuracy, and fair access to effective treatment. Although excluding this population from research could reduce immediate ethical dilemmas, it may nevertheless hinder our understanding of medication safety, and result in the implementation of treatment plans based on half-truths. As a result, ethical research should apply adequate risk–benefit assessments, ensure proper informed consent, justify its design based on scientific grounds, and include appropriate safeguards. Regulatory review of drugs being used in pregnant women should be based on available clinical evidence, non-clinical knowledge, timing of exposure, and implications of not treating a disease in a mother. It is crucial to communicate uncertainty because being unable to prove harm does not mean being able to prove safety. Introduction of

AI-based dosing systems and models poses new challenges of data privacy, bias, transparency, accountability, and validation [56].

14.3 Emerging Technologies in Maternal–Fetal Pharmacology

Newly developed technologies are paving the way for more research into exposure to medicines and more personalized treatments in pregnancy. Pregnancy-specific PBPK models can mimic the changes in physiology occurring in the mother's body and therefore allow for predicting drug concentrations both in the mother and in the fetus. Machine learning can help find various patterns of pharmacokinetic variability and problems related to treatment. When the two methods are combined, it will make the prediction of drug dosage more accurate and help detect drugs needing further investigation. Still, one should remember that any predicted data should be confirmed with either experimental or clinical data. Other promising innovations include novel biosensors, better methods of measuring drug concentration, pharmacogenomic testing, and available electronic medical records. These technologies will allow closer monitoring of the patients, very early diagnostics of treatment-related issues, and improved communication among medical specialists. Future studies may combine clinical data with information related to placental biology and biomarkers. To ensure success in application of the technology, interdisciplinary collaboration and uniform protocols of data collection will be necessary [57].

15. Conclusion

Understanding clinical pharmacology in pregnancy relies on comprehending pregnant women's physiological transformations, changes in drug distribution in relation to pregnancy, transfer through the placenta, and fetus sensitivity to drugs. All these factors can influence the efficacy and safety of treatment and make it necessary to use personalized drug therapy with individual dosage as essential features of care for pregnant women. The significance of trimester-related prescribing practice combined with management of pregnancy complications and timely monitoring of medication safety helps weigh benefits of medication use against potential risks for mother, child in utero and after birth.

New methods used in the field such as PBPK modelling in pregnancy, dosages determined by AI, monitoring of drug therapy, and pharmacogenomics show great potential for improving

estimation of risks related to drug therapy in mother-fetus relations. Nevertheless, there are still significant obstacles on the way of successful implementation of new methods such as shortage of clinical data, difficulties with estimations of fetus exposure, and ethical barriers in taking research results to practical application. High-quality clinical studies and reliable prediction methods should be the main focus of scientific efforts in the future.

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