

# Pharmacotherapy during pregnancy, childbirth and lactation: principles to consider

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## Abstract

Pregnancy, childbirth and lactation pose unique challenges in terms of drug therapy. The pregnant mother and her unborn child are exceptionally vulnerable from a physiological, clinical and ethical point of view. This warrants careful consideration of a number of important aspects, which could firstly influence the decision to opt for drug therapy, and secondly the specific agent that is selected for each indication. In this article, an overview is given of these important aspects.

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## Introduction

Drug therapy (i.e. the use of medication to attain certain clinical outcomes) may pose a significant risk during each of the following vulnerable periods in the human reproductive cycle:

- **Fertilisation of the ripened ovum, followed by complete implantation.** During this period, the two greatest risks would be a spontaneous abortion or the reabsorption of the products of conception,<sup>1,2</sup> which would both probably go unnoticed. This period will last for about two weeks (Figure 1).
- **The unborn child.** Drugs may cross the placental barrier and reach the systemic blood circulation of the unborn child.
  - *Embryonic development and organogenesis.* The embryonic period lasts until the end of the eighth week after fertilisation, and during this time the foetus is exceptionally vulnerable to structural abnormalities.<sup>1-4</sup>
  - *Foetal development and maturation.* During the second and third trimesters, drugs usually only affect the growth and maturation of the foetus, since organogenesis is completed by the end of the embryonic period, although the development of the external genitalia continues into the second trimester and the development of the central nervous system is an ongoing process for the duration of the pregnancy and beyond (Figure 1).<sup>1,2,5,6</sup>

### • The mother and infant

- *Birth process.* Drugs used to manage the intrapartum period may have direct effects on the infant during and directly after birth. For example, when general anaesthetic agents are used to facilitate Caesarean section, the result may be a suppressed level of consciousness or even apnoea in the newborn baby.<sup>7</sup>
- *Breastfeeding.* Drugs may be excreted in the mother's breast milk.<sup>5</sup>

**The development of the newborn child.** All newborns are vulnerable, whether they are of normal gestational age and birthweight, or not. Factors contributing to the challenges that pharmacotherapy poses include their smaller body size and the higher percentage of body water in infants, the fact that hepatic biotransformation is slower in the neonate, and that the neonate also displays a slower rate of renal elimination of certain drugs. Premature babies have an even higher percentage of body water than term neonates do.<sup>5,6</sup>

Drugs can, therefore, exert potentially harmful effects on the unborn child during any stage of the pregnancy, albeit to varying degrees.<sup>2,3</sup>

This article will focus on the principles of pharmacotherapy as they apply to pregnancy, childbirth and lactation. The basic pharmacokinetic and pharmacodynamic terminology referred to in this chapter has been summarised in Table I.

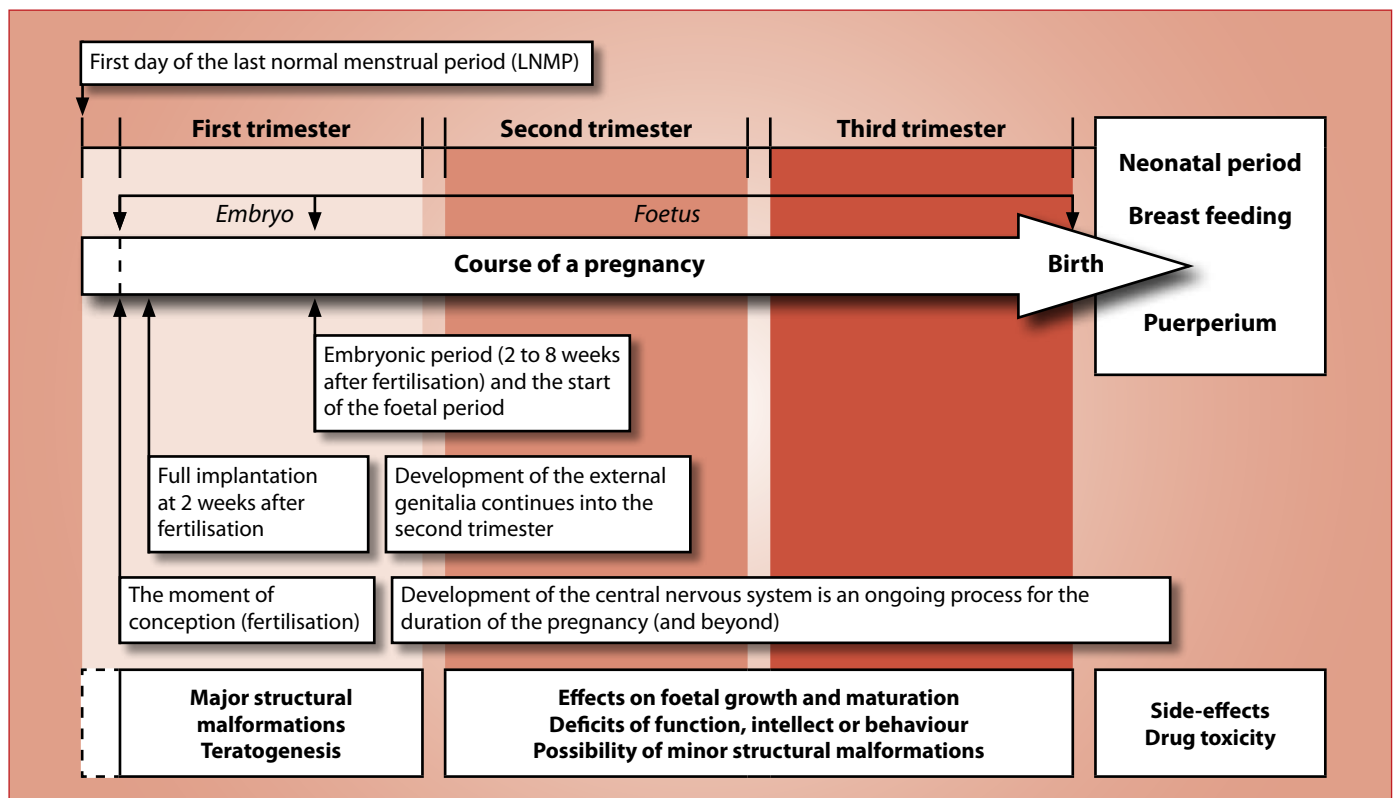


Figure 1: The vulnerability of the unborn child and the neonate to drug therapy

Table I: Basic pharmacokinetic and pharmacodynamic terminology

Term	Definition
Pharmacokinetics	The study of the kinetics of drug absorption, distribution, metabolism and elimination/excretion. In other words, that which happens to the drug within the body.
Pharmacodynamics	The study of the biological effects resulting from the interaction between drugs and biological (body) systems. In other words, that which the drug does to the body.
Biopharmaceutical properties	The relationship between the physical and chemical properties of a drug, in a specific dosage form, and the pharmacological, toxicological or clinical effects that are observed following its administration. This information can be used to optimise drug availability at its site of action.
Therapeutic drug monitoring (TDM)	<ul style="list-style-type: none"> <li>The mathematical relationship between a drug dosing regimen and its resulting serum concentrations (pharmacokinetics).</li> <li>The relationship between drug concentrations at the site of action and the resultant pharmacological response (pharmacodynamics).</li> <li>The use of serum drug concentrations to optimise drug therapy in individual patients, in conjunction with their clinical status and response to therapy.</li> </ul>
Apparent volume of distribution ( $V_d$ )	The apparent volume into which a drug distributes in the body's fluid compartments at equilibrium. This is the volume into which the specific drug dosage will need to be dissolved for it to reach the same concentration as it does in the plasma.
Clearance (CL)	The volume of body fluid which is totally cleared of drug per unit of time.
Systemic bioavailability (F)	The fraction of an orally administered dosage which reaches the systemic blood circulation of the patient. It reflects the extent of absorption and presystemic elimination.
Elimination half-life ( $t_{1/2}$ )	The time it takes for the drug's plasma concentration to be reduced by 50%.
Plasma steady-state concentration ( $C_{p_{ss}}$ )	A stable plasma drug level (or plateau concentration) at which the drug's rate of absorption is equal to its rate of elimination (i.e. the drug's 'input' equals its 'output'). It takes approximately four to five half-lives to reach steady-state.
Absorption	The process by which a drug proceeds from its site of administration to the central blood circulation (the site of measurement within the body). This process is not restricted to oral administration only, but is equally applicable to events that follow other routes of administration, e.g. intramuscular and subcutaneous injection, rectal administration. However, intravenously injected drugs enter the bloodstream directly and, therefore, do not require any absorption to take place.

**Drug therapy during pregnancy, childbirth and lactation**

Pharmacotherapy during pregnancy, childbirth and lactation may be necessary for a number of reasons:

- Acute illness or trauma during pregnancy.
- Chronic illness or disability, particularly:
  - HIV infection and AIDS
  - Diabetes mellitus
  - Hypertension
  - Asthma
  - Epilepsy
  - Migraine
  - Mental health disorders (including depression and anxiety)
  - Conditions requiring long-term anticoagulant therapy (e.g. atrial fibrillation).
- Pregnancy, labour and lactation-related disorders and emergencies.
- In a few instances, the foetus may actually be the target of the drug therapy administered to the mother, as part of a foetal therapy regimen.<sup>1-3,7,8</sup>

In these settings, it is of vital importance to carefully weigh up the possible benefits and risks of pharmacotherapy against the possible outcomes (for both mother and child) of *not treating*

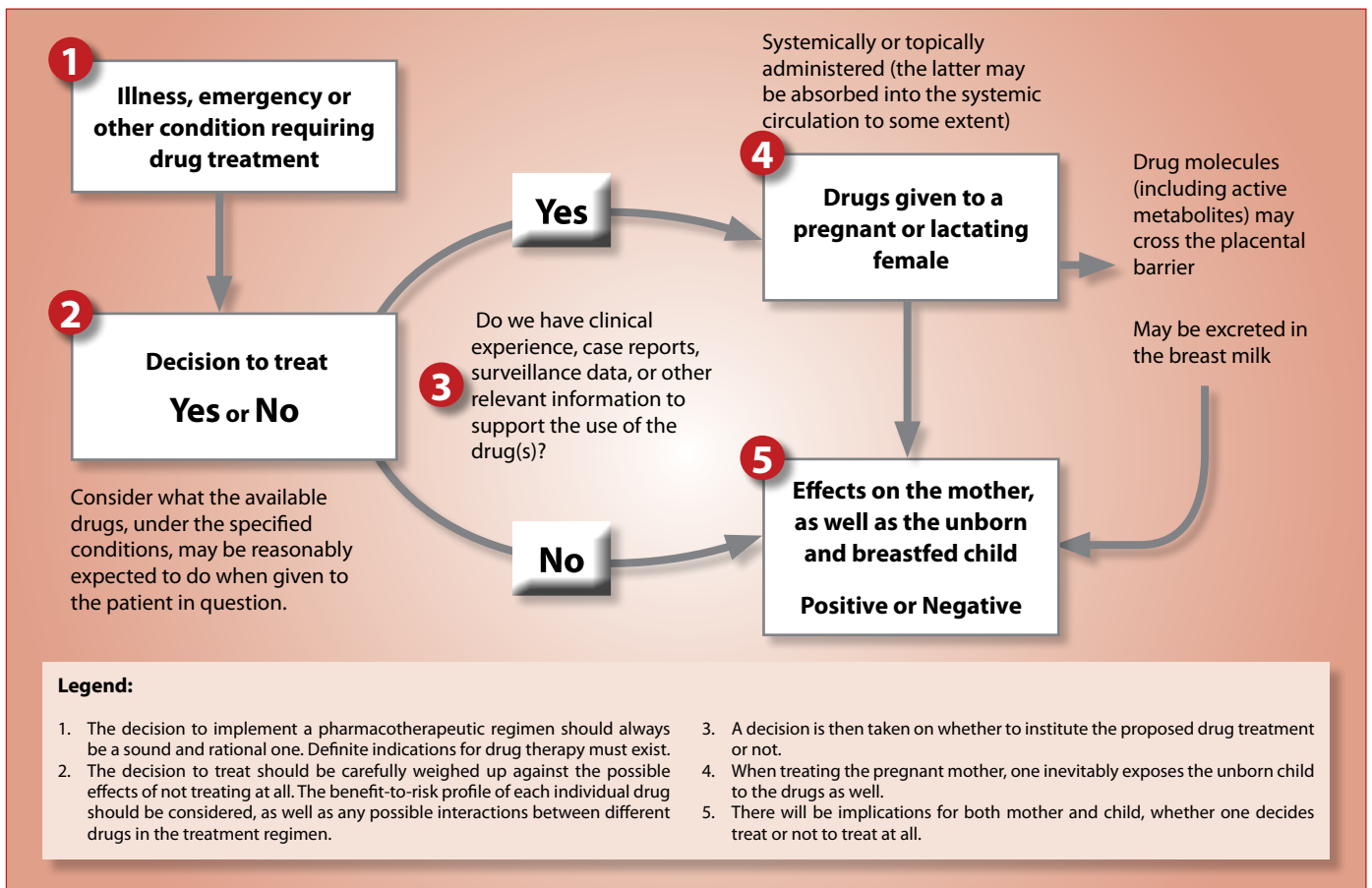
the condition at all. The decision to opt for drug therapy should always be a sound and rational one. The outcomes that the clinician is aiming to achieve should be realistic and take into consideration the effects the available drugs and the specified conditions may be reasonably expected to have on the patient in question. Furthermore, it must be mentioned that treatment cannot necessarily be interrupted, postponed or avoided altogether merely because a female is pregnant or breastfeeding. This poses a complex clinical challenge that requires expert opinion and balanced, evidence-based decision making (Figure 2).<sup>1,3,5</sup>

The following aspects must be considered:

- Physiological changes during pregnancy that may affect drug action and kinetics.
- Drug toxicity during pregnancy.
- Cross-placental transfer of drug molecules and their metabolites.
- Excretion in breast milk.
- Drug safety during pregnancy and lactation.

**Physiological changes during pregnancy that may affect drug action and kinetics**

Certain physiological changes during pregnancy have implications for drug therapy and may affect any of the four basic



**Figure 2:** Pharmacotherapeutic decision-making during pregnancy, childbirth and lactation. This is a simplified diagram to illustrate the intricacies of clinical decision-making when considering drug therapy in any of these vulnerable patient populations.

kinetic processes, namely absorption, distribution, metabolism and elimination/excretion (i.e. the "ADME" processes). Therefore, the following could alter the way in which drug molecules are handled by the body (i.e. alter their pharmacokinetic profiles):

- Increased progesterone levels cause a decrease in gastrointestinal motility (with resultant constipation), as well as a decrease in oesophageal sphincter pressure (which causes heartburn). In addition, placenta-derived human chorionic gonadotropin (hCG) causes nausea and vomiting. The altered gastrointestinal functioning caused by these changes could influence the rate and extent of absorption of orally administered drugs.<sup>1,2</sup>
- Pregnancy also results in increased lung perfusion and pulmonary alveolar drug transfer due to improved cardiac output, meaning that the absorption will be improved for drugs that are administered via the pulmonary route (i.e. nebulisers and inhalers).<sup>3</sup>
- Drug distribution may be affected due to the increased plasma volume that accompanies pregnancy and which may result in an increased volume of distribution ( $V_d$ ) of certain drugs. Furthermore, pregnancy brings about a decreased blood albumin level, which could result in an increased fraction of free drug molecules. This may be especially significant in the case of drugs that are highly protein-bound, also increasing their  $V_d$  and altering other kinetic properties. Note that only the free, unbound fraction will be able to cross the placental barrier. In these instances, the higher fraction of free drug molecules implies that there are higher levels of the active drug in circulation (for both mother and unborn child), and this increases the likelihood of drug toxicity.<sup>1-4,8</sup>
- Altered liver functioning may affect the plasma concentrations of drugs that follow hepatic metabolism.<sup>2,3</sup>
- The increased plasma volume, in turn increases cardiac output (CO), renal blood flow and glomerular filtration rate (GFR). This could increase the renal excretion of drugs that are significantly eliminated via this route.<sup>2-4</sup>
- Drugs and their metabolites may also be excreted in breast milk.<sup>1-3,5</sup>

### Drug toxicity during pregnancy

Drugs may be toxic to the developing embryo and foetus. The first trimester of pregnancy (i.e. the stage of embryonic development and organogenesis) is of particular importance, since the teratogenic effects of certain drugs will influence normal development of the unborn child on a structural or functional level (Figure 1). A teratogen is a drug or other chemical substance that may affect normal embryonic development and cause recognisable congenital defects. During the very early stages of pregnancy, the expectant mother may not even be aware of the fact that she is carrying a developing embryo. She may unknowingly harm her unborn child through the careless or indifferent use of drugs.

Therefore, this is an important topic to include in preconception care. Many pregnancies, however, are unplanned or unexpected, implying that preconception care would not have been rendered at all. With drugs which have been shown to

pose a significant risk to an unborn child, or drugs which have not been proven relatively safe during pregnancy, sufficient precautions in the form of patient education and the use of highly effective contraceptive methods must be taken when treating women of childbearing age or potential. Some drugs must even be avoided in men who may father children during treatment.<sup>1,4,5</sup>

### Cross-placental transfer of drug molecules and their metabolites

Drug treatment during pregnancy inadvertently implies that the unborn child will be exposed to, either the effects of the drug on the mother, the direct effects of the drug on the embryo or foetus, or a combination of both. The placenta acts as a barrier between the circulatory systems of mother and child throughout the duration of the pregnancy. However, in terms of drug molecules, this barrier is not very efficient, implying that, when such molecules enter the maternal blood circulation, they have the potential of crossing this barrier and entering the foetal circulation as well. Lipid-soluble drugs are capable of crossing the placenta via simple diffusion. Most water-soluble drugs can also cross the placenta, because of the relative inefficiency of the barrier. Heparin is an exception. Table II lists the characteristics of drug molecules that are most likely to cross the placenta.<sup>4,5</sup>

**Table II: The characteristics of drug molecules that are most likely to cross the placental barrier<sup>1,3,5,7,8</sup>**

A high degree of fat-solubility (i.e. lipophilic molecules).

A low degree of ionisation (i.e. molecules that do not carry charges).

A low level of protein binding in the maternal bloodstream. Drugs that are highly protein-bound have only small fractions of free molecules capable of crossing membranes.

Low molecular mass (i.e. small molecules), especially in the case of water-soluble drugs. It is generally agreed that drug molecules with a molecular mass < 500 Da will readily cross the placenta, molecules of 500 to 1 000 Da will cross very slowly, while molecules of > 1 000 Da will not cross the placental barrier at all.

### Excretion in breast milk

During lactation, drugs may pass from the bloodstream to the breast milk, especially if they are lipid-soluble or basic drugs (basic drugs will tend to ionise in the breast milk, since it is more acidic than blood), or if they are water-soluble molecules with a relative molecular mass of less than 100 Da.<sup>1,2,5</sup>

### Drug safety during pregnancy and lactation

We have limited data at our disposal regarding the actual safety profiles of many drugs during pregnancy and lactation. There are many reasons for this, including the difficulties of conducting suitable clinical trials in these patient populations, both on ethical and technical grounds. Drugs should, therefore, always be used with caution during pregnancy and lactation.<sup>5</sup>

The pregnancy risk classification used by the US Food and Drug Administration (FDA) is often quoted and consists of five different categories, namely A, B, C, D and X. Category A drugs are considered to be relatively safe during pregnancy, and category X drugs are absolutely contraindicated. The FDA is, however, in the process of introducing a new *Rule on Pregnancy and Lactation Labeling* with pregnancy and lactation subsections, and readers are advised, for more information, to consult the website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>.<sup>1,2,7-9</sup>

It is of great importance to consult suitable drug references when dispensing medicines to pregnant or lactating mothers. Known teratogens should obviously be avoided during pregnancy. However, situations may arise where the benefits of treating the mother with a certain drug may outweigh the possible harm that the drug may or may not do. The package inserts and patient information leaflets of registered medicines should always be consulted for specific information on the use of such agents in the treatment of pregnant and lactating women, or even in women who are of childbearing potential but not pregnant yet.<sup>1,5</sup>

Table III lists a number of well-known teratogenic drugs.

In addition, the following drugs are associated with withdrawal symptoms in the newborn infant:

- Barbiturates
- Benzodiazepines

- Opioid analgesics
- Tricyclic antidepressants

Many factors determine the choice and possible outcomes of drug therapy during pregnancy, childbirth and lactation:

- Age, obstetric history and gestation.
- Physical characteristics (e.g. size and body mass index).
- Diet and nutritional status.
- Gene pool and genetic factors.
- Previous responses and reactions to drug treatment, including allergic reactions and anaphylaxis.
- Other drugs already in use, which may give rise to drug interactions, including over-the-counter (OTC) medicines and herbal remedies.
- Current and pre-existing illness.
- Health status and general standard of living.
- Unwanted and toxic effects of the drugs in question.
- Patient compliance.
- The pharmacological profile of the drug in question, since the altered physiology during pregnancy may affect the way in which the body responds to the drug, as well as how the body deals with the drug molecules and their metabolites.<sup>2,5</sup>

The following treatment principles may be applied when considering or continuing drug therapy during pregnancy and lactation:

- Preferably choose drugs that are known to be safe and effective during pregnancy and lactation.

**Table III: Examples of known teratogenic drugs to avoid during pregnancy.**

**Note: drugs that are not listed here are not necessarily safe to use.**<sup>1,2,5,6,7</sup>

Teratogen	Effect
Anticonvulsants	Valproate is associated with neural tube defects, as is carbamazepine. Phenytoin may cause malformations in the central nervous system and adversely affect foetal growth.
Anticoagulants	Warfarin is associated with haemorrhage in the foetus, as well as malformations in the central nervous system and skeletal system.
Antihypertensive agents	ACE inhibitors cause renal damage and may restrict normal growth patterns in the unborn child.
Antineoplastic agents	High risk of multiple congenital malformations.
Antiretroviral agents	Efavirenz is associated with neural tube defects.
Ethanol	Effects may be cumulative. Foetal alcohol syndrome, abnormal functioning of the central nervous system and disturbances of behaviour.
Isotretinoin	Very high risk of multiple congenital malformations.
Misoprostol	Malformations of the central nervous system and limbs.
Neuroleptic drugs	Lithium is associated with congenital defects of the cardiovascular system.
Nonsteroidal anti-inflammatory drugs	Premature closure of the ductus arteriosus.
Tetracyclines	Malformations of teeth (including permanent discolouration) and bone.
Thalidomide	Malformations of the internal organs and limbs.

- Use the lowest possible dosage of the drug with the shortest plasma half-life, for the shortest possible duration of treatment.
- Try to avoid newly registered drugs, because of less safety data and clinical experience.
- For women of childbearing potential, known teratogens should be avoided, even when not yet pregnant. This should sometimes be done even in fertile males.
- Discourage self-medicating practices and the indiscriminate use of OTC drugs, herbal remedies and nutritional supplements.
- Carefully consider possible drug interactions. For example, commonly used medications in pregnancy include antacids, which may interfere with drug absorption from the gastrointestinal tract.
- Always refer to the most up-to-date drug information available.<sup>1,2,4,7</sup>

### Conclusion

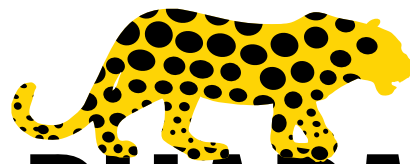
The decision to choose pharmacotherapy during pregnancy, lactation or childbirth will not always be an optional one. Drug treatment may be unavoidable, but will inevitably expose the unborn child to the effects, whether pharmacological or

toxic, of the drug itself. In a few instances, such effects on the foetus may actually be warranted and desired. Irrespective of the reason for exposing the pregnant mother and her unborn child to drug therapy, certain aspects and principles must be considered first, to ensure that the intervention is safe, rational and scientifically sound.

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