

GENERAL PRESCRIBING GUIDELINES FOR PREGNANCY & LACTATION

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Drug Use in Pregnancy

- Medication doses for acute and chronic illnesses are generally the same as those used in non-pregnant adults.
- However, some drugs require dose adjustments or alternative drug selection because pregnancy alters maternal physiology and may affect fetal development.
- The primary goal of drug therapy during pregnancy is to provide benefit to the mother while minimizing risks to the fetus.

Physiology of Pregnancy

Fertilization (Fallopian Tube)



Zygote Formation



Cell Division During Transport



Blastocyst (Day 6)



hCG Production Begins



Implantation in Endometrium



Embryo (Weeks 2–8)

↓ (*Organogenesis*)

Fetus (>8 Weeks)

↓ (*Growth & Maturation*)

Term Pregnancy (~40 Weeks LMP)

1. Fertilization

- Fertilization occurs in the fallopian tube.
- A sperm attaches to the outer layer of the ovum called the zona pellucida.
- This attachment prevents other sperm from entering the egg.
- The sperm releases enzymes that help it penetrate the zona pellucida.
- The sperm membrane and egg membrane fuse together.
- A single cell called a zygote is formed.
- Maternal and paternal chromosomes combine to form one nucleus and initiate cell division.

2. Transport to the Uterus

Time After Fertilization	Event
Day 0	Fertilization occurs in fallopian tube
Day 2	Fertilized egg reaches uterus while dividing
Days 3–5	Continued cell division in uterine cavity
Day 6	Cell mass becomes a blastocyst
Day 6 onward	Implantation begins

3. Blastocyst Formation

- By approximately 6 days after fertilization, the developing cell mass is called a blastocyst.
- The blastocyst begins producing human chorionic gonadotropin (hCG).
- hCG is the hormone detected in pregnancy tests.

4. Implantation

- The blastocyst sheds the zona pellucida.
- It attaches directly to the uterine lining (endometrium).
- The blastocyst grows into the endometrial wall.
- By day 10 after fertilization, implantation is complete.
- Maternal blood begins supplying nutrients to the developing embryo.

5. Embryonic and Fetal Periods

Embryonic Period

- Begins approximately during the 3rd week after fertilization.
- The developing organism is called an embryo.
- Lasts from 2–8 weeks postfertilization.
- Most major organs and body structures form during this period (organogenesis).
- This is the period of greatest susceptibility to teratogenic drugs.

Fetal Period

- Starts after the embryonic period (after 8 weeks postfertilization).
- The embryo is now called a fetus.
- Growth, maturation, and functional development of organs occur.
- Continues until delivery.

Decoding Obstetric Terminology (GTPAL Notation)

G
T
P
A
L

Gravidity (Total number of pregnancies, regardless of outcome. Multiples count as 1).

Term deliveries.

Preterm deliveries (Beyond 20 weeks).

Abortions (Spontaneous or induced, including ectopic).

Living children.

Clinical Example

G4P2113

Pregnant **4** times
2 Term deliveries
1 Preterm delivery
1 Abortion
3 Living children

Characteristics of Pregnancy

Gestational Age

- **Gestational age** is the age of the embryo or fetus measured from the **first day of the last menstrual period (LMP)**.
- Since ovulation and fertilization usually occur about 2 weeks after the LMP:
 - ◆ Gestational age is approximately **2 weeks greater than the actual fetal age**.

Example

- LMP: January 1
- Fertilization: January 15 (approximately)
- On February 12:
 - ◆ Gestational age = 6 weeks
 - ◆ Actual fetal age = 4 weeks

Trimesters of Pregnancy

Pregnancy is divided into **three trimesters**, each lasting approximately **3 calendar months**.

Duration of Pregnancy

- Pregnancy lasts approximately **280 days** from the **first day of the last menstrual period (LMP)**.
- This corresponds to about 38 weeks after fertilization.
- This equals:
 - ◆ **40 weeks**
 - ◆ **9 months**
- Pregnancy duration is conventionally calculated from the LMP, even though fertilization usually occurs about 2 weeks later.

Trimester	Duration
First Trimester	0–13 weeks
Second Trimester	14–27 weeks
Third Trimester	28–40 weeks

Estimated Due Date (EDD)

Naegele's Rule: To calculate the expected date of delivery:

EDD = First day of LMP + 7 days – 3 months + 1 year

Example

- LMP = 10 January 2025
- Add 7 days = 17 January 2025
- Subtract 3 months = 17 October 2024
- Add 1 year = **17 October 2025**

Expected Due Date = 17 October 2025

Fetal Movement (Quickening)

Definition

- First perception of fetal movement by the mother.

Timing

- Usually felt between **14–20 weeks** of gestation.

Influence of Previous Pregnancies

Woman Type	Time of Perceiving Fetal Movement
Multiparous (previous pregnancies)	Earlier
Primiparous (first pregnancy)	Later

EARLY SYMPTOMS OF PREGNANCY



1 Fatigue

- One of the earliest symptoms.
- Occurs due to hormonal changes and increased metabolic demands.



2 Increased Urinary Frequency

- Common during early pregnancy.
- Caused by hormonal changes and pressure on the bladder.



3 Nausea and Vomiting

- Usually begin after the first or second missed menstrual period.
- Commonly called morning sickness.
- Can occur at any time of the day.

DURATION



Usually starts around **4–6 weeks** of gestation.



Typically resolves by **14–16 weeks** of gestation.

SIGNS OF PREGNANCY

1 Cessation of Menses (Amenorrhea)

- Most common early sign.
- Absence of menstrual periods after conception.



2 Changes in Cervical Mucus

- Cervical secretions become thicker and altered in consistency.



3 Bluish Discoloration of Vaginal Mucosa

- Increased pelvic blood flow causes a bluish-purple coloration.
- Known as Chadwick's sign.



4 Increased Skin Pigmentation

- Common changes include:
 - Darkening of nipples and areolae
 - Linea nigra (dark line on abdomen)
 - Melasma/Chloasma ("mask of pregnancy")



5 Breast Changes

- Breast enlargement
- Increased tenderness
- Darkening of areolae
- Prominent superficial veins
- Preparation for lactation.



NOTE: Symptoms may vary from woman to woman. The presence of signs and symptoms does not confirm pregnancy. A pregnancy test and medical evaluation are recommended for confirmation.



Maternal Pharmacokinetic Changes During Pregnancy

Pregnancy produces several physiological changes that alter the **absorption, distribution, metabolism, and excretion (ADME)** of drugs. These changes can influence drug concentrations, therapeutic response, and toxicity, sometimes requiring dosage adjustments.

Pharmacokinetic Process	Physiological Change During Pregnancy	Effect on Drug Therapy
Absorption		
Gastrointestinal motility	↓ Decreased	Slower gastric emptying and intestinal transit; delayed drug absorption
Lung function	↑ Increased	Greater absorption of inhaled medications
Skin blood circulation	↑ Increased	Enhanced absorption of transdermal and topical drugs

Pharmacokinetic Process	Physiological Change During Pregnancy	Effect on Drug Therapy
Distribution		
Plasma volume	↑ Increased	Dilution of water-soluble drugs, lowering plasma concentrations
Total body water	↑ Increased	Increased volume of distribution for hydrophilic drugs
Plasma proteins (especially albumin)	↓ Decreased	Increased free (unbound) fraction of highly protein-bound drugs
Fat deposition	↑ Increased	Increased storage and distribution of lipophilic drugs
Metabolism		
Liver enzyme activity	↑ or ↓ Variable	Some drugs are metabolized faster, others more slowly depending on the enzyme involved
Excretion		
Glomerular filtration rate (GFR)	↑ Increased	Faster renal elimination of drugs excreted unchanged in urine

Pharmacokinetic Process	Pregnancy Change	Clinical Effect
Gastric motility	↓	Delayed drug absorption
Gastric acidity	↓	Altered absorption of weak acids/bases
Pulmonary blood flow	↑	Increased inhalational drug absorption
Plasma volume	↑ 30–50%	Dilution of drugs
Total body water	↑ 8 L	Increased Vd of hydrophilic drugs
Albumin	↓	Increased free drug fraction
Hepatic metabolism	Variable (↑ or ↓)	Drug-specific dose changes
Renal plasma flow	↑ 100%	Increased renal clearance
GFR	↑ 50–70%	Faster elimination of renally excreted drugs

Absorption

Factor	Change During Pregnancy	Effect on Drug Absorption
Gastric Emptying & Intestinal Transit Time	Increases by 30–40% due to progesterone	Delayed absorption and delayed onset of action
Gastric Secretions	Gastric acid decreases, mucus secretion increases, gastric pH increases	Reduced absorption of weak acids; increased absorption of weak bases
Morning Sickness	Nausea and vomiting increase	May reduce absorption of oral medications; parenteral route may be preferred near term for rapid effect
Pulmonary Absorption	Cardiac output, respiratory volume, pulmonary blood perfusion increase; hyperventilation develops	Enhanced absorption of inhalational anesthetics, bronchodilators, volatile drugs, environmental pollutants, and cigarette smoke

Distribution

Factor	Change During Pregnancy	Effect on Drug Distribution
Plasma Volume	Increases by approximately 30–50%	Increased volume of distribution (Vd) and lower plasma drug concentrations
Cardiac Output	Increases by approximately 30%	Enhanced tissue perfusion and drug distribution
Total Body Water	Increases by about 8 L (60% to placenta, fetus, and amniotic fluid; 40% to maternal tissues)	Increased Vd of hydrophilic drugs and reduced plasma concentrations
Renal Blood Flow	Increases by up to 50% by the end of the first trimester	Greater distribution of drugs to the kidneys
Uterine Blood Flow	Increases throughout pregnancy and peaks at 36–42 L/hour at term	Increased drug delivery to the uterus, placenta, and fetus
Clinical Consequences	Altered drug distribution	Some drugs may require larger loading doses and therapeutic drug monitoring

EXAMPLES	Change During Pregnancy	Effect on Drug Distribution
Hydrophilic Drugs	Distributed into expanded body water compartment	Increased Vd and lower plasma concentrations
Lipophilic Drugs	Greater distribution into maternal fat stores	Potentially prolonged drug half-life

Protein Binding

Factor	Change During Pregnancy	Effect on Protein Binding / Clinical Significance
Albumin	Decreases due to hemodilution and increased plasma volume	Reduced binding of acidic drugs (e.g., phenytoin, salicylates, valproic acid)
α1-Acid Glycoprotein	Remains relatively unchanged	Binding of basic drugs (e.g., β -blockers, opioid analgesics) remains largely unchanged
Hormonal Effects	Steroid and placental hormones occupy protein-binding sites	Further increases free (unbound) drug fraction
Free Drug Fraction	Increases as protein binding decreases	Increased pharmacologically active drug concentration
Total Drug Concentration	Often decreases	Does not necessarily indicate reduced therapeutic effect
Clinical Implication	Clinical effect depends on free drug concentration	Dose escalation is usually not required based solely on reduced total drug levels

EXAMPLES	Change During Pregnancy	Effect on Protein Binding / Clinical Significance
Phenytoin	Albumin binding decreases and hepatic metabolism increases	Total concentration falls; free phenytoin monitoring is preferred
Antiepileptic Drugs	Phenytoin, Carbamazepine, and Valproic acid show reduced total concentrations	Free fraction increases; therapeutic monitoring may be required

Metabolism

Factor	Change During Pregnancy	Effect on Drug Metabolism / Clinical Significance
CYP3A4, CYP2D6, CYP2A6, CYP2C9	Activity increases (↑)	Increased drug metabolism, increased clearance, reduced plasma concentrations, may require higher doses
UGT1A1, UGT1A4, UGT2B7	Activity increases (↑)	Enhanced glucuronidation and faster drug elimination
CYP1A2, CYP2C19	Activity decreases (↓)	Reduced metabolism, drug accumulation, increased risk of toxicity, dose reduction may be needed
Progesterone	High circulating levels induce hepatic enzymes	Accelerated metabolism of many drugs, especially lipid-soluble drugs
Clinical Implication	Effects vary among drugs	Therapeutic drug monitoring may be required; dose adjustments should be individualized

Excretion

Factor	Change During Pregnancy	Effect on Drug Excretion / Clinical Significance
Renal Plasma Flow	Increases by approximately 100%	Enhanced renal drug elimination
Glomerular Filtration Rate (GFR)	Increases by approximately 50% within the first few weeks and may reach 70% above non-pregnant values	Increased clearance of renally excreted drugs
Clinical Implication	Renal drug excretion is significantly increased	Lower steady-state plasma concentrations; higher doses or more frequent administration may be required

EXAMPLES	Change During Pregnancy	Effect on Drug Excretion / Clinical Significance
Cardiovascular Drugs	Atenolol, Sotalol, Digoxin show increased renal elimination	Reduced steady-state drug concentrations
Other Drugs	Lithium, Dalteparin sodium, Enoxaparin sodium show increased renal elimination	Enhanced clearance and possible need for dose adjustment
Antibiotics	Ampicillin, Cefuroxime, Ceftazidime, Cefazolin, Piperacillin show 20–65% increased renal elimination	Lower plasma concentrations; dose adjustment may be required
Examples	Lithium, Digoxin, Penicillin	Increased clearance during pregnancy

Fetal–Placental Drug Transfer

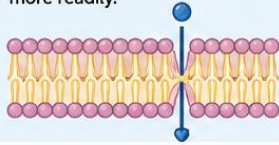
- The **placenta** serves as the interface between maternal and fetal circulation.
- The placenta is not an absolute barrier but a selective membrane.
- Most drugs administered to the mother can cross the placenta and reach the fetus to some extent.
- The extent of drug transfer determines fetal exposure and potential effects.
- The degree of transfer depends on the drug's properties, placental characteristics, and fetal factors.
- **Fetal:maternal drug concentration ratio is less than 1.**

FACTORS AFFECTING PLACENTAL DRUG TRANSFER

DRUG FACTORS

1 LIPID SOLUBILITY

Lipid-soluble (lipophilic) drugs cross the placenta more readily.



2 IONIZATION

Unionized (non-ionized) drugs cross the placenta more easily.



3 MOLECULAR SIZE

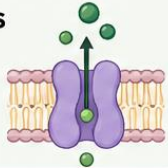
Drugs with low molecular weight cross the placenta more easily.



PLACENTAL FACTORS

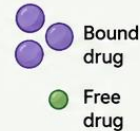
4 PLACENTAL TRANSPORTERS

Efflux transporters (e.g., P-gp, BCRP, MRP3) pump drugs back to maternal circulation and reduce fetal exposure.



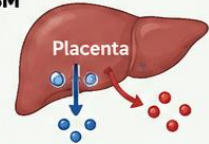
5 PROTEIN BINDING

Highly protein-bound drugs remain in maternal blood. Only free (unbound) drugs cross the placenta.



6 PLACENTAL METABOLISM

Placenta may metabolize (drug inactivation) or activate (bioactivation) some drugs, affecting fetal exposure.



FETAL FACTORS

7 DURATION OF EXPOSURE

Longer duration of drug exposure increases the amount of drug reaching the fetus.



8 FETAL METABOLISM

Fetal liver may metabolize drugs, reducing the amount of active drug in fetal circulation.



9 TISSUE DISTRIBUTION

Distribution of drugs varies among fetal organs and tissues (e.g., brain, fat, lungs), influencing drug effects.



10 DEVELOPMENTAL STAGE

The stage of placental and fetal development determines susceptibility to drug effects. Organogenesis is the most sensitive period.



COMBINATION DRUG EFFECTS



Concurrent drugs may interact to alter placental transfer.



They may increase or decrease fetal drug exposure.



They may enhance or reduce drug toxicity or therapeutic effects in the fetus.

Physiochemical properties

Physicochemical Property	Change / Characteristic	Effect on Placental Transfer	Clinical Significance
Lipid Solubility	Lipophilic (fat-soluble) drugs	Cross the placenta readily	Achieve higher fetal concentrations
	Hydrophilic (water-soluble) or highly ionized drugs	Cross slowly	Lower fetal exposure
Molecular Size	< 500 Da	Crosses readily	Significant fetal exposure possible
	500–1000 Da	Crosses partially	Moderate fetal exposure
	> 1000 Da	Minimal transfer	Limited fetal exposure
	Insulin, Heparin	Negligible transfer	Generally do not reach the fetus in significant amounts

Physicochemical Property	Change / Characteristic	Effect on Placental Transfer	Clinical Significance
Degree of Ionization	Non-ionized drugs	Cross membranes easily	Greater placental transfer
	Ionized drugs	Cross poorly	Reduced placental transfer
Ion Trapping	Fetal blood is slightly more acidic than maternal blood	Weak bases become ionized after entering fetal circulation and cannot easily diffuse back	Accumulation of weakly basic drugs in the fetus

Placental Factors - Protein binding	Change / Characteristic	Effect on Placental Transfer	Clinical Significance
Protein Binding	Only the free (unbound) fraction of a drug can cross the placenta	Determines the amount of drug reaching the fetus	Major determinant of fetal drug exposure
Maternal Albumin	Decreases gradually during pregnancy	Increases free drug fraction in maternal circulation	May increase placental transfer of some drugs
Fetal Albumin	Increases with fetal growth	Alters fetal drug binding capacity	Fetal and maternal drug concentrations may differ
Highly Protein-Bound Drugs	Remain largely bound in maternal blood	Cross the placenta poorly	Lower fetal concentrations
Poorly Protein-Bound Drugs	Higher free drug fraction	Cross the placenta more readily	Higher fetal exposure

Placental Factors	Change / Characteristic	Effect on Placental Transfer	Clinical Significance
Fetal Protein Binding Differences	Ampicillin & Benzylpenicillin: lower fetal affinity; Salicylates: higher fetal affinity	Influences fetal drug concentrations	May alter fetal drug effects
Placental Transporters	P-gp, BCRP, and MRP3 act as efflux transporters	Pump drugs from fetal circulation back to maternal circulation	Reduce fetal drug exposure and accumulation
Placental Metabolism	Placental enzymes metabolize drugs	May detoxify or bioactivate drugs before reaching the fetus	Can either protect the fetus or increase fetal toxicity

FETAL FACTORS

No.	FACTOR	KEY POINTS / CHARACTERISTICS	EFFECT ON FETAL DRUG EXPOSURE	CLINICAL SIGNIFICANCE / OUTCOMES	EXAMPLES / NOTES					
5.	Rate and Amount of Drug Reaching the Fetus 	- Depends on: - Maternal drug concentration - Placental blood flow - Placental surface area - Placental thickness - Duration of maternal exposure	 Higher maternal concentrations generally increase fetal exposure.	Greater fetal exposure with higher maternal levels and favorable transfer conditions.						
6.	Duration of Exposure 	- Short exposure: minimal effects - Prolonged exposure: increases risk of - Teratogenicity - Growth restriction - Functional abnormalities	 Longer exposure = greater fetal risk.	Length of fetal exposure is critical in determining severity of effects.						
7.	Fetal Drug Metabolism 	- Fetal liver has limited metabolic capacity. - Enzyme systems are immature. - Drug metabolism is slower compared with adults.	Drugs remain in fetal circulation for a longer time. Increased risk of toxicity. 	Immature metabolism → prolonged half-life and increased sensitivity to drugs.	e.g., Chloramphenicol (gray baby syndrome), Sulfonamides (kernicterus) 					
8.	Distribution Within Fetal Tissues 	- After entering fetal circulation, drugs distribute differently among organs. - Influenced by: - Tissue blood flow - Lipid content - Organ maturity - Presence of tissue receptors	Some drugs preferentially accumulate in: - Brain - Liver - Bone - Adipose tissue 	Differential distribution can lead to organ-specific toxicity or functional effects.	e.g., Tetracyclines → bone & teeth, Valproate → CNS 					
9.	Stage of Fetal Development 	<table><tr><th>Pre-implantation (0–2 Weeks)</th><th>Embryonic Period (3–8 Weeks)</th><th>Fetal Period (After 8 Weeks)</th></tr><tr><td>"All-or-None" Effect - Exposure may cause embryonic death, or - No lasting effect. </td><td>Organogenesis period - Most organs are forming. - Highest risk for teratogenicity. - Possible outcomes: - Major congenital malformations - Structural abnormalities </td><td>Main effects include: - Growth restriction - Functional abnormalities - CNS effects - Organ toxicity </td></tr></table>	Pre-implantation (0–2 Weeks)	Embryonic Period (3–8 Weeks)	Fetal Period (After 8 Weeks)	"All-or-None" Effect - Exposure may cause embryonic death, or - No lasting effect. 	Organogenesis period - Most organs are forming. - Highest risk for teratogenicity. - Possible outcomes: - Major congenital malformations - Structural abnormalities 	Main effects include: - Growth restriction - Functional abnormalities - CNS effects - Organ toxicity 	Timing of exposure is one of the most important determinants of fetal risk.	e.g., Thalidomide → limb defects (embryonic period), Alcohol → CNS effects (fetal period) 
Pre-implantation (0–2 Weeks)	Embryonic Period (3–8 Weeks)	Fetal Period (After 8 Weeks)								
"All-or-None" Effect - Exposure may cause embryonic death, or - No lasting effect. 	Organogenesis period - Most organs are forming. - Highest risk for teratogenicity. - Possible outcomes: - Major congenital malformations - Structural abnormalities 	Main effects include: - Growth restriction - Functional abnormalities - CNS effects - Organ toxicity 								
10.	Effects of Drug Combinations 	Simultaneous exposure to multiple drugs can alter fetal risk.	Possible outcomes: - Additive effects - Synergistic effects - Increased teratogenicity - Altered placental transfer 	Polypharmacy during pregnancy should be minimized whenever possible.	e.g., Alcohol + other CNS depressants → increased neurotoxicity 					

Maternal Pharmacodynamic Changes During Pregnancy

- Drug exposure during pregnancy can affect the **mother, fetus, and neonate.**
- These effects may be **therapeutic, predictable pharmacological effects**, or **unpredictable (idiosyncratic/teratogenic) effects.**
- Pharmacological effects are the predictable effects produced by a drug because of its known mechanism of action.
- **Characteristics**
 1. Most common type of fetal drug effect.
 2. Usually **dose-dependent.**
 3. Generally **predictable.**
 4. Often **reversible.**
 5. Occur much more frequently than teratogenic or idiosyncratic effects.

DRUG EFFECTS DURING PREGNANCY



1. Maternal Drug Administration



2. Drug Reaches Maternal Circulation



3. Crosses Placenta



4. Fetal Exposure



A. Therapeutic Effect



(Beneficial / Intended)

Drugs used to treat or protect the fetus.

Examples:

- Corticosteroids
- Flecainide



B. Pharmacological Effect

(Predictable & Reversible)

Expected effect due to the known action of the drug.

Examples:

- CNS depression (sedation)
- Opioids → respiratory depression



C. Toxic Effect

(Predictable Toxicity)

Drugs may cause toxicity in the fetus.

Examples:

- ACE inhibitors → fetal renal damage, oligohydramnios, neonatal death



D. Teratogenic Effect

(Permanent Damage)

Drugs may cause congenital malformations.

Examples:

- Thalidomide
- Retinoids (Isotretinoin)



5. NEONATAL OUTCOMES



1. Drug Accumulation

Due to immature metabolism and excretion.



2. Toxicity

May cause adverse effects after birth.



3. Withdrawal Syndrome

Occurs when maternal drug supply stops abruptly.

THERAPEUTIC DRUG ACTIONS IN THE FETUS

Sometimes the fetus itself is the intended target of drug therapy.

EXAMPLE 1: CORTICOSTEROIDS

Indication

Risk of preterm delivery.



Drugs

- Betamethasone
- Dexamethasone



Effect

Stimulate fetal lung maturation.



Benefit

Reduce:

- Respiratory distress syndrome
- Neonatal morbidity
- Neonatal mortality



EXAMPLE 2: FLECAINIDE

Indication

Fetal tachycardia (fetal arrhythmia).



Effect

Crosses the placenta and treats the fetal cardiac rhythm disturbance.



EXAMPLE 3: PHENOBARBITAL

Administration

Given to the mother near term.



Effect

Induces fetal hepatic enzymes.



Benefit

Enhances bilirubin glucuronidation.



Result

Reduced incidence of neonatal jaundice.



IDIOSYNCRATIC DRUG EFFECTS

Definition

Unexpected, uncommon drug effects that are not related to the usual pharmacological action of the drug.



Characteristics

- Rare
- Unpredictable
- Often serious
- May result in permanent abnormalities



Examples

- Teratogenic effects
- Genetic susceptibility reactions
- Congenital malformations



PREDICTABLE TOXIC DRUG ACTIONS IN THE FETUS

Some drugs produce known and predictable toxic effects.

EXAMPLE: ACE INHIBITORS

Examples

- Enalapril
- Lisinopril
- Ramipril



Mechanism

Cause fetal hypotension.



Consequences



Reduced renal perfusion



Fetal renal failure



Oligohydramnios



Pulmonary hypoplasia



Neonatal death

Important Point

ACE inhibitors can cause irreversible fetal renal damage, particularly during the second and third trimesters.

TERATOGENIC DRUG ACTIONS

Definition

Teratogenicity refers to the ability of a drug to cause congenital malformations or developmental abnormalities.

MECHANISMS

1 Directly Damage Developing Tissues

Interfere with:

- Cell division
- Differentiation
- Organ formation



2 Alter Placental Function

Reduce transfer of:

- Oxygen
- Nutrients
- Essential growth factors



3 Interfere with Critical Metabolic Processes

Such as:

- DNA synthesis
- Protein synthesis
- Folate metabolism



IMPORTANT EXAMPLES OF TERATOGENS

1. THALIDOMIDE

Effect

Severe limb defects (phocomelia).



Historical Significance:

One of the most famous examples of drug-induced congenital malformations.

2. VITAMIN A ANALOGUES (RETINOIDS)

Examples

- Isotretinoin
- Acitretin

Effects

- Craniofacial abnormalities
- Cardiac defects
- CNS malformations



3. FOLATE DEFICIENCY

Consequence

Neural tube defects.

Examples

- Spina bifida
- Anencephaly



Prevention:

Folic acid supplementation before conception and during early pregnancy.

PHARMACODYNAMICS IN PREGNANCY

Definition

Pharmacodynamics refers to the effects of drugs on the body and the body's response to drugs.



MATERNAL DRUG ACTIONS

Pregnancy can alter drug responses in reproductive tissues.

Uterus

Drug sensitivity may change.

Examples:

- Oxytocin
- Tocolytic agents



Breast Tissue

Responses related to lactation may be altered.



TISSUES GENERALLY UNCHANGED

Drug responses in most maternal organs remain largely unchanged.



Heart



Lungs



Kidneys



Central Nervous System

However, physiological changes of pregnancy may modify the overall clinical response.

MECHANISMS OF FETAL DRUG EFFECTS

Drugs may affect the fetus in two ways

1. INDIRECT EFFECTS THROUGH THE MOTHER

Drugs alter maternal physiology, which subsequently affects the fetus.

EXAMPLES



Reduced maternal blood pressure



Reduced uteroplacental blood flow



Maternal hypoxia

CONSEQUENCES



Reduced fetal oxygen supply



Reduced nutrient delivery



Fetal growth restriction

2. DIRECT EFFECTS ON THE FETUS

Many drugs cross the placenta and act directly on fetal tissues.

EXAMPLES



CNS depressants causing fetal sedation



Opioids causing respiratory depression



ACE inhibitors causing fetal renal damage

RESULT

These drugs can impair fetal organ function, growth, and overall well-being.

EFFECTS ON THE NEONATE



Drug exposure may continue to affect the infant after birth.

1. WHY NEONATES ARE MORE VULNERABLE

Neonates possess:



Immature liver function



Reduced metabolic capacity



Reduced renal excretion

CONSEQUENCE

Drugs may accumulate and cause toxicity.



2. NEONATAL DRUG TOXICITY

Signs may become apparent only after delivery when the infant must metabolize and eliminate the drug independently.

EXAMPLES



Sedation



Respiratory depression



Hypotension



Feeding difficulties

3. NEONATAL WITHDRAWAL SYNDROME

After birth, the maternal drug supply abruptly stops.

RESULT

Withdrawal symptoms may occur.

COMMON DRUGS CAUSING WITHDRAWAL

- Opioids



- Benzodiazepines



- Antidepressants



- Barbiturates



SYMPTOMS

- Irritability
- Tremors
- Excessive crying
- Feeding problems
- Seizures (severe cases)



4. MANAGEMENT



May require pharmacological treatment and supportive care.

Drug Therapy in Pregnancy: Dosing, Drug Selection, and Counseling

The management of medications during pregnancy requires balancing the **benefits to the mother** against the **potential risks to the fetus**.

Drug therapy should be individualized, evidence-based, and guided by a careful risk–benefit assessment.

DRUG DOSING IN PREGNANCY

1. GENERAL PRINCIPLES



The lowest effective dose should be used whenever possible.



Drug therapy should only be prescribed when the expected maternal benefit outweighs potential fetal risks.



Ideally, dose optimization should occur before conception or as soon as pregnancy is diagnosed.

2. DOSE REDUCTION DURING PREGNANCY

A. BEFORE CONCEPTION

For women with chronic diseases:

- Review all medications.
- Discontinue unnecessary drugs.
- Reduce therapy to the lowest effective dose.
- Consider safer alternatives if available.



B. NEAR TERM (THIRD TRIMESTER)

If a drug may adversely affect the neonate after birth:

- Gradual dose reduction may be considered.
- Goal: minimize neonatal toxicity or withdrawal.

Examples:

- Antidepressants
- Antipsychotics

However, this decision is often complex.



3. ANTIDEPRESSANTS AND ANTIPSYCHOTICS: CURRENT PERSPECTIVE

HISTORICALLY



Women were advised to taper antidepressants before delivery.

REASONS

- Reduce neonatal withdrawal syndrome.
- Avoid possible risk of persistent pulmonary hypertension of the newborn (PPHN) with SSRIs.



NEONATAL WITHDRAWAL SYMPTOMS



Jitteriness



Irritability



Altered muscle tone



Poor feeding

CURRENT CONCERNS

Evidence is insufficient to determine:

- Whether tapering truly benefits neonates.
- The optimal timing of dose reduction.

Potential risks of stopping therapy include:

- Maternal relapse
- Psychiatric deterioration
- Postpartum depression
- Increased risk to mother and infant



CLINICAL MESSAGE



Routine discontinuation is not universally recommended and should be individualized.

4. WHY DRUG DOSES CHANGE DURING PREGNANCY

Pregnancy causes major physiological changes affecting pharmacokinetics.

ABSORPTION



Delayed gastric emptying.

DISTRIBUTION



- Increased plasma volume
- Increased body water
- Increased fat stores

METABOLISM



Increased or decreased hepatic enzyme activity.

EXCRETION



- Increased renal blood flow
- Increased glomerular filtration rate (GFR)

Some drugs require higher doses.



AS A RESULT

Others require lower doses.



Some require no adjustment.



5. THERAPEUTIC DRUG MONITORING (TDM)

Monitoring plasma concentrations is particularly important for drugs:

- With narrow therapeutic indices.
- Whose plasma levels correlate well with efficacy.

EXAMPLES OF DRUGS REQUIRING TDM

Drug	Reason for Monitoring
Phenytoin	Increased clearance and altered protein binding
Carbamazepine	Increased clearance
Lithium	Increased renal elimination
Digoxin	Increased renal elimination

6. MONITORING HIGHLY PROTEIN-BOUND DRUGS

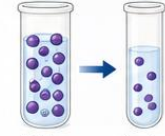
Pregnancy decreases albumin concentrations.

Consequently:

- Total plasma concentration may decrease.
- Free (active) drug concentration may remain unchanged.

Therefore:

Monitoring free drug levels is often more useful than measuring total concentrations.



Total drug (bound + free)

Free drug (active)

- Bound drug (inactive)
- Free drug (active)

7. EFFECT OF PREGNANCY ON DISEASE ACTIVITY

Pregnancy itself can alter disease severity, which may change dosage requirements.

CONDITIONS THAT MAY IMPROVE

- Rheumatoid arthritis



CONDITIONS THAT MAY WORSEN

- Asthma
- Epilepsy
- Hypertension



CLINICAL IMPLICATION

Dosage requirements may change because of disease activity as well as pharmacokinetic changes.



8. EFFECTS ON THE NEONATE

DRUG EXPOSURE

Drug exposure may continue to affect the infant after birth.



WHY NEONATES ARE MORE VULNERABLE

Neonates possess:

- Immature liver function
- Reduced metabolic capacity
- Reduced renal excretion

CONSEQUENCE

Drugs may accumulate and cause toxicity.



NEONATAL DRUG TOXICITY

Signs may become apparent only after delivery when the infant must metabolize and eliminate the drug independently.

EXAMPLES

- Sedation
- Respiratory depression
- Excretion
- Feeding difficulties



NEONATAL WITHDRAWAL SYNDROME

After birth, the maternal drug supply abruptly stops.

RESULT: Withdrawal symptoms may occur.

COMMON DRUGS CAUSING WITHDRAWAL

- Opioids
- Benzodiazepines
- Antidepressants
- Barbiturates



SYMPTOMS

- Irritability
- Tremors
- Excessive crying
- Feeding problems
- Seizures (severe cases)



MANAGEMENT

May require pharmacological treatment and supportive care.

2. DRUG SELECTION IN PREGNANCY

1. GENERAL PRINCIPLES



Only a small number of drugs have been conclusively proven to be teratogenic.

PREFERRED APPROACH

- ✓ Choose drugs with extensive experience in pregnancy
- ✓ Choose drugs with established safety records
- ✗ Avoid newly marketed drugs when safer alternatives exist

2. EXAMPLE: METHYLDOPA

NON-PREGNANT PATIENTS

Rarely used today for hypertension.



PREGNANT PATIENTS

Historically preferred because:

- Long history of safe use.
- Extensive pregnancy data available.



3. RISK-BENEFIT ASSESSMENT

Every prescribing decision should consider:

MATERNAL RISKS



- Disease progression
- Complications
- Loss of disease control

FETAL RISKS



- Teratogenicity
- Growth restriction
- Neonatal toxicity



KEY PRINCIPLE

Untreated maternal disease may be more dangerous than medication exposure.

4. FDA PREGNANCY CATEGORIES (HISTORICAL)

Historically, drugs were classified into categories:



PROBLEMS

- These categories oversimplified risk.
- Did not account for dose or timing.
- Often led to inappropriate prescribing decisions.

5. CURRENT APPROACH (REPLACED FDA CATEGORIES)

The FDA has replaced these categories with detailed information including:



FETAL RISKS

Information on potential effects on fetal development, including teratogenicity, growth restriction, and other adverse outcomes.



MATERNAL CONSIDERATIONS

Effects on the mother, including disease management, treatment benefits, and potential adverse effects.



AVAILABLE EVIDENCE

Summary of clinical and nonclinical studies, human data (when available), and the quality and limitations of the evidence.



CLINICAL RECOMMENDATIONS

Practical guidance to help clinicians make informed prescribing decisions based on a comprehensive evaluation of risks and benefits.



OVERALL GOAL

Select the safest and most effective medication by balancing maternal benefit and fetal risk, based on the best available evidence.



- ✓ Use drugs with proven safety and extensive pregnancy experience.
- ✓ Individualize therapy based on risk-benefit assessment.
- ✓ Continuously review new evidence and update prescribing decisions.

FDA Pregnancy Risk Categories (Historical Classification)

Cate gory	Definition	Examples	Risk/Recommendation
A	Controlled human studies show no fetal risk .	Multivitamins (recommended doses), Magnesium sulfate	✅ Safest category
B	Animal studies show no fetal risk , but adequate human studies are lacking.	Amoxicillin, Paracetamol (Acetaminophen)	✅ Generally considered safe
C	No adequate human studies; animal studies show adverse effects or data are lacking.	Morphine, Atropine	⚠️ Use only if benefits outweigh risks
D	Positive evidence of fetal risk exists, but benefits may justify use in serious conditions.	Aspirin (especially high doses), Phenytoin	⚠️ Use when clearly indicated
X	Proven fetal abnormalities; risks clearly outweigh any possible benefit.	Thalidomide, Estrogens (historical classification), Isotretinoin	❌ Contraindicated in pregnancy

MODERN FDA PREGNANCY AND LACTATION LABELING SYSTEM (PLLR)



The FDA replaced the old A, B, C, D, X categories with the **Pregnancy and Lactation Labeling Rule (PLLR)** in 2015.

Instead of assigning a letter category, drug labels now provide detailed clinical information in **three sections** to support individualized risk-benefit decisions.



1 PREGNANCY



Risk summary, clinical considerations, and supporting data regarding drug use during pregnancy.

1. PREGNANCY SECTION

RISK SUMMARY



- Summarizes known fetal risks based on human and animal data.

CLINICAL CONSIDERATIONS



- Guidance regarding maternal and fetal risks
- Dose adjustments
- Management during pregnancy

DATA



- Detailed evidence from human studies.
- Detailed evidence from animal studies.

INCLUDES INFORMATION ON:



Background risk of birth defects and miscarriage



Disease-associated maternal and fetal risks



Dose adjustments during pregnancy and postpartum



Adverse maternal or fetal reactions



Effects during labor and delivery

2 LACTATION



Information on drug transfer into breast milk, effects on the breastfed infant, and effects on milk production.

2. LACTATION SECTION

RISK SUMMARY



Extent of drug transfer into breast milk.

CLINICAL CONSIDERATIONS



Benefits of breastfeeding versus potential infant exposure.

DATA



- Human lactation studies.
- Animal lactation studies.

INCLUDES INFORMATION ON:



Drug concentration in breast milk



Potential effects on the infant



Potential effects on milk production

3 FEMALES AND MALES OF REPRODUCTIVE POTENTIAL



Information on pregnancy testing, contraception recommendations, and effects on fertility.

3. FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

PREGNANCY TESTING



Recommendations before initiating therapy.

CONTRACEPTION



Need for effective contraception during and after treatment.

INFERTILITY



Potential effects on male or female fertility.

COMPARISON: OLD vs MODERN FDA SYSTEM

OLD FDA CATEGORIES (A, B, C, D, X)		MODERN PLLR SYSTEM	
A B C D X	Letter categories (A, B, C, D, X)		Detailed narrative risk information
	Oversimplified risk assessment		Individualized risk assessment
	Did not consider timing, dose, or disease severity		Considers timing, dose, maternal condition, and available evidence
	Often misinterpreted as "safe" or "unsafe"		Encourages clinical decision-making based on risk-benefit analysis
	Limited clinical guidance		Provides practical prescribing recommendations



KEY CLINICAL MESSAGE:

The modern PLLR system does not classify drugs as A, B, C, D, or X.

It provides a comprehensive assessment of fetal risk, maternal benefit, lactation safety, and reproductive considerations to help clinicians make the best decisions for each patient.





3. PRE-CONCEPTION ADVICE



IMPORTANCE

The highest risk of congenital malformations occurs during:

FIRST TRIMESTER

Particularly the:

EMBRYONIC PERIOD (WEEKS 3–8)

This is the period of organ formation (organogenesis).



MEDICATION REVIEW BEFORE PREGNANCY

Women planning pregnancy should:



Review all medications.



Stop unnecessary treatments.



Switch to safer alternatives when possible.

COUNSELING FOR CHRONIC ILLNESS

Women with chronic diseases should receive specialist counseling before conception.

Examples:

- Epilepsy
- Asthma
- Diabetes
- Hypertension
- Inflammatory bowel disease

EXAMPLE: EPILEPSY

Goals:

- ✓ Use monotherapy whenever possible.
- ✓ Avoid multiple antiepileptic drugs.
- ✓ Use the lowest effective dose.

This reduces teratogenic risk while maintaining seizure control.



MEDICATION ADHERENCE

Many women reduce or stop medication because of concerns about fetal harm.

! This can be dangerous.

Examples: Inadequately treated:

- Asthma
- Epilepsy
- Inflammatory bowel disease

may pose greater risks than the medications themselves.

GENERAL PRE-CONCEPTION RECOMMENDATIONS

Women planning pregnancy should avoid:



Recreational drugs



Herbal or "natural" remedies without medical advice



Alcohol



Smoking



Vitamin A products (retinoids)



Excessive caffeine

FOLIC ACID SUPPLEMENTATION

STANDARD RECOMMENDATION

At least 400 micrograms (0.4 mg) daily



BENEFITS

Reduces risk of:

- Neural tube defects
- Spina bifida
- Anencephaly



HIGH-RISK WOMEN

Higher dose recommended:

4–5 mg/day

For women:

- With epilepsy
- With previous child affected by a neural tube defect

RUBELLA IMMUNIZATION

Rubella infection during early pregnancy may cause:

CONGENITAL RUBELLA SYNDROME

- Manifestations include:
- Deafness
 - Congenital heart defects
 - Intellectual disability
 - Miscarriage



Women lacking immunity should receive rubella vaccination before conception.



KEY PRINCIPLE:

Untreated maternal disease may be more dangerous than medication exposure. Careful planning, appropriate counseling, and medication optimization before conception help achieve the best outcomes for both mother and baby.



4. POST-CONCEPTION ADVICE



IMPORTANT PRINCIPLE

Advice before conception differs from advice after exposure has already occurred.



BEFORE PREGNANCY

A drug may be avoided because:

- ✓ Safety data are limited.
- ✓ Safer alternatives exist.



AFTER PREGNANCY EXPOSURE

Exposure does not automatically mean:

- ✗ Drug discontinuation
- ✗ Pregnancy termination
- ✗ Fetal abnormality
- ✗ Need for invasive testing



MANAGEMENT AFTER EXPOSURE

STEP 1 ASSESS



- Drug involved
- Dose
- Timing of exposure
- Duration of exposure

STEP 2 PERFORM INDIVIDUALIZED RISK ASSESSMENT



Consider:

- Available evidence
- Gestational age
- Dose and duration
- Maternal condition

STEP 3 PROVIDE EVIDENCE-BASED COUNSELING



Explain potential risks and available data. Address concerns and answer questions.

STEP 4 OFFER ADDITIONAL FETAL INVESTIGATIONS IF INDICATED



Examples:

- Detailed anomaly scan
- Fetal echocardiography
- Other targeted tests

REASSURANCE

In many cases:

A healthy baby remains the most likely outcome despite medication exposure.



APPROPRIATE COUNSELING HELPS PREVENT:



Unnecessary anxiety



Medication non-adherence



Disease relapse



Unnecessary pregnancy termination



KEY MESSAGE:

Individualized assessment and empathetic, evidence-based counseling help ensure informed decisions and the best possible outcomes.

Stages of Pregnancy and Drug Effects

Stage	Duration	Developmental Characteristics	Possible Drug Effects	Key Clinical Point
1. Pre-implantation Stage (Blastocyst Stage)	Conception to implantation (0–16 days after fertilization)	Rapid cell division; cells are undifferentiated	All-or-None Phenomenon: (a) Embryonic death/spontaneous abortion or (b) No lasting effect with normal development	No teratogenesis occurs during this stage
2. Organogenesis Period	17–56 days after fertilization ($\approx$ 3–8 weeks gestation)	Formation of major organs (heart, brain, limbs, eyes, ears, kidneys)	No measurable effect, abortion, gross anatomical defects (limb defects, cardiac defects, neural tube defects), or permanent functional/metabolic defects	Period of maximum teratogenic risk

Stage	Duration	Developmental Characteristics	Possible Drug Effects	Key Clinical Point
3. Second and Third Trimesters	After organogenesis until birth	Growth and functional maturation of organs	Growth retardation (IUGR, low birth weight), brain development abnormalities, behavioral defects, premature labor, neonatal toxicity, delayed postnatal effects (e.g., cancer, reproductive abnormalities)	Functional development is most vulnerable during this period
4. Labour and Delivery Stage	During labor and immediately before birth	Continued placental drug transfer; immature neonatal liver and kidneys	Respiratory depression, CNS depression, poor feeding, neonatal toxicity, withdrawal syndrome (opioids, benzodiazepines, antidepressants)	Neonatal toxicity is the major concern

Drug Prescribing During Pregnancy

Drugs may be prescribed during pregnancy for:

1. **Treatment of common minor ailments**
2. **Treatment of pre-existing or pregnancy-aggravated medical illnesses**

The guiding principle is to use the **safest effective drug at the lowest effective dose** while balancing maternal benefits against fetal risks.

1. Treatment of common minor ailments

Condition	Preferred/Safe Drugs	Important Notes
Pain & Fever (Analgesics/Antipyretics)	Paracetamol (Acetaminophen)	Drug of choice; safe at recommended doses throughout pregnancy
	Aspirin	May decrease neonatal platelet adhesiveness and increase maternal intrapartum blood loss
Nausea & Vomiting	Meclizine, Cyclizine	Generally considered safe
	Promethazine	Possible association with congenital dislocation of the hip
	Metoclopramide	Useful for severe nausea and vomiting; can be used during labor and anesthesia
Heartburn & Dyspepsia	Aluminum hydroxide, Magnesium trisilicate	Preferred non-absorbable antacids
	Sucralfate, H₂-receptor blockers, Bismuth subsalicylate	Considered safe options

Condition	Preferred/Safe Drugs	Important Notes
Constipation	Bran, Isapghula (Psyllium), Methylcellulose	Bulk-forming laxatives are preferred
	Stimulant laxatives	Avoid; may cause uterotonic effects and uterine contractions
Common Cold	Loratadine, Fexofenadine, Cetirizine	Non-sedating antihistamines
	Chlorpheniramine, Diphenhydramine	Sedating antihistamines
	Phenylephrine, Pseudoephedrine	Oral decongestants
Cough	Guaifenesin, Ipecac, Terpin hydrate	Expectorants
	Codeine, Dextromethorphan	Antitussives

2. Treatment of pre-existing or pregnancy-aggravated medical illnesses

Condition	Preferred/Safe Drugs	Important Notes
Bronchial Asthma	Salbutamol, Terbutaline	May cause maternal/fetal tachycardia; maternal hyperglycemia; fetal hypoglycemia
	Salmeterol	Long-acting β_2 agonist
	Beclomethasone, Budesonide	Preferred inhaled corticosteroids
	Nedocromil	Minimal systemic adverse effects
	Oral corticosteroids	May increase risk of pre-eclampsia

Condition	Preferred/Safe Drugs	Important Notes
Hypertension	Methyldopa	Drug of choice; safe throughout pregnancy
Hypertensive Emergency	Hydralazine IV, Labetalol IV	Used for severe hypertension
Atrial Flutter/Fibrillation	Digoxin	Drug of choice
Arrhythmias	Quinidine	Relatively safe in late pregnancy
Anticoagulation	Heparin	Does not cross placenta
Thrombolysis	Streptokinase, Urokinase, t-PA	Generally acceptable when indicated
Use with Caution	Atenolol, Acebutolol, Labetalol	Traditionally avoided during first 28 weeks

Condition	Preferred/Safe Drugs	Important Notes
Epilepsy	Phenobarbital, Phenytoin, Carbamazepine	Use lowest effective dose
	Valproate - Contraindicated	Neural tube defects and major congenital malformations
Folic Acid Supplementation	5 mg/day	Recommended for all women with epilepsy
Anxiety/Panic Disorders	Diazepam, Lorazepam, Midazolam, Alprazolam	Chronic use may cause neonatal withdrawal
Depression	Fluoxetine, Sertraline	SSRIs generally safe
Antipsychotic Therapy	Chlorpromazine	No increased malformation risk
Use with Caution	Lithium	Risk of neonatal goiter, floppy baby syndrome, Ebstein anomaly

Condition	Preferred/Safe Drugs	Important Notes
Diabetes Mellitus	Insulin	Preferred treatment
	Diet modification	First-line management
Hyperthyroidism	Propylthiouracil (PTU)	Preferred due to less placental transfer
Alternative	Methimazole/Carbimazole	May be used when PTU toxicity is a concern
Contraindicated	Radioactive iodine, Stable iodine	Fetal thyroid damage

Category	Drugs	Notes
Safe	Penicillins, Amoxicillin	Widely used
Safe	Cephalosporins	Short half-life, safe
Safe	Aztreonam	Safe
Safe	Erythromycin base	Preferred macrolide
Avoid	Erythromycin estolate	Hepatotoxicity
Contraindicated	Chloramphenicol	Gray baby syndrome
Contraindicated	Tetracyclines	Teeth and bone toxicity
Avoid	Co-trimoxazole	Folate antagonism, kernicterus
Avoid	Quinolones	Generally avoided
Use if Necessary	Gentamicin, Tobramycin	Preferred aminoglycosides

Category	Notes
Rifampicin	Safe
Isoniazid	Give with pyridoxine
Ethambutol	Safe
Streptomycin	Avoid (ototoxicity)

Category	Drugs	Notes
Safe	Chloroquine	Preferred
Resistant Malaria	Quinine	Acceptable
Avoid	Primaquine	Hemolysis in G6PD deficiency

Condition	Drugs
Candidiasis/Moniliasis	Nystatin, Miconazole, Clotrimazole

Condition	Drugs
Herpes/Varicella	Acyclovir
HIV Infection	Zidovudine

Condition	Drugs
Scabies/Lice	Lindane
Amoebiasis	Metronidazole, Diodoquin, Diloxanide

Category	Notes
General Anesthetics	No currently used agent is a proven teratogen
Local Anesthetics	Accidental fetal exposure may cause neonatal seizures

Vitamin	Effect
Folic Acid	Prevents neural tube defects
High-dose Vitamin K	May cause hemolysis, jaundice, hepatotoxicity
High-dose Vitamin A	Teratogenic; causes renal, CNS, and neural tube defects

THE THALIDOMIDE TRAGEDY

A Promise That Turned Into a Tragedy,
A Tragedy That Changed the World

1 THE BEGINNING (1950s)



In the 1950s, a German company, Grünenthal, developed Thalidomide.

It was found to have sedative and antiemetic (anti-vomiting) properties.

It was marketed as a **"WONDER DRUG"**.

- ✓ Treats morning sickness
- ✓ Relieves anxiety
- ✓ Induces better sleep
- ✓ Considered completely safe

It was sold in 46 countries including Europe, Australia and parts of Asia.

2 WIDESPREAD USE (1950s)



Thalidomide was widely prescribed to pregnant women for:

- Morning sickness
- Anxiety
- Tension
- Sleep disturbances

Over **10,000** pregnant women used it in Europe alone, believing it was completely safe.

3 WIDESPREAD USE (1957–1960)



Babies were born with severe congenital malformations, especially:

- **Phocomelia** (absence or severe shortening of limbs)
- Ear defects
- Eye defects
- Organ malformations



Dr. Widukind Lenz, a German pediatrician, was the first to connect the dots and suspected Thalidomide as the cause.

4 THE DISASTER EMERGES (1960–1961)

Soon, doctors began noticing something horrifying...



The drug was **withdrawn from the market in November 1961**.

By then, it was too late.

More than **10,000 babies** were born with deformities.

5 THE TRUTH REVEALED (1961)

Investigations confirmed that Thalidomide was causing birth defects.



They faced lifelong physical challenges, social stigma and emotional trauma.

But they also showed tremendous courage and became symbols of hope and resilience.

6 THE VICTIMS

The children affected were called **"Thalidomide Babies"**.



7 GLOBAL IMPACT



The Thalidomide tragedy shocked the world. It was a turning point in medical history.

It revealed that:

- ✗ Drugs can be dangerous even if they seem safe.
- ✗ Animal testing alone is not enough.
- ✗ Stronger drug regulations are essential.

8 CHANGE FOR A SAFER FUTURE

The tragedy led to strict new laws and ethical standards.



Stricter Drug Laws
New regulations required proof of safety before a drug could be approved.



Clinical Trials
Human trials must be carefully monitored in phases.



Informed Consent
Patients must be informed about possible risks before taking part in studies.



Pharmacovigilance
Ongoing monitoring of drug safety even after approval.

9 A LEGACY OF LESSONS

Thalidomide, once a symbol of hope, became a symbol of caution.



It taught the world that behind every medicine, there is a responsibility to protect human life.

The courage of the Thalidomide survivors and their families continues to inspire the fight for justice, safety and dignity.



THALIDOMIDE TRAGEDY – AT A GLANCE

Drug	Thalidomide
Used for	Morning sickness, anxiety, sleep
Years used	1957–1961
Affected babies	>10,000
Major defect	Phocomelia (limb malformations)
Outcome	Stricter drug laws, safer medicines

REMEMBER

"One tragedy led to a safer world."



The Thalidomide tragedy is a powerful reminder that...

- Science must be careful
- Medicine must be ethical
- Patient safety must always come first

A TRAGEDY THAT CHANGED MEDICINE FOREVER



From a **"miracle drug"** to a global lesson —
The Thalidomide tragedy will never be forgotten.

Teratogens and Fetotoxic Drugs in Pregnancy

Teratogenicity is the ability of a drug, chemical, infection, radiation, or environmental agent to cause **congenital malformations (birth defects)** or **abnormal fetal development** when exposure occurs during pregnancy.

A substance that causes such abnormalities is called a **teratogen**.

A **teratogen** is any drug, chemical, infectious agent, physical factor, or environmental exposure that can cause **permanent structural, functional, behavioral, or developmental abnormalities** in the embryo or fetus when exposure occurs during pregnancy.

Even without exposure to any known teratogen, the risk of congenital abnormalities in pregnancy is approximately 3%.

Criteria for a Substance to be Considered Teratogenic

A substance should:

1. Produce a Characteristic Pattern of Fetal Defects

Example: Thalidomide → limb reduction defects

2. Act During a Specific Developmental Stage

Usually during organogenesis (3–8 weeks gestation).

3. Demonstrate Dose Dependence

Higher exposure leads to greater risk and severity.

Wilson's Six Principles of Teratology (1959)

These principles remain the foundation of modern teratology.

1. Genetic Susceptibility: Susceptibility to teratogenesis depends on:

- Genotype of the embryo/fetus
- Interaction with environmental factors

2. Timing of Exposure: Teratogenic effects vary according to the developmental stage at exposure.

3. Specific Mechanism of Action: Teratogens act through specific mechanisms on developing tissues and cells.

4. Access to Developing Tissues: The ability of a teratogen to reach fetal tissues influences its effect.

5. Types of Developmental Outcomes: Teratogens may cause:

1. Death
2. Malformation
3. Growth retardation
4. Functional impairment

6. Dose-Response Relationship: The frequency and severity of abnormalities increase with increasing dose.

Major Teratogenic and Potentially Toxic Drugs

Drug/Class	Major Fetal Effect
Vitamin A derivatives (Isotretinoin)	Craniofacial, cardiac, CNS defects
ACE inhibitors	Fetal renal failure, oligohydramnios
Warfarin	Fetal warfarin syndrome
Estrogens and Androgens	Sexual differentiation abnormalities
Alcohol	Fetal alcohol syndrome
Lithium	Ebstein anomaly, neonatal toxicity
Anticonvulsants	Neural tube defects and congenital malformations
Antineoplastics	Multiple congenital anomalies
Finasteride	Abnormal male genital development
Tetracyclines	Tooth discoloration and bone growth inhibition

Important Drug-Specific Teratogenic Effects

Drug/Class	Teratogenic Effect	Major Manifestations
Thalidomide	Phocomelia	Severe limb reduction defects ("seal limb" deformity)
Androgens & Progestins	Virilization of female fetus	Ambiguous genitalia, masculinization
Tetracyclines	Dental and skeletal toxicity	Permanent tooth discoloration, enamel hypoplasia, retarded bone growth
Alcohol	Fetal Alcohol Syndrome (FAS)	Low IQ, cognitive impairment, behavioral abnormalities, growth retardation
Antithyroid Drugs	Thyroid dysfunction	Fetal goiter, congenital hypothyroidism
Isotretinoin (Retinoids)	Multiple congenital malformations	Craniofacial abnormalities, congenital heart defects, CNS abnormalities

Drug/Class	Teratogenic Effect	Major Manifestations
Warfarin	Fetal Warfarin Syndrome	Depressed nasal bridge, eye abnormalities, hand defects, growth retardation
Phenytoin	Fetal Hydantoin Syndrome	Hypoplastic distal phalanges, cleft lip/palate, microcephaly, growth retardation
Carbamazepine	Neural tube and craniofacial defects	Neural tube defects, craniofacial abnormalities, other congenital malformations

Mechanisms of Teratogenesis

- Teratogenic drugs produce congenital abnormalities by interfering with normal embryonic and fetal development.
- Six major mechanisms have been identified that explain how medications cause teratogenic effects.

1

FOLATE ANTAGONISM

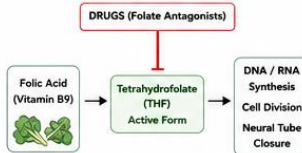
MECHANISM

Folate is essential for:

- DNA synthesis
- RNA synthesis
- Cell division
- Neural tube closure

Drugs that interfere with folic acid metabolism reduce cellular proliferation and impair organ development.

KEY PATHWAY



CONSEQUENCES

- Neural tube defects (NTDs)
- Growth retardation
- Craniofacial abnormalities



EXAMPLES

DRUG	EFFECT
Methotrexate	Neural tube defects, craniofacial defects
Trimethoprim	Folate deficiency-related malformations
Phenytoin	Reduced folate levels
Valproic acid	Neural tube defects

CLINICAL PREVENTION



Folic acid supplementation:

- Normal pregnancy: 400 µg/day
- High-risk women (e.g., epilepsy, previous NTD, on antiepileptics): 4–5 mg/day

2

NEURAL CREST CELL DISRUPTION

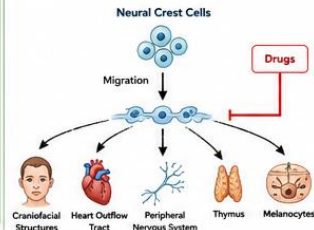
MECHANISM

Neural crest cells are embryonic cells that migrate to form:

- Craniofacial structures
- Heart outflow tract
- Peripheral nervous system
- Thymus
- Melanocytes

Drugs interfering with migration, differentiation, or survival of neural crest cells cause characteristic defects.

KEY PATHWAY



CONSEQUENCES

- Craniofacial abnormalities
- Cardiac defects
- Thymic abnormalities
- CNS malformations



EXAMPLES

DRUG	DEFECTS
Isotretinoin	Craniofacial and cardiac defects
Retinoids	Neural crest developmental abnormalities



NOTE

Critical during weeks 3–8 of gestation when neural crest cells migrate and differentiate.

3

ENDOCRINE DISRUPTION

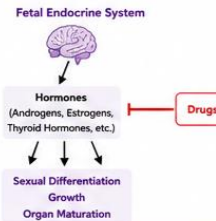
MECHANISM

Some drugs alter fetal hormonal signaling.

- Hormones regulate:
- Sexual differentiation
 - Growth
 - Organ maturation

Interference with endocrine pathways may permanently alter fetal development.

KEY PATHWAY



CONSEQUENCES

- Ambiguous genitalia
- Virilization
- Reproductive abnormalities
- Thyroid dysfunction



EXAMPLES

DRUG	EFFECT
Androgens	Virilization of female fetus
Diethylstilbestrol (DES)	Reproductive tract abnormalities
Antithyroid drugs	Fetal hypothyroidism and goiter
Finasteride	Abnormal male genital development



Endocrine disruption can cause permanent changes in fetal development even at low doses.

4

OXIDATIVE STRESS

MECHANISM

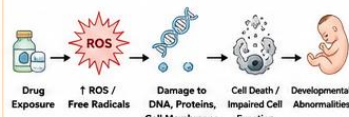
- Certain drugs generate:
- Reactive oxygen species (ROS)
 - Free radicals

These molecules damage:

- DNA
- Proteins
- Cell membranes

Embryonic tissues are particularly vulnerable because antioxidant defense systems are immature.

KEY PATHWAY



CONSEQUENCES

- Cell death
- Growth retardation
- Congenital malformations



EXAMPLES

DRUG	EFFECT
Phenytoin	Fetal hydantoin syndrome
Valproic acid	Neural tube defects
Alcohol	CNS damage and growth restriction



Antioxidant Defense (Immature)

High oxidative stress during organogenesis increases risk of structural defects.

5

VASCULAR DISRUPTION

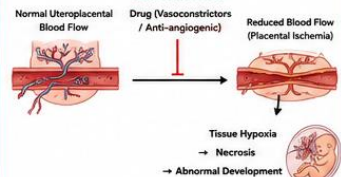
MECHANISM

Some drugs reduce blood flow to developing fetal tissues.

This results in:

- Ischemia
- Tissue necrosis
- Abnormal organ development

KEY PATHWAY



CONSEQUENCES

- Limb defects
- Growth restriction
- Organ hypoplasia



EXAMPLES

DRUG	DEFECTS
Thalidomide	Phocomelia (limb defects)
Vasoconstrictive agents	Reduced fetal perfusion
Cocaine	Placental insufficiency and fetal growth restriction



Adequate uteroplacental perfusion is critical for normal fetal development.

6

SPECIFIC RECEPTOR- OR ENZYME-MEDIATED TERATOGENESIS

MECHANISM

Some medications act directly on:

- Specific receptors
- Enzymes
- Signaling pathways

These pathways are essential for embryonic development.

Disruption causes characteristic developmental abnormalities.

EXAMPLES

ACE INHIBITORS	Mechanism: Block fetal renin-angiotensin system	Effects: Fetal renal failure, Oligohydramnios, Pulmonary hypoplasia
ISOTRETINOIN (RETINOIDS)	Mechanism: Binds retinoic acid receptors involved in embryonic development	Effects: Craniofacial defects, Cardiac malformations, CNS abnormalities
WARFARIN	Mechanism: Interferes with vitamin K-dependent developmental processes	Effects: Nasal hypoplasia, Skeletal abnormalities, Growth restriction

KEY POINT



These mechanisms explain why some drugs cause specific patterns of defects because they interfere with critical molecular pathways in development.

Fetotoxic Drug Effects

Fetotoxicity refers to harmful pharmacological effects on the developing fetus that do not necessarily produce structural malformations.

Fetotoxic Effects

Fetotoxic Effect	Drugs/Substances Involved	Major Manifestations/Consequences
Fetal CNS Depression	Barbiturates, Tranquilizers, Antidepressants, Narcotic analgesics, General anesthetics	Reduced fetal activity, neonatal respiratory depression, poor feeding
Neonatal Bleeding	NSAIDs, Anticoagulants	Prolonged bleeding, hemorrhagic complications
Neonatal Withdrawal Syndrome	Barbiturates, Opioids, Benzodiazepines, Alcohol	Irritability, tremors, jitteriness, feeding difficulties, seizures
Reduced Birth Weight	Cigarette smoking, Alcohol, Illicit drug abuse	Low birth weight, impaired fetal growth, increased neonatal morbidity

Mechanisms by Which Drugs Affect the Fetus

Drugs may affect fetal development through:

1. Direct Action on the Embryo/Fetus

- Lethal effects
- Toxic effects
- Teratogenic effects

2. Alteration of Placental Function

- Reduced nutrient transfer
- Reduced oxygen transfer

3. Changes in Myometrial Activity

- Premature uterine contractions
- Preterm labor

4. Alteration of Maternal Physiology

- Maternal hypotension
- Maternal hypoxia
- Metabolic disturbances

Substance Use During Pregnancy and Fetal Effects

Substance	Placental Transfer / Exposure	Major Fetal & Neonatal Effects
Alcohol	Crosses placenta freely; fetal alcohol levels may approach maternal levels due to immature fetal metabolism	Fetal Alcohol Syndrome (FAS) , growth restriction, low birth weight, poor postnatal growth, intellectual disability, learning difficulties, behavioral disorders
Smoking (Cigarettes)	Nicotine and other toxic substances cross the placenta	Low birth weight, intrauterine growth restriction (IUGR), preterm birth, respiratory problems, increased neonatal mortality, cerebral palsy, learning and behavioral disorders

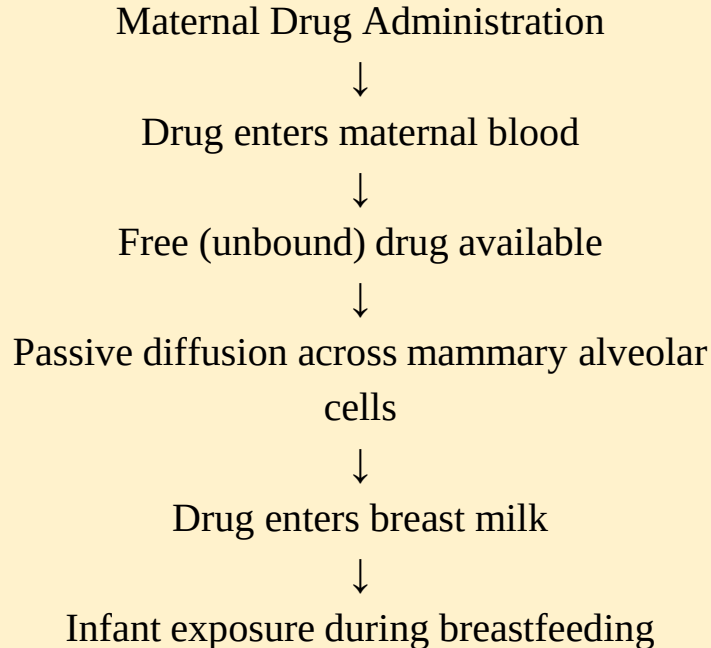
Illicit drugs/ Recreational drugs	Placental Transfer / Exposure	Major Fetal & Neonatal Effects
Marijuana	Crosses placenta	Low birth weight, developmental delay, behavioral problems
Cocaine	Crosses placenta readily	Low birth weight, congenital abnormalities, developmental and behavioral disorders
Heroin	Crosses placenta readily	Neonatal withdrawal syndrome, low birth weight, developmental problems
Amphetamines	Cross placenta	Growth restriction, congenital abnormalities, behavioral disorders
Ecstasy (MDMA)	Crosses placenta	Low birth weight, developmental delay, behavioral abnormalities

Drug Use in Lactation (Breastfeeding)

- Breast milk is the **best source of nutrition** for infants.
- Provides all essential nutrients and energy for the **first 6 months of life**.
- Recommended exclusively for 6 months by: World Health Organization (WHO) and United Nations Children's Fund (UNICEF)
- Protects infants against:
 - ◆ Gastrointestinal infections
 - ◆ Respiratory tract infections
 - ◆ Urinary tract infections
- Reduces the risk of: Obesity later in life
- Supplies protective antibodies: **IgA, IgM**
- These immunoglobulins help protect against **gastroenteritis and infections**.

- Almost all drugs can enter breast milk.
- The main mechanism is **passive diffusion**.
- Only the **un-ionized (non-charged)** and **unbound (free)** form of the drug crosses easily.
- Drugs pass through the **lipid membranes of mammary alveolar cells**.
- Drug transfer follows the **pH partitioning theory**.

Flow of Drug Transfer



The amount of drug reaching the infant depends on:

Maternal Dose
+
Maternal Plasma Concentration
+
Drug Properties
+
Duration of Breastfeeding
Infant Drug Exposure

Drug Characteristics Associated with Minimal Milk Transfer

- ✓ Acidic drugs
- ✓ Highly protein-bound drugs
- ✓ Low to moderate lipophilicity

Example: Most NSAIDs, warfarin

Drug Characteristics Associated with High Milk Transfer

- ✓ Weakly basic drugs
- ✓ Low protein binding
- ✓ Highly lipophilic drugs

Example: Sotalol, erythromycin

Factors Affecting Drug Transfer into Breast Milk

<https://whimsical.com/ayesha964/placental-drug-transfer-DD27i7GvGmAR3LNEcriXEs>

Factor	Effect on Drug Transfer into Milk	Examples / Notes
Milk pH (7.2) vs Plasma pH (7.4)	Milk is slightly more acidic, causing ion trapping of weak bases	Weak bases (e.g., erythromycin) accumulate in milk; weak acids (e.g., penicillins) remain in plasma
pKa (Degree of Ionization)	Drugs that are more ionized cross less readily	Drugs with higher pKa values generally have higher milk/plasma ratios
Protein Binding	Only free (unbound) drug enters milk	Highly protein-bound drugs have low milk concentrations
Lipophilicity	Lipid-soluble drugs cross milk more easily	Many CNS-active drugs enter milk readily
Molecular Weight	Smaller molecules cross more readily	<200 Da: readily cross; >6000 Da (e.g., insulin, heparin): virtually excluded

Factor	Effect on Drug Transfer into Milk	Examples / Notes
Maternal Plasma Concentration	Higher maternal blood levels increase milk concentrations	Drug transfer is proportional to maternal concentration
Stage of Lactation	Drug transfer is greater in colostrum than mature milk	Colostrum contains more protein and less fat
Alveolar Cell Gaps (First Week Postpartum)	Increased permeability allows more drug passage	Gaps close by the end of the first week under prolactin influence
Milk Composition	Variations in fat and protein content can alter transfer	End-of-feed milk contains more fat than beginning-of-feed milk
Active Transport (Pumping Systems)	Some drugs are actively secreted into milk	Iodides can achieve high concentrations in breast milk

Milk-to-Plasma Ratio (M/P Ratio)

Definition

The **Milk-to-Plasma Ratio (M/P Ratio)** is the ratio of:

$$\text{M/P Ratio} = \frac{\text{Drug concentration in breast milk}}{\text{Drug concentration in maternal plasma}}$$

Interpretation

M/P Ratio	Interpretation
< 1	Lower concentration in milk than plasma
= 1	Equal concentration in milk and plasma
> 1	Higher concentration in milk than plasma
High M/P ratio	Greater transfer of drug into breast milk

A high M/P ratio **does not necessarily mean toxicity** because infant exposure also depends on:

1. Oral Bioavailability of the Drug

- Some drugs may be present in high concentrations in milk.
- However, they are poorly absorbed from the infant's gastrointestinal tract.
- Therefore, actual infant exposure remains low.

2. Infant Drug Clearance

- Premature infants and newborns have:
 - ◆ Immature liver function
 - ◆ Reduced renal function
 - ◆ Slower drug elimination
- Even small amounts of drug may accumulate and cause toxicity.

3. Drug Elimination Rate

- Drugs with rapid clearance are removed quickly from the infant.
- Thus, exposure may remain low despite a high M/P ratio.

Potential Risks Despite Low Exposure

Although pharmacological toxicity is uncommon, some infants may develop:

1. **Idiosyncratic Reactions** : Unpredictable, Rare, Not dose dependent
2. **Increased Sensitivity**: Some infants may be unusually sensitive to very small drug amounts, especially:
 - a. Premature infants
 - b. Neonates
 - c. Infants with hepatic impairment
 - d. Infants with renal impairment

Medication Timing in Breastfeeding Mothers

If a nursing mother must take a medication that is considered relatively safe:

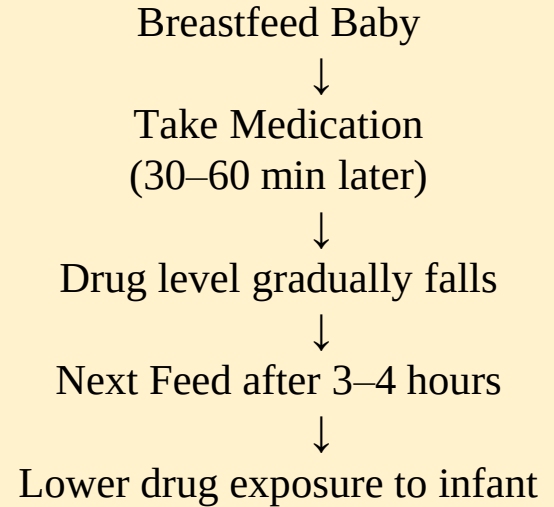
Take the medication 30–60 minutes after breastfeeding

AND

Take it 3–4 hours before the next feeding

This strategy helps to:

- Reduce the drug concentration in breast milk during the next feed.
- Minimize infant exposure to the medication.
- Maintain breastfeeding while ensuring maternal treatment.



Drugs That Suppress or Inhibit Lactation

Drug/Class	Effect on Lactation
Bromocriptine	Suppresses prolactin secretion → inhibits milk production
Estradiol (Estrogens)	Reduces milk supply
High-dose Oral Contraceptives	Decrease breast milk production
Levodopa	Suppresses prolactin release and lactation
Trazodone	May reduce milk production
Bendroflumethiazide	Can suppress lactation, especially at higher doses

Assessing the Risk to the Breastfed Infant

- Focuses on **how much harm the drug may cause to the infant**
- Infant risk during breastfeeding depends on the drug's toxicity, amount transferred into milk, oral bioavailability, presence of active metabolites, half-life, infant maturity, maternal dosing regimen, and route of administration.
- Premature infants and those receiving exposure to long-term maternal therapy are at the greatest risk of adverse drug effects.

Factors Affecting Infant Risk from Maternal Drug Therapy

Factor	Significance / Effect on Infant Risk	Examples / Notes
Drug Adverse Reaction Profile	Inherent toxicity of the drug is a major determinant of infant safety.	Antineoplastic drugs, radionuclides, iodine-containing compounds are high-risk.
Relative Infant Dose (RID)	Estimates the amount of maternal drug received by the infant through breast milk. Lower RID generally indicates lower risk.	Commonly used to assess breastfeeding safety.
Oral Bioavailability	Drugs poorly absorbed from the infant's gastrointestinal tract produce less systemic exposure.	Drug may be present in milk but not significantly absorbed.
Active Metabolites	Active metabolites can prolong infant exposure and increase accumulation.	Diazepam → Desmethyldiazepam.
Drug Half-Life	Long half-life drugs remain in the infant longer and may accumulate.	Fluoxetine.

Factor	Significance / Effect on Infant Risk	Examples / Notes
Infant Maturity / Gestational Age	Premature infants have immature hepatic and renal function, resulting in slower drug elimination.	A 30-week gestation infant has ~10% of maternal drug clearance.
Maternal Drug Regimen	Chronic therapy and multiple drugs increase infant exposure and toxicity risk.	Psychotropics and anticonvulsants may have additive effects.
Route of Maternal Administration	Determines maternal plasma concentration and therefore breast milk concentration.	Topical/Inhalational < Oral < Systemic therapy.
Single vs Chronic Therapy	Single doses or short courses are usually low risk; chronic therapy increases accumulation risk.	Long-term treatment requires closer monitoring.
Multiple Maternal Medications	Simultaneous use of several drugs increases the risk of adverse effects in the infant.	Psychotropic drugs, anticonvulsants.
Pharmacogenetic Factors	Genetic differences in drug metabolism may alter infant susceptibility to adverse effects.	Variability in drug clearance and toxicity.

Infant Drug Clearance

Infant Status	Drug Clearance Capacity	Clinical Implication
Premature infant (~30 weeks gestation)	~10% of maternal clearance	Highest risk of drug accumulation and toxicity
Full-term infant	Higher than premature infant	Lower risk but still reduced compared with adults
Infant aged 6–7 months	Approaches adult values	Drug elimination becomes more efficient

REDUCING RISK TO THE BREASTFED INFANT

The goal of therapy during lactation is to maximize maternal benefit while minimizing infant exposure to medications through breast milk.

1 TIMING OF MATERNAL MEDICATION



PURPOSE

- Avoid feeding during peak milk drug concentrations.
- Reduce infant exposure.

MOST USEFUL WHEN

- ✓ Drug has a short half-life
- ✓ Peak and trough concentrations are predictable



LIMITATION:

Often impractical because young infants may feed every 2 hours.

2 TEMPORARY INTERRUPTION OF BREASTFEEDING



EXAMPLE
Radiopharmaceuticals

RECOMMENDATION

- Suspend breastfeeding temporarily.
- Resume after an adequate washout period.



WASHOUT PERIOD

Washout Period = $5 \times$ Drug Half-life
This allows most of the drug to be eliminated from maternal circulation.



LIMITATION: Drugs with very long half-lives may require prolonged interruption of breastfeeding.

3 AVOID SELF-MEDICATION



Avoid over-the-counter medications without advice.



Avoid herbal products without established safety data.



Seek professional medical advice before using any medication.

4 SIMPLIFY MATERNAL DRUG THERAPY



- Use the fewest medications necessary.
- Avoid polypharmacy whenever possible.
- Minimize duration of treatment.

5 REVIEW THERAPY BEFORE DELIVERY



- ✓ Reduce neonatal drug exposure.
- ✓ Identify safer alternatives.
- ✓ Prevent adverse neonatal effects.

6 PREFER ESTABLISHED DRUGS



CHOOSE:

Drugs with extensive lactation safety data.



AVOID:

Newly marketed drugs when a safer, well-studied alternative exists.



7 MONITOR THE INFANT

All infants exposed to drugs through breast milk should be observed for:



Excessive sleepiness



Irritability



Poor feeding



Vomiting



Diarrhea



Rash



Inadequate weight gain



KEY POINTS

- Most medications are compatible with breastfeeding.
- Risk can be minimized by choosing well-studied drugs, using the lowest effective dose for the shortest duration,
- avoiding unnecessary medications, and monitoring the infant.

Individual Drugs During Lactation

Drug/Class	Safety in Breastfeeding	Important Notes / Infant Effects
Ibuprofen	✅ Safe	Preferred analgesic during lactation.
Indomethacin	⚠️ Generally safe	Low transfer into milk; seizures have been reported rarely.
Aspirin	⚠️ Short-term use acceptable	Theoretical risk of Reye's syndrome; prolonged use should be avoided.
Paracetamol (Acetaminophen)	✅ Safe	Very little excreted into breast milk; well tolerated by infants.
Morphine	✅ Safe	Low oral bioavailability in the infant.
Fentanyl	✅ Safe	Low oral availability; minimal infant exposure.
Meperidine (Pethidine)	❌ Avoid if possible	May cause seizures and CNS effects in the infant.
Codeine	⚠️ Use cautiously	Rarely causes infant sedation; monitor infant.

Drug/Class	Safety in Breastfeeding	Important Notes / Infant Effects
Heparin	✓ Safe	Large molecular weight; negligible transfer into milk.
Warfarin	✓ Safe	Highly protein bound; infant observation recommended.
Corticosteroids	⚠ Caution with high doses/long-term use	May suppress infant growth and endogenous steroid production.
Penicillins	✓ Safe	May occasionally cause loose stools in the infant.
Cephalosporins	✓ Safe	Generally well tolerated.
Erythromycin	✓ Safe	Compatible with breastfeeding.
Aminoglycosides	✓ Generally safe	Poorly absorbed from infant gut; minimal systemic exposure.
Sulfonamides	⚠ Use cautiously	Avoid if infant has G6PD deficiency or hyperbilirubinemia.
Sulfisoxazole	✓ Preferred sulfonamide	Lowest excretion into breast milk.

Drug/Class	Safety in Breastfeeding	Important Notes / Infant Effects
Tetracyclines	⚠ Short-term use acceptable	Safe up to 10 days; long-term use may stain teeth and affect enamel.
Chloramphenicol	✗ Contraindicated	Risk of serious toxicity in the infant.
Chloroquine	⚠ Avoid if possible	Potential risk of retinal damage in the infant.
Metronidazole	⚠ Special precautions required	If 2 g single dose is given, suspend breastfeeding for 24 hours and discard expressed milk.
Ketoconazole	✓ Safe	Highly protein bound; low milk transfer.
Acyclovir	✓ Safe	Minimal infant exposure; considered compatible with breastfeeding.

Drugs to Be Avoided During Lactation

Drug/Class	Potential Effect on Breastfed Infant	Safer Alternative / Recommendation
Anticancer drugs	Serious toxicity to infant	Contraindicated
Radiopharmaceuticals	Radiation exposure to infant	Contraindicated
Ergot derivatives (Ergotamine, Methysergide)	Adverse infant effects; suppress lactation	Contraindicated
Chloramphenicol	Risk of serious toxicity (Gray baby syndrome)	Contraindicated
Phenylbutazone	Serious adverse effects	Contraindicated
Thiouracil	Thyroid suppression in infant	Contraindicated
Iodides	Thyroid dysfunction in infant	Contraindicated
Mercurials	Neurotoxicity	Contraindicated

Drugs with Documented Adverse Effects During Breastfeeding

Drug	Adverse Effects in Infant	Preferred Alternative / Advice
Acebutolol	Hypotension, tachypnea	Avoid
Atenolol	Hypotension, cyanosis	Propranolol preferred
Clemastine	Drowsiness, feeding problems, neck stiffness	Cetirizine, Loratadine
Amiodarone	Thyroid and cardiovascular toxicity	Monitor infant thyroid and cardiac function if used long-term
Chlorpromazine	Sedation, reduced developmental score	Avoid if possible
Haloperidol	Reduced developmental score	Use cautiously
Diazepam	Infant sedation and accumulation	Midazolam preferred
Lamotrigine	Significant infant exposure	Monitor infant plasma levels

Drug	Adverse Effects in Infant	Preferred Alternative / Advice
Acebutolol	Hypotension, tachypnea	Avoid
Atenolol	Hypotension, cyanosis	Propranolol preferred
Clofazimine	Red discoloration and skin pigmentation	Avoid if possible
Ephedrine	Irritability	Avoid
Aminophylline (>200 mg every 6 hrs)	Irritability	Use cautiously
Combined Oral Contraceptives (Estrogen + Progesterone)	Reduced milk production	Progestin-only pills or barrier methods