Pharmacotherapy during pregnancy, childbirth and lactation: points and principles to consider (a 2015 update)

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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 standpoint. This warrants careful consideration with respect to a number of important aspects, which could firstly influence the decision to opt for drug therapy, and secondly, could influence the specific agent selected for each indication. The US Food and Drug Administration has introduced changes to the content and format of information presented in prescription drug labelling to assist healthcare providers when assessing benefit versus risk, and in the subsequent counselling of pregnant woman and nursing mothers who need to take medication. This change came into effect at the end of June 2015. This article provides an overview of these important aspects.

Keywords: embryo, foetus, lactation, neonate, pregnancy

Introduction

Obstetrics and neonatology drug therapy, also referred to as pharmacotherapy, represents a major medical challenge to practising healthcare workers. This is because drug therapy, i.e. the use of medication to attain a certain clinical outcome, poses a significant risk during vulnerable periods of the human reproductive cycle.

Vulnerable periods of the human reproductive cycle

Fertilisation of the ripened ovum and the attainment of complete implantation

The two greatest risks during fertilisation of the ripened ovum and the attainment of complete implantation are spontaneous abortion or the reabsorption of the products of conception,[1,2] both of which would probably go unnoticed. This period lasts for approximately two weeks (Figure 1).

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, during which the foetus is exceptionally vulnerable to structural abnormalities.[1-4]

Foetal development and maturation

During the second and third trimester, 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[1,2,5,6] (Figure 1).

Mother and infant

The birthing process

Drugs used to manage the intrapartum period may have a direct effect on the infant during and directly after the birth, e.g. the result could be a suppressed level of consciousness or even apnoea in the newborn infant when a general anaesthetic agent is used to facilitate a Caesarean section.[7]

Breastfeeding

Drugs may be excreted in the mother's breast milk.[5]

The development of the newborn child

Newborn infants are vulnerable, whether or not they are of normal gestational age and birthweight. Various factors contribute to the challenges created by pharmacotherapy in infants. These include their smaller body size, higher percentage of body water, the fact that liver biotransformation, for example, is slower in the neonate, and that the neonate also displays a slower rate of renal elimination of certain drugs. Premature infants have an even higher percentage of body water than neonates.[5,6]

Therefore, drugs can exert a potentially harmful effect on the unborn infant during any stage of the pregnancy, albeit in varying degrees.[2,3]
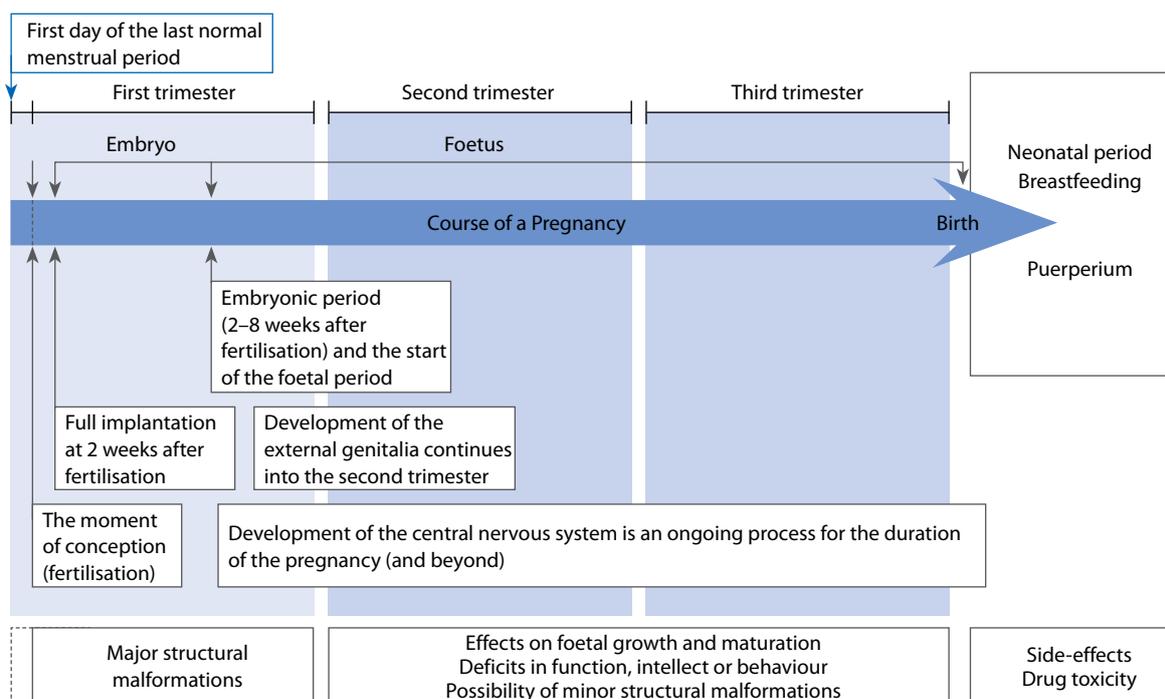
Figure 1: The vulnerability of the unborn child and neonate to drug therapy

Table 1: Basic pharmacokinetic and pharmacodynamic terminology

Term	Definition
Pharmacokinetics	The study of the kinetics of drug absorption, distribution, metabolism and elimination or excretion in humans and animals. In other words, it describes what happens to drugs in the body
Pharmacodynamics	The study of the biological effects resulting from an interaction between drugs and biological (body) systems. In other words, it describes the effect that drugs have on the body
Biopharmaceutical properties	The relationship between the physical and chemical properties of a drug, in a specific dosage from, and the pharmacological, toxicological or clinical effects which are observed following its administration. This information can be used to optimise drug availability at the site of action of the drug
Therapeutic drug monitoring	The mathematical relationship between a drug-dosing regimen and its resulting serum concentrations (pharmacokinetics)
	The relationship between the drug concentration at the site of action of the drug and the resultant pharmacological response (pharmacodynamics)
	The use of serum drug concentrations to optimise drug therapy in individual patients, in conjunction with their clinical status and response to therapy
Apparent volume of distribution	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 in order for it to reach the same concentration as it does in the plasma
Clearance	The volume of body fluid which is totally cleared of the drug per unit of time
Systemic bioavailability	Defined as 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	This is the time it takes for the drug's plasma concentration to be reduced by 50%
Plasma steady-state concentration	Implies a stable plasma drug level, or plateau concentration, during 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 4–5 half-lives before the steady state is reached
Absorption	This may be defined as 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 which follow other routes of administration, i.e. intramuscular and subcutaneous injection and rectal administration. However, intravenously injected drugs enter the bloodstream directly, and therefore absorption is not required to take place

Pharmacology is a vast and complex subject. Therefore, this article only focuses on the principles of pharmacotherapy with respect to how they apply to pregnancy, childbirth and lactation. The basic pharmacokinetic and pharmacodynamics terminology referred to in this chapter is summarised in Table 1.

Drug therapy during pregnancy, childbirth and lactation

Pharmacotherapy during pregnancy, childbirth and lactation may be required for a number of reasons, including acute illness or trauma during the course of a pregnancy, and chronic illness or disability, including a few conditions which are of particular importance in this setting. These are human immunodeficiency

virus infection and acquired immune deficiency syndrome, diabetes mellitus, hypertension, asthma, epilepsy, migraine headaches, mental health disorders (including depression and anxiety), and conditions requiring long-term anticoagulant therapy, e.g. atrial fibrillation. It also refers to pregnancy, labour and lactation-related disorders and emergencies. The foetus may actually be the target of the drug therapy given to the mother, as part of a foetal therapy regimen, in a few instances.[1-3,7,8]

It is of vital importance in these settings to carefully weigh up the possible benefits and risks of pharmacotherapy of not treating the condition at all against the possible outcomes for both mother and child. The decision to opt for drug therapy should always be a sound and rational one. The outcomes which the clinician aims to achieve should be realistic. It should be considered what the available drugs, under the specified conditions, may be reasonably expected to achieve when given to the patient in question. Furthermore, treatment cannot necessarily be interrupted, postponed or avoided altogether merely because a female is pregnant or breastfeeding. This poses a complex clinical challenge for which expert opinion and balanced, evidence-based, decision-making is required (Figure 2).[1,3,5]

The following aspects need to be considered.

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 kinetic processes of absorption, distribution, metabolism and elimination or excretion. Therefore, the following aspects could alter the way in which drug molecules are handled by the body, i.e. alter their pharmacokinetic profile.

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 causes nausea and vomiting. The altered gastrointestinal functioning caused by these changes influences the rate and extent of drug absorption of orally administered drugs.[1,2]

Pregnancy also results in increased lung perfusion and pulmonary alveolar drug transfer owing to the improved cardiac output, meaning that absorption is improved for drugs administered via the pulmonary route, i.e. via nebulisers and inhalers.[3]

Drug distribution may be affected due to the increased plasma volume which accompanies pregnancy, and which may result in an increased volume of distribution of certain drugs. Furthermore, pregnancy results in a decreased blood albumin level, which can result in an increased fraction of free drug molecules. This is especially significant in the case of drugs which are highly protein bound, also increasing their volume of distribution, and altering other kinetic properties. Only the free, unbound fraction is able to cross the placental barrier. The higher fraction of free drug molecules in these instances 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.[1-4,8]

Altered liver functioning may affect the plasma concentrations of drugs which follow hepatic metabolism.[2,3]

The increased plasma volume, in turn increases cardiac output, renal blood flow and glomerular filtration rate. This can increase the renal excretion of drugs which are significantly eliminated via this route.[2-4]

Drugs and their metabolites are also excreted in breast milk.[1-3,5]
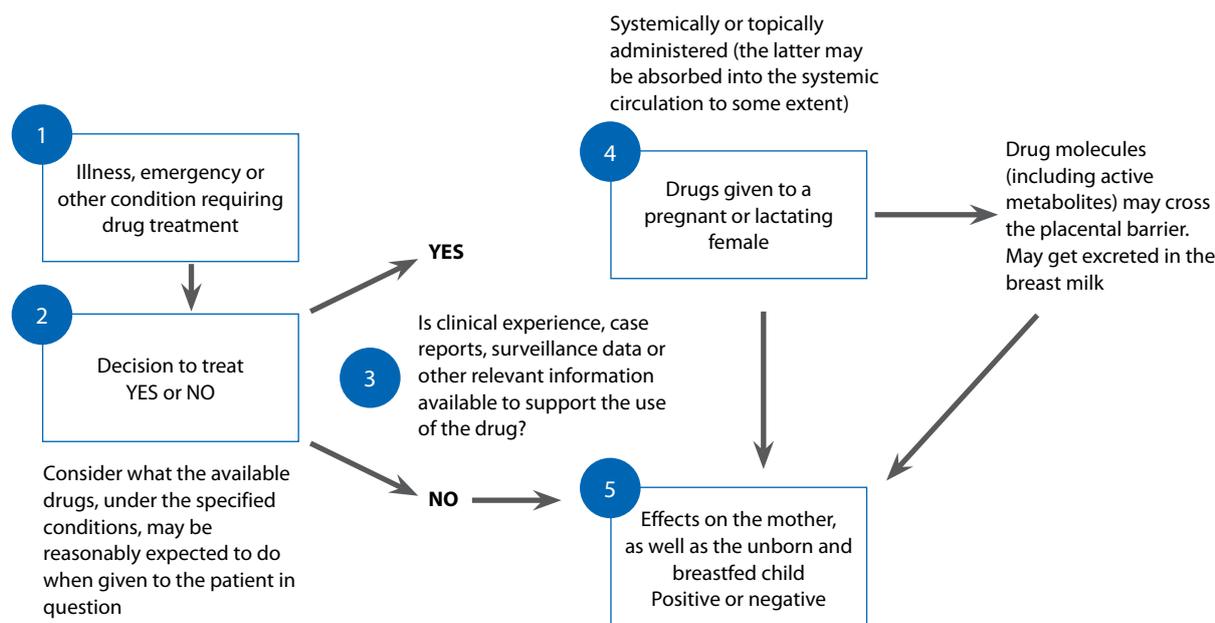
* This is a simplified diagram to illustrate the intricacies of clinical decision-making when drug therapy is being considered in any of these vulnerable patient populations
1. The decision to implement a pharmacotherapeutical regimen should always be a sound and rational one. Definite indications for drug therapy must exist
2. The decision to treat should be carefully weighed up against the possible effects of not treating at all. The benefit-to-risk profile of each individual drug should be considered, as well as any possible interactions between different drugs in the treatment regimen
3. A decision is then taken as to whether or not to institute the proposed drug treatment
4. The unborn child is also invariably exposed to the drugs when the pregnant mother is being treated
5. There are implications for both the mother and child, whether the decision is to treat or not to treat at all

Figure 2: Pharmacotherapeutic decision-making during pregnancy, childbirth and lactation*

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 influence the normal development of the unborn child on a structural or functional level (Figure 1). A teratogen is a drug, or other chemical substance, which may affect normal embryonic development and cause recognisable congenital (birth) defects. The expectant mother may not even be aware of the fact that she is carrying a developing embryo during the very early stages of pregnancy. 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. However, many pregnancies are unplanned or unexpected, implying that preconception care would not have been rendered at all. Sufficient precaution needs to be taken in the form of patient education, and highly effective contraceptive methods instituted, when treating women of childbearing age or potential in the event of drugs which have been shown to pose a significant risk to an unborn child, or drugs with insufficient evidence of relative safety during pregnancy. Some drugs even need to be avoided in men who may farther children while being treated with them.[1,4,5]

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 the mother and child throughout the duration of the pregnancy. However, this barrier is not very efficient in terms of drug molecules. This implies 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. The four characteristics of drug molecules which are most likely to cross the placenta are highlighted in Table 2.[4,5]

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 tend to ionise in the breast milk since it is more acidic than blood). Drugs can also pass from the bloodstream to the breast milk if they contain water-soluble molecules with a relative molecular mass of less than 100 daltons (Da). The Da is the unit of measurement used to express molecular mass, and is indicative of the size of a molecule.[1,2,5]

Drug safety during pregnancy and lactation

There are limited data at disposal on the actual safety profiles of many drugs during pregnancy and lactation. There are many reasons for this, including the difficulties in conducting suitable clinical trials, both on ethical and technical grounds.[9,10] However, many women still take 3–5 medications during their

Table 2: The four characteristics of drug molecules which are most likely to cross the placental barrier[1,3,5,7,8]

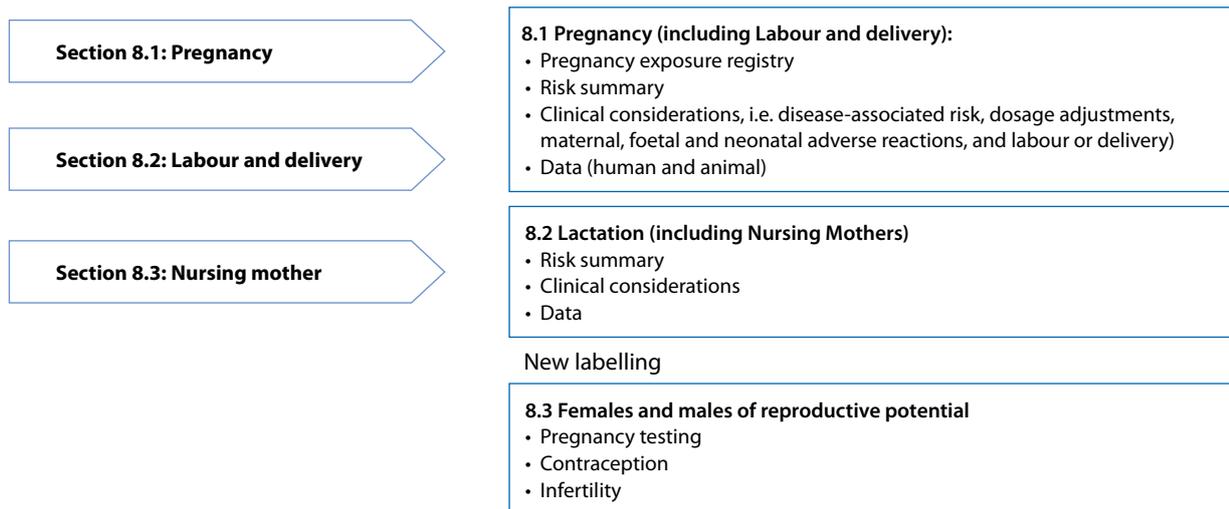| |
| --- |
| A high degree of fat-solubility, i.e. lipophilic molecules |
| A low degree of ionisation, i.e. molecules which do not carry charges |
| A low level of protein binding in the maternal bloodstream, i.e. only small fractions of free molecules are capable of crossing membranes in drugs that are highly protein bound |
| A low molecular mass, i.e. comprising 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 500–1 000 Da will cross very slowly, while molecules of ≥ 1 000 Da will not cross the placental barrier at all |

Da: daltons

pregnancy.[11,12] The prescriber must make pharmacotherapeutical decisions that pertain to each individual patient. Due consideration must be given to their unique maternal, foetal and infant risk-benefit profile. This highlights the importance of healthcare providers having access to a system which enables them to make better and safer drug choices for pregnant and lactating patients.[11-13]

Towards the end of 2014, the US Food and Drug Administration (FDA) announced an amendment to the content and format of information presented in prescription drug labelling. This refers to the new Pregnancy and Lactation Labeling Final Rule. The FDA's goal with this amendment is to provide pregnant or breastfeeding mothers, as well as their healthcare providers, with the best possible information on the use of available agents during the various stages of pregnancy and lactation. These amendments came into effect on 30 June 2015.[11-13]

The old FDA requirements consisted of the five-letter categories, A, B, C, D and X. These categories attempted to broadly identify risk, while using a specific medication.[9,11-13] This simplified system did not provide sufficient information to allow healthcare providers to make the most informed decisions on drug choices for pregnant or lactating mothers. This system was misinterpreted as a grading system, and the lack of information presented a potential risk to both mothers and their foetusses.[11,13] The new rule (Figure 3) consists of up-to-date and well-organised information to provide healthcare providers with better information during the different stages of pregnancy.[9] This labelling also assists healthcare providers during the counselling of patients on the correct use of their medication during pregnancy and lactation.[9,12,13]

The FDA also amended its requirements in terms of the relevant labelling subsections and their content. Therefore, the subheadings of "Pregnancy", "Labor and delivery" and "Nursing mothers" have been replaced or updated with "Pregnancy (to include labour and delivery)", "Lactation (to include nursing mothers)" and "Females and males of reproductive potential". Both the pregnancy and lactation sections are further divided into a risk summary, clinical considerations and data section. The guideline also assists with the labelling of new products, and reversing or amending existing labelling.[9,11–13]

Information on the use of a specific drug during all three trimesters of pregnancy is also provided in the "Pregnancy"

Section 8.1: Pregnancy	8.1 Pregnancy (including Labour and delivery):
	• Pregnancy exposure registry • Risk summary • Clinical considerations, i.e. disease-associated risk, dosage adjustments, maternal, foetal and neonatal adverse reactions, and labour or delivery) • Data (human and animal)

Section 8.2: Labour and delivery	

Section 8.3: Nursing mother	8.2 Lactation (including Nursing Mothers) • Risk summary • Clinical considerations • Data

New labelling

8.3 Females and males of reproductive potential
• Pregnancy testing
• Contraception
• Infertility

Figure 3: A comparison between the previous prescription drug labelling requirements and the new Pregnancy and Lactation Labeling Final Rule of the US Food and Drug Administration (subsections 8.1–8.3)[11]

subsection. This subsection also includes registers in which data are collected and maintained on how the said drug can affect pregnancy during the certain trimester, or after birth and into childhood.[9,11,13] The new label also includes information on physiological changes during pregnancy, and how these affect dosage and risk during the stages of pregnancy, as well as the postpartum period. Information is provided on maternal adverse reactions, foetal or neonatal adverse reactions, and the effects of drugs during delivery or labour.[9] Disease-associated risks to mothers, embryos and foetuses are also included.[9,12]

The "Lactation" subsection provides more information on whether or not the active ingredient will have an effect on the infant during breastfeeding. The new "Females and males of reproductive potential" subsection contains information on how certain medications can affect fertility, pregnancy testing and contraception.[9,11–13]

It is of great importance to consult suitable drug references when prescribing medicines to pregnant or lactating mothers. Known teratogens should obviously be avoided during pregnancy. However, situations may arise in which the benefits of treating the mother with a certain drug may outweigh the possible harm which the drug may or may not do. The package inserts and patient information leaflets of registered medicines should also 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 who are not yet pregnant.[1,5]

Well known examples of teratogenic drugs include:

• Isotretinoin, used in the treatment of severe forms of acne.
• Methotrexate, an antineoplastic and immunosuppressant agent.
• Antiepileptic agents, phenytoin and valproate (the latter is also an antiretroviral agent).
• Warfarin, an oral anticoagulant.

Using ethanol (drinking alcohol) during pregnancy may cause foetal alcohol syndrome.[5] There are many more examples (Table 3).

Table 3: Examples of known teratogenic drugs to avoid during pregnancy [1,2,7*]

Teratogen	Effect
Anticonvulsants	Valproate and carbamazepine are associated with neural tube defects. 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 and and skeletal systems
Antihypertensive agents	Angiotensin-converting enzyme inhibitors cause renal damage, and may restrict normal growth patterns in the unborn child
Antineoplastic agents	Antineoplastic agents are linked to a high risk of multiple congenital malformations
Ethanol (drinking alcohol)	The effects of ethanol may be cumulative, and include foetal alcohol syndrome, abnormal functioning of the central nervous system and disturbances in behaviour
Isotretinoin	Isotretinoin is linked to a very high risk of multiple congenital malformations
Misoprostol	Misoprostol is associated with malformations of the central nervous system and limbs
Neuroleptic drugs	Lithium is associated with congenital defects of the cardiovascular system
NSAIDs	NSAIDs are linked to premature closing of the ductus arteriosus
Tetracycline	Tetracycline is associated with malformations of the teeth (including permanent discoloration) and bone
Thalidomide	Thalidomide is associated with malformations of the internal organs and limbs

In addition, the following drugs are associated with withdrawal symptoms in the newborn infant:
• Barbiturates
• Benzodiazepines
• Opioid analgesics
• Tricyclic antidepressants

NSAIDs: nonsteroidal anti-inflammatory drugs
* Drugs that are not listed here are not necessarily safe to use

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

These factors include:

- 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 medicines and herbal remedies.
- The influence of current and pre-existing illness.
- Health status and general standard of living.
- Unwanted and toxic effects of the drug 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.[2,5]

The following treatment principles may be applied when considering or continuing drug therapy during pregnancy and lactation. Preferably, drugs should be selected that are well known to be safe and effective during pregnancy and lactation. The drug with the shortest plasma half-life should be used at the lowest possible dosage, for the shortest possible duration of treatment. New drugs should be avoided owing to the lack of associated data and clinical experience. Known teratogens should be avoided, even when not yet pregnant, in women of childbearing potential, and sometimes even in fertile males. Self-medicating practices must be discouraged, together with the indiscriminate use of over-the counter drugs, herbal remedies and nutritional supplements. Possible drug interactions must be carefully considered. Commonly used concomitant medications in pregnancy include antacids, for example, which may interfere with drug absorption from the gastrointestinal tract. The most up-to-date drug information should always be consulted.[1,2,4,7]

Conclusion

The decision to choose pharmacotherapy during pregnancy, lactation or childbirth is not always optional. Drug treatment may be unavoidable, but will inevitably expose the unborn child to the effects, whether pharmacological or toxic, of the drug itself. Effects on the foetus may be warranted and desired in a few instances. Irrespective of the reason for exposing the pregnant mother and her unborn child to drug therapy, certain aspects and principles need to be considered before commencing the pharmacotherapy to ensure that the intervention is safe, rational and scientifically sound.

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