PREGNANCY

(2) GENERAL PRINCIPLES OF DRUG USE IN PREGNANCY

By Patricia R. McElhatton, 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.

There are few data available on the use or safety of alternative remedies such as herbal or homoeopathic 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 balls 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...
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.³ 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 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

TERATOGENS

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

( 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 preconception (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)

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Table 1: Drugs associated with fetotoxic effects when taken in the first three months

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

Table 2: Drugs associated with fetotoxic effects when taken after the first three months

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

Teratogenesis in humans

In some cases, the pharmacokinetic and metabolic differences between animals and humans have led to a response 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.1-4 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.9

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).

References