A Textbook of

Clinical Pharmacy

for Pharmacy Students

Lesson 7:

Clinical Pharmacy in Pediatric Patients & Pregnant or Lactating Women

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Lesson 7: Clinical Pharmacy in Pediatric Patients & Pregnant or Lactating Women

Contents

Neonates, infants, children, adolescents, pregnant women, and lactating women are classically grouped as special populations in pharmacotherapy because their physiology differs substantially from that of non-pregnant adults, leading to distinct patterns of drug disposition and response. In the fetus, newborn, and child, organs and systems are still maturing, whereas in pregnancy there is a dynamic, time-dependent remodeling of maternal cardiovascular, renal, hepatic, and endocrine function, with additional complexity introduced by the fetoplacental unit and, later, milk production. These developmental and gestational changes alter all phases of pharmacokinetics and pharmacodynamics, so that simply extrapolating doses and treatment strategies from adult studies is often inappropriate and may compromise both effectiveness and safety.

The concept of **developmental pharmacology** encompasses the impact of growth and maturation on drug absorption, distribution, metabolism, and excretion, as well as on target receptor expression and downstream pharmacodynamic effects throughout childhood. Neonates and young infants, for example, have a higher proportion of total body water, lower protein binding capacity, immature hepatic enzyme systems, and reduced glomerular filtration, which together result in age-dependent differences in exposure to many commonly used medicines when compared with older children and adults. In parallel, gestational pharmacology examines how pregnancy-related physiological adaptations modify maternal pharmacokinetics and pharmacodynamics and how drugs cross the placenta and into breast milk, creating a dual focus on maternal indications and fetal or infant exposure. Understanding these principles is a prerequisite for rational dose selection, titration, and monitoring in both pediatric and maternal care.

Historically, these populations have been **under-represented or explicitly excluded from clinical trials** and drug development programs, leading to a persistent evidence gap at the time many therapies enter routine practice. Therefore, a substantial proportion of medicines used in neonatal and pediatric care are **prescribed off-label**, frequently with limited age-specific data on optimal dosing, efficacy, and safety, while pregnant and lactating women and their clinicians must frequently make decisions in the absence of robust trial evidence.

7.1 Clinical Pharmacy in Pediatric Patients

7.1.1 Developmental pharmacology in neonates and children

Developmental pharmacology describes how growth and maturation modify the disposition and effects of medicines from birth through adolescence, thereby shaping all pharmacotherapeutic decisions in children. **Neonates, infants, children, and adolescents are not simply "small adults"**. The structure and function of gastrointestinal tract, skin, body water and fat compartments, liver, kidneys, and drug targets evolve rapidly, so that the same dose per kilogram may produce very different exposures and responses at different ages. Understanding these trajectories is essential to select appropriate initial doses, design adjustment schemes over time, anticipate altered sensitivity to therapeutic and adverse effects, and interpret therapeutic drug monitoring and clinical endpoints in a developmentally informed way.[1]

Several classification systems have been proposed to capture relevant developmental stages, reflecting both regulatory perspectives and clinical practice. The United States Food and Drug Administration broadly defines the **pediatric population as encompassing patients from birth to 16 years**, commonly subdivided into neonates, infants, children, and adolescents, while other schemes propose finer stratification such as neonate, infant, toddler, early childhood, late childhood, and adolescent, sometimes linking each category to typical body-weight ranges.[2] Although numerical cut-offs vary between systems, they share the recognition that:

- The neonatal period is distinct,
- The first two years of life are characterized by particularly intense physiological change,
- Adolescence brings another transition as most organ functions approach adult values.

Maturational changes in absorption affect enteral, parenteral, and transdermal routes. In neonates and young infants, gastric pH is relatively high, gastric emptying and intestinal motility are slower and more variable, bile acid production is reduced, and the intestinal surface area and transporter expression are still developing, all of which can **delay or decrease the absorption of some orally administered drugs** while increasing that of acid-labile compounds. Percutaneous absorption is enhanced in newborns because of a thinner stratum corneum, greater skin hydration, and a larger surface-area-to-weight ratio, which may lead to unexpectedly high systemic exposure to topical agents, whereas intramuscular absorption is influenced by reduced muscle mass and variable blood flow.

Distribution is also profoundly age-dependent. Neonates have a larger total body water fraction and smaller fat fraction than older children and adults, contributing to larger apparent volumes of distribution for hydrophilic drugs and smaller ones for lipophilic compounds. Plasma protein concentrations, especially albumin and α1-acid glycoprotein, are lower in early life, and binding affinity may differ, increasing the free fraction of highly bound drugs such as phenytoin or some antibiotics. The blood-brain barrier is functionally immature in neonates, which can facilitate central nervous system penetration of certain agents, contributing to both therapeutic effects and neurotoxicity.

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[1] Ruggiero A, Ariano A, Triarico S, et al. Neonatal pharmacology and clinical implications. Drugs Context. 2019;8:212608.
[2] Althammer A, Prückner S, Gehring GC, et al. Systemic review of age brackets in pediatric emergency medicine literature and the development of a universal age classification for pediatric emergency patients - the Munich Age Classification System (MACS). BMC Emerg Med. 2023;23(1):77.

Metabolism and excretion show some of the most striking ontogenetic patterns. Hepatic biotransformation pathways, including cytochrome P450 isoenzymes, conjugating enzymes, and drug transporters, display isoform-specific developmental profiles, with some being nearly absent at birth and increasing over months to years, while others are relatively more active in the perinatal period than later in life. For example, immaturity of certain oxidative and conjugative pathways contributes to prolonged half-lives and accumulation of many medicines in neonates, whereas in older infants and young children, higher relative hepatic clearance can lead to shorter half-lives and higher weight-normalized maintenance dose requirements for some drugs when compared with adults. Renal function also matures postnatally: glomerular filtration rate, tubular secretion, and reabsorption are all reduced at birth and increase over the first months and years of life, which directly influences the elimination of renally cleared medicines and justifies age- and size-adjusted dosing schedules.

Beyond pharmacokinetics, **developmental pharmacodynamics** concerns age-related differences at the level of receptors, ion channels, transporters, and signaling pathways that modulate sensitivity to medicines. Differences in opioid receptor density, subunit composition of GABA and NMDA receptors, or adrenergic receptor expression, for instance, may partly explain the distinct responses of neonates and children to opioids, sedatives, and anesthetic agents, including both desired effects and adverse events such as respiratory depression. Similarly, developmental variation in transporters in the brain, liver, and kidney can affect not only exposure but also the relationship between concentration and effect, as seen with drugs whose efficacy or toxicity is linked to transporter polymorphisms and maturation.

7.1.2 Major Drug Classes in Neonates and Pediatrics

The clinical use of medicines in neonates and children is structured by therapeutic area but is fundamentally shaped by developmental pharmacokinetics and pharmacodynamics, the care setting (NICU[3], PICU[4], or general pediatrics), and the balance between efficacy and prevention of avoidable adverse events. Across all major drug classes, dose selection, formulation and route, and monitoring strategies must therefore be explicitly age-adapted rather than extrapolated from adult practice.

See below for some of the drugs most frequently used in neonatal and pediatric patients. The purpose of this section is to demonstrate the importance of developmental pharmacokinetics and pharmacodynamics, as well as the necessity of using these drugs according to age-specific instructions rather than adjusting their doses based on children's weight.

Anti-infectives

Antimicrobial therapy is one of the most frequent reasons for drug exposure in neonatal and pediatric care, with substantial differences in indication patterns, dosing, and monitoring when compared with adults. Empirical regimens often target perinatal pathogens in the NICU, broader community-acquired infections in general pediatrics, and complex nosocomial pathogens in PICU, while always needing to account for **age-dependent distribution volumes**, renal maturation, and organ support modalities such as extracorporeal membrane oxygenation.

Aminoglycosides (e.g., as gentamicin, tobramycin, and amikacin) illustrate how developmental pharmacokinetics determines dosing: very high total body water and reduced glomerular

[3] NICU: Neonatal Intensive Care Unit.
[4] PICU: Pediatric Intensive Care Unit.

filtration in preterm and term neonates result in larger volumes of distribution and lower clearance, which justify relatively higher doses per kilogram but extended dosing intervals and early use of therapeutic drug monitoring to avoid nephrotoxicity and ototoxicity. In older infants and children, maturation of renal function allows shorter dosing intervals or once-daily regimens, and pharmacokinetic–pharmacodynamic modeling supports extended-interval dosing as a safe and effective strategy that reduces time outside the therapeutic range and may simplify monitoring.

For **beta-lactam antibiotics**, time-dependent killing and the need to maintain free drug concentrations above the minimum inhibitory concentration are complicated in neonates by larger extracellular fluid compartments, immature renal clearance, and frequent hemodynamic instability, which together increase pharmacokinetic variability. In PICU, prolonged or continuous infusions of beta-lactams are more frequently considered to optimize target attainment, especially in children with augmented renal clearance or on organ support, whereas in general pediatrics intermittent dosing usually suffices, provided dosing is weight- and age-adjusted and renal function is monitored in the presence of sepsis, dehydration, or concomitant nephrotoxins.

Vancomycin, used for invasive Gram-positive infections, requires special consideration because of its narrow therapeutic window and complex pharmacokinetics in neonates and critically ill children. Immature renal function in the first weeks of life, profound shifts in volume status, and use of vasoactive drugs or extracorporeal support justify lower initial doses with longer intervals in preterm neonates, followed by early therapeutic drug monitoring targeting area-under-the-curve-based exposure, while in older children higher weight-normalized doses are typically required due to higher clearance. Therapeutic drug monitoring is further explored in Biopharmacy and Pharmacokinetics course (4th year).

Antimicrobial preventable adverse events in NICU and PICU frequently stem from incorrect extrapolation of adult doses, failure to adapt to rapidly changing renal function, and inadequate monitoring of serum levels.

Cardiovascular drugs

Hemodynamic support with inotropes, vasopressors, vasodilators, and diuretics is essential to neonatal and pediatric intensive care, but drug responses differ substantially from adults because of developmental changes in myocardial structure, adrenergic receptor density, and autonomic regulation.

Catecholaminergic inotropes (e.g., dopamine, dobutamine, epinephrine, and norepinephrine) are widely used to treat septic and cardiogenic shock, but their pharmacokinetics and pharmacodynamics are influenced by postnatal age, underlying cardiac lesions, and concomitant therapies.

Non-catecholamine inotropes, (e.g., milrinone and cardiac glycosides) have roles in postoperative cardiac patients and some forms of heart failure, but their use in neonates requires vigilance because of longer half-lives, higher susceptibility to hypotension or arrhythmias, and interactions with co-administered diuretics and vasodilators. Milrinone clearance, for example, is reduced in neonates and infants, so loading doses are often avoided and maintenance infusions started at the lower end of the dosing range, with close monitoring of blood pressure, renal function, and, where available, echocardiographic parameters of cardiac output.

Diuretics such as furosemide are frequently used in NICU and PICU to manage fluid overload and support respiratory function, but premature neonates are particularly vulnerable to electrolyte disturbances, nephrocalcinosis, and ototoxicity, especially when high cumulative doses are combined with other ototoxic drugs. In general pediatrics, long-term diuretic therapy for chronic cardiac or renal conditions demands structured monitoring of weight, hydration status, electrolytes, and renal function, while also considering formulation issues, as extemporaneous liquid preparations may differ in bioavailability and stability from tablet formulations used in adults.

Antiarrhythmic drugs (e.g., amiodarone, adenosine, and beta-blockers) play important roles in the management of supraventricular and ventricular arrhythmias in children, but their dosing and risk profiles differ from adults because of age-dependent changes in conduction system properties and drug metabolism.

Analgesia and sedation

Pain and anxiety are often under-recognized and undertreated in neonates and children. Analgesic and sedative strategies must therefore integrate developmental pharmacology with careful assessment tools adapted to age and communication ability, while avoiding patterns of exposure that may contribute to respiratory depression, delirium, withdrawal, or long-term neurocognitive harm.

Paracetamol is a initial analgesic and antipyretic across all pediatric age groups, but neonates and young infants exhibit lower clearance, which requires lower weight-normalized doses and extended dosing intervals to avoid accumulation and hepatotoxicity.

Nonsteroidal anti-inflammatory drugs, particularly ibuprofen and ketorolac, are widely used for nociceptive pain related to surgery or trauma and, when properly dosed, they provide analgesia comparable to opioids while often reducing opioid requirements and not compromising overall pain control. In neonates and young infants, NSAID use is more restricted because of concerns about renal perfusion, gastrointestinal complications, and effects on the ductus arteriosus[5].

Opioids such as morphine and fentanyl remain important for moderate to severe pain and deep sedation, particularly in NICU and PICU, but developmental differences in receptor expression, blood–brain barrier permeability, and clearance increase the risk of respiratory depression and accumulation in neonates. Consequently, dosing in early life is typically conservative, with slow titration, avoiding rapid intravenous boluses, and close observation of respiratory rate, oxygen saturation.

Sedative agents, including benzodiazepines and alpha-2 agonists, are commonly used to facilitate mechanical ventilation and invasive procedures, yet their pharmacokinetics and pharmacodynamics vary widely with age and underlying illness.

[5] The ductus arteriosus is a normal fetal blood vessel that connects the pulmonary artery to the descending aorta, allowing blood to bypass the non-functioning lungs before birth and usually closing soon after delivery.

Respiratory drugs

Respiratory medications are ubiquitous in pediatric practice, but age-dependent differences in airway anatomy, receptor distribution, and inhalation technique have important implications for drug selection and delivery.

Bronchodilators, mainly short-acting beta-2 agonists such as salbutamol, are first-line agents for acute bronchospasm, but their role and responsiveness differ between preschool wheezing, classic atopic asthma, and viral bronchiolitis.

Inhaled corticosteroids are used in the long-term management of persistent asthma in children, and their therapeutic index is influenced by age, device, and adherence. Although systemic adverse effects such as growth suppression are generally modest at recommended doses, cumulative exposure over years, especially when combined with intranasal or topical corticosteroids, warrants regular assessment of growth, adrenal function in selected cases, and optimization of the lowest effective dose.

Systemic corticosteroids, particularly prednisolone and dexamethasone, are used for acute asthma exacerbations, and other inflammatory conditions, but in neonates and preterm infants their use demands special caution because of potential neurodevelopmental and endocrine sequelae.

Antiepileptics and psychotropics

Antiepileptic pharmacotherapy in neonates and children must account for age-specific seizure etiologies, rapid developmental changes in drug metabolism, and the potential impact of long-term exposure on neurocognitive and behavioral outcomes. Many antiepileptics, including phenobarbital and phenytoin, have long half-lives and narrow therapeutic windows in neonates, where immature hepatic metabolism and protein binding lead to higher free concentrations at lower total levels, making therapeutic drug monitoring and careful interpretation of total versus free levels particularly important.

Newer antiepileptics such as levetiracetam and topiramate are increasingly used in pediatric epilepsy because of more favorable interaction profiles, but their pharmacokinetics still vary with age, and higher weight-normalized maintenance doses may be required in young children due to increased clearance.

Psychotropic drugs, including antidepressants, antipsychotics, and stimulants, are used more frequently in adolescents than in younger children, but their use remains largely off-label and guided by extrapolation from adult data and limited pediatric trials. Developmental differences in neurotransmitter systems and ongoing brain maturation raise concerns about long-term effects on cognition, growth, and metabolic health, so treatment plans in child and adolescent psychiatry emphasize careful baseline assessment, slow dose titration, and structured monitoring of weight, metabolic parameters, extrapyramidal symptoms, and suicidality, with explicit involvement of caregivers in shared decision-making.

7.1.3 Clinical Issues in Neonatal and Pediatric Pharmacotherapy

Clinical issues in neonatal and pediatric pharmacotherapy reflect the interaction between developmental biology, gaps in regulatory evidence, and the complexity of daily prescribing and administration practices. These themes occur irrespective of therapeutic area and must be

explicitly considered whenever medicines are selected, dosed, prepared, administered, and monitored in neonates and children.

Off-label and unlicensed use of medicines is a prevalent feature of pediatric practice, driven largely by the historical exclusion of children from clinical trials and the slow pace of age-appropriate product development. Roughly one in ten and three-quarters of prescriptions are off-label, and up to one-third may involve unlicensed use, with the highest prevalences consistently observed in NICU and PICU and among children younger than two years.[6] Such prescribing can be clinically justified when no licensed alternatives exist, but it is associated with increased incidence and seriousness of adverse reactions. Regulatory initiatives have increased the number of products with pediatric labelling, yet large gaps remain, especially for neonates, rare diseases, and chronic psychotropic or biologic therapies, maintaining the need for structured risk management whenever off-label use is unavoidable.[7]

Dose calculation in children is intrinsically prone to error because most medicines require individualization by weight, body surface area, or age, often combined with dilution steps and unit conversions.[8] Formulation problems are another major cross-cutting issue because most commercially available medicines are developed for adults, forcing clinicians, pharmacists, and caregivers to manipulate dosage forms to achieve child-appropriate doses. This may involve splitting or crushing tablets, opening capsules, or preparing extemporaneous oral liquids, practices that can alter bioavailability, stability, and palatability and introduce substantial variability in delivered doses, particularly for narrow-therapeutic-index drugs. In neonates and infants, excipients that are inert in adults, such as certain solvents, preservatives, sweeteners, and coloring agents, can be harmful because of immature metabolic pathways and organ function.[9]

Therapeutic drug monitoring is particularly relevant in neonatal and pediatric pharmacotherapy for medicines with narrow therapeutic windows, high inter-individual pharmacokinetic variability, or serious concentration-dependent toxicity. In this population, examples include aminoglycosides, vancomycin, several antiepileptics, immunosuppressants, and some cytotoxic drugs, where age-dependent differences in distribution, protein binding, metabolism, and renal elimination can change rapidly over days or weeks, especially in preterm neonates or critically ill children. TDM will be further explored in Biopharmacy and Pharmacokinetics course (4th year).

[6] Gore R, Chugh PK, Tripathi CD, Lhamo Y, Gautam S. Pediatric Off-Label and Unlicensed Drug Use and Its Implications. Curr Clin Pharmacol. 2017;12(1):18-25.
[7] https://www.ema.europa.eu/en/documents/other/evidence-harm-label-or-unlicensed-medicines-children_en.pdf
[8] Lesar TS. Errors in the use of medication dosage equations. Arch Pediatr Adolesc Med. 1998;152(4):340-344.
[9] Barbosa R, Sampaio C, Sousa L, et al. Exposure to potentially harmful excipients in neonates admitted to intensive care units using compounded medicines. Eur J Hosp Pharm. doi:10.1136/ejhpharm-2024-004340

7.2 Clinical Pharmacy in Pregnant Women

Pregnancy is accompanied by profound and time-dependent changes in maternal and fetal pharmacology that modify both exposure and response to medicines and therefore have direct implications for dose selection, and risk assessment throughout gestation. These adaptations arise from coordinated alterations in maternal physiology and the unique characteristics of the placenta and fetus, so that the same regimen may produce very different maternal and fetal concentrations at different stages of pregnancy in comparison with non-pregnant adults.

7.2.1 Maternal pharmacokinetics and pharmacodynamics

From early pregnancy, plasma volume, extracellular water, and total body water increase substantially, with maternal blood volume typically expanding by 40–50% by the late second and third trimesters and cardiac output rising in parallel. These changes **enlarge the apparent volume of distribution of hydrophilic agents**, often leading to lower peak concentrations for a given dose, while increased adipose tissue mass can modestly expand the distribution of lipophilic drugs, especially in late pregnancy.[10],[11]

Plasma albumin and, to a lesser extent, α1-acid glycoprotein concentrations decrease during pregnancy because of hemodilution and altered synthesis, **reducing protein binding and increasing the free fraction of highly bound drugs** such as phenytoin or some beta-lactams. For drugs where free concentration rather than total plasma concentration is the main driver of effect and toxicity, this can partly offset lower total levels, but it also complicates interpretation of therapeutic drug monitoring if only total concentrations are measured.

Gastrointestinal physiology is also modified. Progesterone-mediated smooth muscle relaxation and mechanical compression by the gravid uterus **slow gastric emptying and intestinal motility**, while changes in gastric pH, bile acid secretion, and nausea or vomiting can **influence the extent and rate of absorption of orally administered medicines**. For most drugs these effects mainly affect time to peak rather than overall exposure, but they can be clinically relevant for agents requiring rapid onset or when adherence is compromised by hyperemesis gravidarum.

Renal function shows some of the most consistent pregnancy-associated changes. Glomerular filtration rate increases by approximately 40–50% from early gestation and renal blood flow is similarly augmented, leading to **higher clearance of many renally eliminated drugs** such as lithium, certain beta-lactams, and low-molecular-weight heparins. For these agents, standard non-pregnant doses may produce subtherapeutic concentrations, particularly in the second and early third trimesters, which may justify higher or more frequent dosing or closer monitoring of clinical and, where available, pharmacokinetic targets.

Hepatic drug metabolism is modified in an enzyme-specific manner. Activity of some cytochrome P450 isoenzymes, notably CYP3A4, CYP2D6, and CYP2A6, tends to increase, while others, such as CYP1A2 and CYP2C19, often show decreased activity, with additional changes in conjugation pathways such as glucuronidation. These divergent patterns mean that exposure to drugs cleared by CYP3A4 (e.g., amlodipine, verapamil, diltiazem, several statins, azole antifungals) and by CYP2D6 (e.g., paroxetine and fluoxetine, beta-blockers, codeine, tramadol)

[10] Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. Semin Perinatol. 2015;39(7):512-519.
[11] Pariente G, Leibson T, Carls A, et al. Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review. PLoS Med. 2016;13(11):e1002160.

may fall during pregnancy. On the other hand, drugs cleared by CYP1A2 (e.g., caffeine and theophylline, clozapine and olanzapine, certain fluoroquinolones) may accumulate.

At the pharmacodynamic level, pregnancy influences the sensitivity of target organs and systems to many medicines. Altered expression of receptors and transporters, changes in autonomic tone, and adaptations in coagulation and renin–angiotensin–aldosterone systems contribute to modified responses to antihypertensives, anticoagulants, and other cardiovascular agents when compared with non-pregnant adults. For example, vasodilatory responses may be enhanced, baseline coagulation is shifted towards a pro-thrombotic state, and insulin resistance increases in later gestation, which together shape the response to antihypertensives, low-molecular-weight heparins, and antidiabetic therapies.

7.2.2 Placental transfer and fetal pharmacokinetics

The placenta is a highly specialized organ that serves as both a canal and a barrier between maternal and fetal circulations, enabling nutrient and gas exchange while modulating the passage of xenobiotics. **Drugs can cross the placenta by several mechanisms, including passive diffusion, facilitated diffusion, active transport, and, less commonly, pinocytosis**, with most small, lipophilic, weakly bound, and non-ionized molecules crossing primarily by passive diffusion down their concentration gradients.[12]

Placental transfer is influenced by maternal and fetal blood flow, placental surface area and thickness, and the expression and activity of numerous transporters, such as P-glycoprotein (ABCB1), breast cancer resistance protein (ABCG2), and organic anion-transporting polypeptides, which can limit or facilitate fetal exposure to specific drugs. These transporters show gestational-age-dependent expression, with some being more abundant in early pregnancy and others increasing later, implying that the same drug may have different fetal:maternal concentration ratios at different stages of gestation.[13] **Efflux pumps** such as P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) are generally more abundant and functionally active in early pregnancy, when organogenesis is ongoing, thereby enhancing maternal-to-fetal protection for their substrates and tending to keep fetal:maternal concentration ratios relatively low in the first trimester. As gestation advances, expression of these efflux systems often declines, while the capacity of certain **influx transporters and nutrient carriers** increases in parallel with rising fetal metabolic demands. Consequently, for drugs that are substrates of these systems, the net balance between protective efflux and permissive influx can shift with advancing gestation, so that the same maternal dose may produce different fetal:maternal exposure ratios at different stages of pregnancy. For P-gp (and BCRP) substrates such as digoxin, methadone and several antiretroviral protease inhibitors, higher efflux capacity in the first trimester is expected to limit early fetal exposure, whereas declining P-gp/BCRP abundance towards term may allow relatively greater transfer later in pregnancy. By contrast, for drugs that are substrates of influx transporters that increase in abundance with gestational age, such as cationic substrates of non-ATP-dependent OCT3 (metformin) or anionic substrates of ATP-dependent OAT4 (olmesartan and pravastatin), the

[12] Duhaim A, Almatroudi TA, Alghidani ZA, et al. Pharmacokinetics of Maternal Drug Administration: Insights into Placental Transfer and Fetal Exposure. J Pharm Bioallied Sci. 2024;16(Suppl 4):S3743-S3745.
[13] Fein KC, Arral ML, Kim JS, et al. Placental drug transport and fetal exposure during pregnancy is determined by drug molecular size, chemistry, and conformation. J Control Release. 2023;361:29-39.

progressive upregulation of these carriers in the second and third trimesters can enhance placental uptake and thereby increase fetal exposure over time.

Once a drug reaches fetal circulation, its disposition is governed by fetal physiology, which differs markedly from that of the mother. **Fetal plasma protein binding is lower, total body water is proportionally higher, and the pattern of organ blood flow is unique**, with the liver and placenta receiving a substantial fraction of cardiac output, while the lungs are largely bypassed through the *ductus arteriosus* and *foramen ovale*. Hepatic and renal elimination pathways are immature in the fetus, so that many drugs that enter the fetal compartment are cleared slowly and may recirculate via the amniotic fluid after fetal swallowing, prolonging exposure even when maternal dosing is intermittent.

Fetal metabolism relies partly on placental biotransformation, which can both detoxify and activate xenobiotics, and partly on limited fetal hepatic enzyme activity, with important variability between pathways. For some drugs, the placenta may generate metabolites that have different pharmacological or toxicological profiles than the parent compound, making it difficult to predict fetal effects solely from maternal pharmacokinetic data.

These maternal–placental–fetal interactions create a situation in which **maternal dose–concentration relationships cannot be directly extrapolated to fetal exposure**, even when maternal pharmacokinetics are well described. Consequently, when fetal benefit or risk is central to the indication, such as in antiarrhythmic therapy for fetal arrhythmias or in the use of antiepileptics and psychotropic drugs, clinical decisions need to integrate the limited available data on fetal concentrations, mechanistic understanding of placental transport, and careful ultrasound and clinical monitoring of fetal well-being.

7.2.2 Timing of exposure and gestational risk

The timing of exposure relative to embryonic and fetal development is a key determinant of the type and severity of adverse developmental effects. During the **pre-implantation period** (approximately the first 2 weeks post-conception), exposures are often described as following an “all-or-none” pattern, leading either to early pregnancy loss or to survival without major structural anomalies, although subtle effects cannot be excluded. The **period of organogenesis**, roughly from weeks 3 to 8 post-conception (5–10 weeks of gestational age), is the most critical window for structural malformations, because major organs and limbs are forming and teratogenic insults can produce characteristic patterns of congenital anomalies.

In the **second and third trimesters**, the risk profile shifts towards effects on growth, functional development, and maturation of organs such as the brain, lungs, kidneys, and endocrine systems. Exposures during these later stages are more likely to result in intrauterine growth restriction, functional deficits, or reversible pharmacological effects (for example, fetal and neonatal adaptation syndromes with psychotropics or beta-blockers) rather than major structural malformations, although there are exceptions such as *ductus arteriosus* constriction with late-pregnancy non-steroidal anti-inflammatory drugs.

Teratogenic and fetotoxic risk is therefore not a fixed property of a drug but reflects the interplay between its mechanism of action, placental transfer, fetal pharmacokinetics and pharmacodynamics, and the specific gestational window of exposure. From a clinical standpoint, this means that past or planned exposures need to be interpreted with careful attention to the exact timing in gestational weeks, dose and duration, and co-existing maternal or fetal conditions, rather than based on drug name alone.

7.2.3 Pregnancy-specific Conditions

Pregnancy-specific conditions often require pharmacotherapy that must be adapted to gestational age, because maternal benefit and fetal risk shift from early organogenesis to late pregnancy and the postpartum period. The main clinical challenges arise in hypertensive disorders including pre-eclampsia, nausea and vomiting of pregnancy, and prevention and treatment of venous thromboembolism, where both the drug selection and timing of use are critical.[14]

Hypertensive disorders of pregnancy, particularly pre-eclampsia, are managed with the dual aim of preventing maternal complications such as stroke and eclampsia and mitigating placental insufficiency and fetal compromise, while recognizing that delivery is the only definitive cure. Pre-eclampsia is characterized by new-onset hypertension accompanied by proteinuria or other signs of end-organ dysfunction such as thrombocytopenia, renal insufficiency, elevated liver enzymes, or cerebral and visual disturbances. It is thought to originate from abnormal placental development and consequent release of antiangiogenic factors into the maternal circulation. Agents that target the renin-angiotensin system are usually withdrawn before or as soon as pregnancy is recognized because first-trimester exposure has been associated with congenital malformations and later exposure with fetopathy, whereas labetalol, nifedipine, and methyldopa are preferred oral options from early gestation onwards given their more favorable fetal safety profiles. In the second and third trimesters, acute severe hypertension is treated with rapidly acting drugs such as intravenous labetalol or hydralazine or oral nifedipine, and magnesium sulfate is added for seizure prophylaxis in pre-eclampsia and eclampsia, with dosing tailored to maternal renal function and close monitoring around delivery.

Nausea and vomiting of pregnancy, including *hyperemesis gravidarum*, usually peak in the first trimester, when baseline teratogenic risk is highest and concerns about malformations are greatest. Initial management emphasizes non-pharmacological approaches, followed by vitamin B6 and doxylamine or other H1-antihistamines, which have an extensive and generally reassuring first-trimester safety record and can be continued into later trimesters if symptoms persist, with sedation as the main limiting factor. Dopamine antagonists and 5-HT3 antagonists are reserved for refractory cases. For ondansetron, most data do not show a large increase in overall malformations, although some reports of small increases in orofacial clefts or cardiac anomalies with early exposure lead many clinicians to restrict its first-trimester use to situations where other regimens have failed and maternal health is clearly compromised.

Gestational diabetes mellitus is one of the most common metabolic complications of pregnancy, typically diagnosed between 24 and 28 weeks of gestation through oral glucose tolerance testing, and its prevalence continues to rise worldwide. Initial management centers on medical nutrition therapy and regular physical activity, which suffice for many women to achieve fasting glucose below 95 mg/dL and one-hour postprandial glucose below 140 mg/dL. When lifestyle measures fail to maintain glycemic targets, insulin remains the preferred first-line pharmacological agent because it does not cross the placenta and can be titrated precisely to match evolving insulin resistance as gestation advances, with rapid-acting analogues such as lispro and aspart generally preferred over regular insulin for prandial coverage, and NPH or long-acting insulins for basal needs. Although metformin and glyburide are widely used in practice, the American Diabetes Association and the American College of Obstetricians and

[14] Dathe K, Schaefer C. The Use of Medication in Pregnancy. Dtsch Arztebl Int. 2019;116(46):783-790.

Gynecologists caution against their use as first-line agents: both cross the placenta, metformin achieves fetal concentrations comparable to maternal levels and has uncertain long-term offspring implications, and glyburide is associated with higher rates of neonatal hypoglycemia and macrosomia compared with insulin in meta-analyses of randomized trials.

Venous thromboembolism risk rises steadily through pregnancy and peaks in the early postpartum period, particularly after cesarean section, pre-eclampsia, or prolonged immobility. Low-molecular-weight heparins are the agents of choice for both prophylaxis and treatment in all trimesters because they do not cross the placenta and have predictable pharmacokinetics, allowing dosing to be adjusted as maternal weight and renal function change with advancing gestation. In contrast, warfarin and other vitamin K antagonists cross the placenta and are associated with embryopathy when exposure occurs between 6 and 12 weeks, so they are generally avoided in early pregnancy and again near term, with substitution by heparin before conception or once pregnancy is detected in most women on long-term anticoagulation.

7.3 Clinical Pharmacy lactation and the breastfed infant

Medicines taken by lactating women can reach the breastfed infant through breast milk, but for most used agents the absolute infant dose is small, and breastfeeding can be safely supported with appropriate selection and monitoring. Understanding the physicochemical and pharmacokinetic determinants of milk transfer allows more nuanced decisions than simply stopping breastfeeding whenever pharmacotherapy is needed.

Passage into breast milk depends on several properties of the drug and the mother–infant pair. **Low molecular weight, high lipophilicity, low protein binding, and passive diffusion favor transfer**, while large, hydrophilic, and highly protein-bound molecules generally appear in milk at very low concentrations. Weak bases tend to concentrate in milk because human milk is slightly more acidic than plasma, leading to ion trapping, whereas weak acids usually achieve lower milk concentrations for a given plasma level.

Drugs with long half-lives, active metabolites, or slow-release formulations can lead to higher and more sustained infant exposure than short-acting agents, especially when feeds occur near the time of peak maternal concentration. Conversely, medicines with short half-lives, rapid distribution, and limited oral bioavailability in the infant often result in negligible systemic exposure even when measurable amounts are present in milk.

Two descriptive metrics are widely used. The **milk-to-plasma ratio** compares average concentrations in milk and maternal plasma but does not alone indicate infant risk, because it ignores total maternal dose and feeding volume. The **relative infant dose**, usually expressed as the infant's dose in mg/kg/day via milk divided by the maternal mg/kg/day dose, integrates milk concentration, volume ingested, and maternal dosing. Relative infant doses below about 10% are commonly considered compatible with breastfeeding, if the drug has no specific toxicity to neonates.

In clinical practice, **preference is usually given to agents with low oral bioavailability in infants, short half-lives, low relative infant doses, and substantial experience in breastfeeding women**. For many therapeutic areas, such as analgesia, antihypertensives, and antidepressants, one can often select a drug from within the class (for example, paracetamol

rather than codeine, labetalol rather than atenolol, sertraline rather than less-studied antidepressants) that combines maternal efficacy with reassuring lactation safety data.

When a medicine with genuinely concerning lactation safety (for example, cytotoxic chemotherapy, radioactive isotopes, or high-dose immunosuppressants) is unavoidable, options include temporary interruption of breastfeeding with maintenance of milk production by pumping and discarding, permanent transition to formula, or, occasionally, deferring therapy if clinically safe. Whenever breastfeeding must be interrupted, clear plans for the duration of interruption, safe storage or disposal of expressed milk, and the timing of re-initiation relative to drug elimination half-life help minimize both infant risk and disruption of lactation.