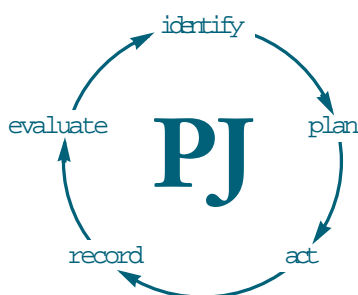


## (2) GENERAL PRINCIPLES OF DRUG USE IN PREGNANCY

By Patricia R. McElbatton, PhD

*The evaluation of the risks and benefits of drug therapy in pregnancy is difficult. This article sets out some principles to bear in mind when advising on the use of drugs in pregnancy*



### identify gaps in your knowledge

1. Name two drugs associated with fetotoxic effects when taken in pregnancy.
2. Which United Kingdom organisation can provide information on drugs and pregnancy?
3. How would you deal with a woman who is worried about having taken medicines before discovering she was pregnant?

This article relates to the Royal Pharmaceutical Society's core competencies of "appropriate advice, referral or selection of treatment" and "evidence-based practice" (see "Medicines, ethics and practice — a guide for pharmacists", number 26, June 2002, pp105–6). You should consider how it will be of value to your practice.

It has been estimated that about 80 per cent of pregnant women have used either prescribed or over-the-counter medicines.<sup>1</sup> In one study, 12 per cent of pregnant women were found to have used analgesics, and 9 per cent were on prescribed medicines for chronic conditions (eg, hypertension and asthma).<sup>2</sup> Physiological changes, such as increased total body water, liver metabolism and renal blood flow, and decreased plasma protein concentration, that occur during pregnancy can significantly alter the pharmacokinetics and hence the plasma levels of some drugs. For example, ampicillin clearance is doubled in pregnancy so increased doses are needed for serious systemic infections, although not for urinary tract infections. However, in most cases pharmacokinetic changes in pregnant women are not clinically relevant.

Most medicines given in pregnancy are for the benefit of the mother, and the fetus is an unintended recipient. Drugs taken by a pregnant woman may pass to the fetus via the placenta and many can have pharmacological effects on the fetus. For example, the use of beta-blockers can result in fetal bradycardia and hypoglycaemia. More significantly, some medicines can harm the developing baby (ie, act as teratogens). Although most prescribers are familiar with the product warning labels that were introduced after the thalidomide tragedies of the 1960s, in practice, these labels are less than helpful — guidance is often lacking as to what the risks are, or what can be used safely in pregnancy. Examples of phrases commonly used in warnings about using a drug in pregnancy include:

- Use with caution, especially in the first trimester . . .
- There is no evidence as to drug safety in human pregnancy . . .
- . . . nor is there evidence from animal work that it is free from hazard . . .
- Do not use in pregnancy unless there are compelling reasons . . .
- The benefits should be weighed against the potential or unknown hazards to the fetus . . .

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There are few data available on the use or safety of alternative remedies such as herbal or homeopathic preparations. Data on the effects of paternal use of drugs on the fetus are scarce.

### GIVING ADVICE

Many pregnant women take medicines inadvertently (before they realise that they are pregnant) and pharmacists may find themselves being asked about the risks incurred by worried mothers-to-be. Although pharmacists might wish to reassure an anxious pregnant woman, false reassurance is dangerous so it is important to take care in choosing what to say.

With regard to fetal malformations, during the pre-embryonic phase (which lasts until 17 days after conception) an "all or nothing" concept is thought to apply. During this period, if extensive damage occurs due to toxic insult, failure of implantation and miscarriage can occur. If the damage to the ball of cells (undifferentiated blastocyst) is minor, and caused by an agent with a short half-life, damaged cells will be replaced by extra division of the remaining cells, which will then implant and develop normally. So if a pregnancy is maintained despite toxic insult during this phase, the risk of fetal malformations is likely to be no greater than the risk in the general population (ie, a one in 40 chance). Clearly, it is important to be certain about the relevant dates and caution is needed if the drug taken has a long half-life.

The risk posed by medicines taken after the pre-embryonic phase, or by a drug with a long half-life, depends on the drug taken. For some drugs, a fair amount of information on whether or not it is a teratogen is available. For example, paracetamol has been used for many years and has a good safety record in pregnancy. Therefore a pregnant woman taking paracetamol would probably be at no greater risk of having a malformed baby than a pregnant woman who had not taken any medicines.

If the drug taken does pose a risk, it may be worth pointing out that not everyone will be affected (ie, people metabolise drugs differently and have a different genetic make-up), before referring the woman to her GP who will know more about her obstetric and medical history. As a result, the GP might send the woman for some tests or scans.

Queries need to be dealt with in a sensitive way. One of the most common reasons for a woman to seek advice about drug or chemical

## GUIDELINES FOR MAKING ENQUIRIES TO THE NATIONAL TERATOLOGY INFORMATION SERVICE

The National Teratology Information Service (NTIS) is funded by the Department of Health. It performs risk assessments for pregnant women exposed to drugs or chemicals and provides pre-conception advice regarding drug and chemical exposures in both men and women. The service is accessible by health care professionals. Common enquiries from pharmacists include: "Is it safe to sell product X over the counter to a pregnant woman?" and "Is it safe to dispense drug X for a pregnant woman?"

The NTIS deals with many other queries, including retrospective ones. For example, after an adverse pregnancy outcome, a parent might want to know if the outcome could have been affected by exposure to a drug or chemical. In any situation, in order to give accurate, evidenced-based advice, as much of the following maternal and paternal information as possible should be included to enable accurate risk assessment:

- Detailed patient identification details; including age (preferably date of birth) to enable follow up if appropriate
- Current drug or chemical exposure, maternal or paternal

exposure during pregnancy is that she has already had a miscarriage, or one affected child, and is naturally concerned about the risks to the fetus she is carrying. For some malformations (eg, spina bifida, cleft palate, clubfoot), the recurrence risks are higher and may be unrelated to medication.

## TERATOGENS

An agent is a teratogen if its administration to the pregnant mother directly or indirectly causes structural or functional abnormalities in the fetus or in the child after birth, which may not be apparent until later life.<sup>3</sup> Effects that can be induced by teratogens include:

- Chromosomal abnormalities
- Impairment of implantation of the conceptus
- Resorption or abortion of the early embryo
- Structural malformations
- Intrauterine growth retardation
- Fetal death
- Functional impairment in the neonate, eg, deafness
- Behavioural abnormalities
- Mental retardation

**Detecting teratogenic effects** The incidence of spontaneous malformations in newborn babies in Europe is 2–3 per cent (1:40 live births). This makes detecting a drug-induced increase in incidence difficult. For example, to be reasonably sure that a drug doubles the incidence of cleft palate (< 1:1000 expected), a study of 23,000 pregnancies would be needed.<sup>4</sup> Even when severe, rare defects such as amelia (absence of limbs) or phocomelia (a limb defect involving the absence of all long bones so that hands and feet are joined to the trunk)

(includes details of the exposure substance, the dose, duration of exposure, medical condition of the parent, any effects of the substance being experienced and occupation of the parent)

- Pregnancy status, including pre-conception (trying for a baby at the time of exposure, stage of pregnancy [weeks], last menstrual period, estimated due date and maternal age)
- Past obstetric history (number of pregnancies, family history of malformations, miscarriages, elective terminations and prenatal diagnosis of problems)
- Relevant past medical history (details of illness, pregnancy induced conditions and medication)

A more detailed version of the guideline questions will shortly be available via the United Kingdom Medicines Information group.

## CONTACT DETAILS FOR THE NTIS:

Monday to Friday 8.30am to 5pm, tel 0191 232 1525  
Out of hours, tel 0191 223 1307 (urgent enquiries only)

occurred with thalidomide, it took approximately 10 years and several hundred malformed babies to establish a causal relationship.

The spontaneous miscarriage rate in clinically recognised pregnancies is 10–20 per cent. A number of these miscarriages may be due to life-threatening malformation but there have been few post mortem examinations.

**Evaluation of studies** The evaluation of epidemiological studies and human case reports of drug use in pregnancy provides useful information. However, data on human exposure to most drugs and chemicals are scarce because they are not routinely tested in women of childbearing age, although changes are being considered.<sup>5</sup> Usually, the only information available is from preclinical studies in animals, or from *in vitro* tests. Extrapolation of the data from such studies to human pregnancy is difficult.<sup>1–3</sup>

## PRINCIPLES OF TERATOGENESIS

Little is known about specific teratogenic mechanisms but some general principles have been formulated.<sup>5–8</sup>

**Timing of exposure** Drugs and other chemicals can cause adverse effects at any stage of pregnancy, not just in the first three months, so to limit "use with caution" to the first three months is an underestimation of the risks involved to the embryo or fetus.

Exposure to a teratogen in the first three months is more likely to cause structural malformations (eg, spina bifida) and exposure after the first three months is more likely to result in growth defects. However, early malformations can have a knock on effect on later development. Also, fetal development can be impaired when as little as 10 per cent of the placenta is adversely affected by infarction or fibrosis.

When a woman first learns she is pregnant, organogenesis (formation of major organs) may have already begun. For example, neural tube closure may already be in progress, or be completed (up to 28 days post conception). Therefore, in many instances the embryo is inadvertently exposed to maternal drug therapy in the early stages of development.

**Differences in susceptibility** Maternal and fetal susceptibility to a drug can be entirely different and, therefore, it is possible for a drug which is harmless to the mother to cause severe damage to the embryo or fetus. Because there is no specific placental barrier to the passage of most drugs or chemicals, the fetus is inevitably exposed to them. However, a drug does not need to cross the placenta to affect the fetus. For example, insulin does not cross the placenta, but the glucose produced during episodes of maternal hyperglycaemia can cross, causing the fetus to produce insulin that cannot be cleared.

**Genetic variation** Risk can differ among individuals, for example, as a result of genetic variation in drug metabolism.

## action : practice points

1. Review the advice on prescribing in pregnancy in Appendix 4 of the current British National Formulary.
2. For the next antibiotic you dispense, find out what information is available about its use in pregnant women. Possible sources include Martindale, the Data Sheet Compendium and the manufacturer (case reports).
3. Consider how you would advise a pregnant woman planning a holiday to India who is worried about taking antimalarials.

## evaluate

How could your learning have been more effective?  
What will you do now and how will this be achieved?

**TABLE 1: DRUGS ASSOCIATED WITH FETOTOXIC EFFECTS WHEN TAKEN IN THE FIRST THREE MONTHS**

Drug taken by the mother	Possible effect on the infant
ACE inhibitors and angiotensin-II receptor antagonists	Possibly lung and kidney hypoplasia, hypocalvaria (ossification of the skull)
Antiepileptics	Cardiac, facial and limb defects, mental retardation, neural tube defects
Cytotoxic drugs	Multiple defects, abortion, growth retardation, stillbirth
Drugs of abuse	Multiple defects, intrauterine growth retardation
Alcohol	Fetal alcohol syndrome
Androgens	Virilisation of female fetus
Diethylstilbestrol	Genital anomalies in female and male infants, transplacental carcinogen — vaginal adenocarcinoma
Other oestrogens	Feminisation of male fetus
Lithium	Cardiovascular and other defects
Misoprostol (when used as an abortifacient)	Moebius sequence (paralysis of 6th and 7th cranial nerves)
Retinoids	Ear, cardiovascular, skeletal defects, central nervous system (CNS) dysfunction
Thalidomide	Limb reduction and other defects
Warfarin	Nasal hypoplasia, chondrodysplasia punctata (a type of dwarfism)

**Teratogenesis in humans** In some cases, the pharmacokinetic and metabolic differences between animals and humans have led to a number of drugs (eg, aspirin) being falsely identified as teratogenic in humans, following animal tests. However, all compounds that are accepted as human teratogens have produced defects in animals, usually rodents, and drugs that are teratogenic in several species, especially at low doses, are generally suspect.

**Dose-response relationships** As with other toxicological evaluations, teratogenic effects are usually dose-dependent and the dose response curve is steep, ie, for a small increment in dose, there may be a large increase in fetal toxicity. In addition, the time of administration after conception is critically important in determining the effects of an agent on the fetus and agents can act synergistically.

Estimates of the cumulative exposure of the fetus to the drug are probably more important than determination of the extent and rate of drug transfer across the placenta.

#### PRESCRIBING IN PREGNANCY

The principles of teratogenesis not only help to guide prescribing during a pregnancy, but they also help to assess the risks to the fetus when maternal drug treatment has already occurred. Drug treatment should only be given if it is clearly necessary because the fetus is at risk of developing both structural malformations and functional abnormalities (eg, treatment could interfere with receptor development). However, it is important to balance the risk to the fetus from drug related effects against the risks to both the mother and the fetus from failing to treat the mother's illness. When treatment is deemed necessary, the lowest effective dose of a single drug should be used, and treatment should be stopped as soon as possible. New drugs are best avoided, because of the lack of human data available.

Using known teratogens in non-pregnant women of child bearing age should also be avoided.<sup>1-8</sup> If this is not possible, steps should be taken to ensure that the patient is fully aware of the dangers.

Table 1 shows drugs associated with fetotoxicity when taken in the first three months of pregnancy and their possible effects on the infant. Table 2 shows the possible effects of drugs associated with fetotoxicity when taken after the first three months. Where the cause of potential abnormalities is known, detailed ultrasound scanning at about 20 weeks of pregnancy, and subsequently, can give accurate information on gestational age and may detect anomalies while therapeutic abortion is still possible.<sup>9</sup>

The next article in this series looks at the use of drugs in particular groups of pregnant women (eg, those suffering from depression or epilepsy). A later article will look at the treatment of common ailments of pregnancy (eg, morning sickness and backache).

**TABLE 2: DRUGS ASSOCIATED WITH FETOTOXIC EFFECTS WHEN TAKEN AFTER THE FIRST THREE MONTHS**

Drug taken by the mother	Possible effect on the infant
ACE inhibitors and angiotensin II receptor antagonists	Oligohydramnios (deficiency of amniotic fluid), growth retardation, lung and kidney hypoplasia, hypocalvaria, neonatal convulsions, hypotension, anuria
Aminoglycosides	Deafness, vestibular damage
Antidepressants	Neonatal withdrawal symptoms
Antiepileptics	Mental retardation, possibly autism/Asperger's syndrome
$\beta$ -adrenoceptor antagonists	Possibly intrauterine growth retardation, neonatal bradycardia, hypoglycaemia
Benzodiazepines	Floppy infant syndrome, neonatal respiratory depression, withdrawal symptoms
Cytotoxic drugs	Intrauterine growth retardation, stillbirth
Diethylstilbestrol	Vaginal adenocarcinoma transplacental carcinogen
Drugs of abuse	CNS dysfunction, intrauterine growth retardation
Narcotics	Neonatal respiratory depression, withdrawal symptoms
Non-steroidal anti-inflammatory drugs	Possible prolongation of gestation and labour, premature closure of ductus arteriosus, neonatal pulmonary hypertension
Phenothiazines	Neonatal withdrawal symptoms, impaired thermoregulation, extrapyramidal effects
Retinoids	CNS dysfunction
Salicylates	Fetal/neonatal haemorrhage
Sex hormones	Virilisation of female fetus/ feminisation of male fetus
Sulphonamides	Hyperbilirubinaemia, kernicterus
Tetracyclines	Staining of deciduous teeth, impaired bone growth
Warfarin/coumarins	Fetal haemorrhage, CNS abnormalities

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