When evaluating drug use in pregnancy maternal needs and treatment risks to the fetus must be considered

This is the first article of a new series that aims to address the many issues involved in medication-taking during pregnancy. Here, Sally Stephens and Kenneth Hodson outline considerations that should be made when a woman taking medication becomes pregnant, including asking whether she needs her medication — and whether stopping medication might pose a greater risk of harm to her fetus.

Introduction

The thalidomide and diethylstilbestrol disasters of the 1960s have left heavy scars on the history of pharmaceutical development. Fear of litigation and ethical constraints have hampered efforts to undertake objective clinical trials assessing drug efficacy and safety in human pregnancy.[1] Animal toxicity studies, while essential for drug development, do not consistently predict human teratogenicity.[2] Case reports of 'drug-induced' malformations are difficult to interpret because it is impossible to distinguish between causality and chance for an isolated incident. Most information on drug use in pregnancy has been assimilated from observational studies, which are open to recall and reporting biases and, as such, have limited validity. Additionally, while such studies may demonstrate an association between having taken a drug and fetal anomaly, this does not necessarily prove causality.

In the UK collation of large data sets has been made particularly difficult by the absence of a centralised congenital anomaly registry and by the widespread lack of computerised prescribing data linked to clinical information about the recipients. Data protection issues and ethical considerations hinder progress further. Analysis of data, even from large cohorts and birth registries, are not without problems including multiple testing, recall bias, incomplete ascertainment of exposure and confounders. Caution is necessary when interpreting conclusions drawn from data where these errors may exist.

Teratogenicity

A teratogen is a substance, which causes a structural or functional abnormality in the fetus that is sometimes only detected in the child after birth. In the UK the background risk for all congenital abnormalities is 2–3% (1 in 40 live births).[3] Of these it is estimated that between 2% and 5% are secondary to drug or toxin exposure.[4] The incidence of detected congenital anomalies increases during childhood as central nervous system dysfunction and other behavioural problems become apparent. The range of possible teratogenic effects is shown in Table 1.

Table 1. Teratogenic effects

Induced effects of teratogens include:

- ☐ Chromosomal abnormalities
- ☐ Impairment of implantation of the conceptus
- ☐ Resorption or abortion of an early embryo
- ☐ Structural malformations
- ☐ Intrauterine growth retardation
- ☐ Fetal death
- ☐ Functional impairment in the neonate, such as deafness
- ☐ Behavioural abnormalities
- ☐ Learning disabilities
- ☐ Transplacental carcinogenesis

Physiological and pharmacological changes occurring during pregnancy

Pregnancy is associated with dramatic changes in physiology. Total body water is increased by approximately 8 litres, plasma volume and glomerular filtration rate increase by up to 50%[5,6] and liver metabolism is upregulated.[6] Drug concentrations are therefore often reduced in pregnancy through a combination of haemodilution, increased metabolism and increased excretion. This may have clinical implications, for example larger doses of lamotrigine and lithium are often required to maintain therapeutic levels.[6,7]

Mechanisms of teratogenicity

Time of exposure

Timing of exposure is critically important when considering potential teratogenicity. Gestational age is calculated from the first day of the last menstrual period, thus in the first two gestational weeks a women is not actually pregnant. The third and fourth weeks are known as the preimplantation and implantation periods, where the blastocyst is rapidly dividing. A drug insult to the embryo occurring during the preimplantation period is likely either to result in complete embryo destruction, or to have minimal impact upon survival or outcome: the 'all or nothing' hypothesis. This principle applies only where the drug is rapidly eliminated and assigning causality is reliant upon accurate dating of conception.

Organogenesis begins from day 18 and continues to the end of gestational week 10. Damage during this sensitive stage of fetal development is more likely to cause malformations. However, the critical period for some teratogenic effects extends beyond this time. For example, tetracyclines may permanently stain tooth enamel following exposure during the second and third trimesters.[8] The effect of drugs on fetal growth and neurological development is a potential concern throughout pregnancy.

Genetic determinants

Genetic factors are involved in determining responses to teratogens — both between species and between different individuals. Receptor sensitivity and pharmacokinetic differences between species cause variation in susceptibility. However, this is poorly understood. In humans most of the evidence concerning the role of genetic factors has come from studies involving antiepileptic drugs. Thus a drug such as phenytoin that is known to cause cleft palate in humans does not produce this defect in every exposed pregnancy, but only in a sensitive population.[9] The degree of sensitivity depends on the particular genetic constitution of the woman and fetus. The relative importance of genetic versus drug factors differs for each drug and is unknown for most drugs.

Dose-response relationships

Teratogens usually have a steep dose-response curve, where small increments in dose are accompanied by large increases in effect. Warfarin, for example, causes embryopathy in 6.4% of cases, but the risk is reduced at doses less than 5mg and can be further reduced by avoiding first trimester exposure.[10,11] A significant relationship has also been shown between the incidence of neural tube defects and the dosage of sodium valproate.[12]

Duration of exposure

Duration of exposure to a potential teratogen is sometimes an important factor in determining outcome. Some drugs, for example isotretinoin, are thought to produce fetotoxic effects by accumulating in the fetus. However, short-term treatment regimens can be of greater teratogenic insult for some other drugs, which target specific periods of organogenesis, such as thalidomide. Long-term exposure outside of this critical period may have little or no consequences.

Placental transfer

The placenta is not an efficient barrier to most drugs and chemicals, and virtually all drugs reach the fetus in measurable concentrations. Most drugs have a molecular weight of less than 600 Daltons and so are able to cross freely.[13] Only drugs with large molecular weights, such as heparin or insulin, are prohibited from crossing. In effect, one should assume that most drugs, with a few exceptions, are capable of crossing the placenta.

Prescribing in pregnancy

The first consideration when prescribing in pregnancy should be to decide whether medication is absolutely necessary or whether conservative, non-drug measures could be trialled first, such as physiotherapy for backache. A general recommendation to avoid all drugs in the first trimester is both unrealistic and potentially dangerous. The benefits of treatment should always be weighed against potential risks to the fetus. If treatment is required then the lowest effective dose of a single agent should be used wherever possible.

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above: *massage may help to relieve backache and reduce the need for pain relief during pregnancy*

Counselling patients about risk

There is, understandably, reluctance among pregnant women to take medication.[14] One can certainly understand that a mother has a compelling desire to protect her unborn baby. However, despite good intentions, stopping treatment of chronic conditions can be detrimental to both mother and baby. One should bear in mind that the wellbeing of the fetus depends upon a healthy mother.

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When counselling pregnant women it is important to consider the risks of non-treatment of the mother where worsening of her condition can occur versus the (often poorly defined) risk of the treatment to the fetus. For example, stopping taking anti-epileptic medicines could result in seizures, which could pose significant risk to the fetus. Women should be encouraged to continue medication where it is necessary and safe to do so — for example, using inhaled steroids and bronchodilators for asthma.

Often there is a 'grey area' where drugs may be of considerable benefit to the mother, but teratology information is limited or conflicting, for example selective serotonin reuptake inhibitors. In these circumstances it is important for the mother to discuss the pros and cons of treatment with a health care professional to help her reach an informed decision.

The case for each drug should be assessed on an individual patient basis. For example, warfarin is considered by many to be contraindicated in pregnancy. However, in a patient with a metallic heart valve it may be acceptable given the life-threatening consequences of valve thrombosis. Prescribing information and advice for a wide range of drugs can be obtained from the National Teratology Information Service and other sources (see Table 2).

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Pre-pregnancy counselling

In an ideal world, women with chronic medical problems would be reviewed before conception. This would serve two purposes, firstly, to optimise the medical condition (pregnancy can pose significant physiological stress on the body) and secondly, to review medication and offer 'pregnancy-safer' options. For example, certain antiepileptic drugs, such as sodium valproate, are associated with higher malformation rates than others, such as lamotrigine. Where clinically appropriate and safe, a switch of agents, under medical supervision, would therefore be desirable several months before conception so that the woman is stabilised on her new treatment regimen. Ideally, however, women of child-bearing age would be well managed with medication that is least likely or unlikely to cause malformations, so that rapid medication changes do not become necessary.

Unfortunately, pregnancy is often unplanned or unexpected, which makes pre-conception counselling difficult. Additionally, there is poor availability of pre-conception clinics and expertise in this area. General practitioners and pharmacists play an important role in providing contraceptive advice and reminding women who take long-term medication about the importance of pre-conception planning. Women who start taking known teratogenic drugs, such as, methotrexate or retinoids, must be counselled appropriately. For these women the provision of a reliable method of contraception is essential. Written advice should be provided and documented in their medical notes.

Summary points

- ☐ Most drugs can cross the placenta.
- ☐ The background risk for all congenital abnormalities is between 2–3% irrespective of drug exposure.
- ☐ Consider the risks of non-treatment of the mother versus the risk to the fetus.
- ☐ The effects of pregnancy on drug pharmacokinetics should be considered.
- ☐ Gestational age and duration of exposure are important factors when prescribing in pregnancy.
- ☐ Use the lowest effective dose for the shortest possible time.
- ☐ The pros and cons of each drug should be assessed on an individual patient basis.
- ☐ Women of childbearing age who are taking medication with significant teratogenic effects must be counselled appropriately. A reliable method of contraception must be provided.
- ☐ Reliable clinical data are required to specify the risk and safety of drug use during pregnancy. ✣

Declarations of interest

The authors have no interests to declare.

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Table 2. Additional prescribing advice resources

- ☐ UK National Teratology Information Service (NTIS) provides information and guidance on drugs and chemical exposures in pregnancy and provides written monographs on the safety of drugs and chemicals via TOXBASE (see below). To contact the NTIS telephone 0191 232 1525 BEFORE April 2009 or 0844 892 0909 AFTER April 2009 between 8:30 and 17:00 from Monday to Friday. Outside of these hours the service is available for urgent enquiries only.
- ☐ TOXBASE includes information on the safety of drugs in pregnancy and lactation in addition to poisoning information (www.toxbase.org; free registration for health care professionals in the UK and Ireland).
- ☐ *Drugs during pregnancy and lactation*, edited by Schaefer, Peters and Miller, (Elsevier, 2007) offers treatment options and risk assessments with recommendations.
- ☐ *Drugs in pregnancy and lactation*, edited by Briggs, Freeman and Yaffe, (Lippincott, Williams and Wilkins, 2008) is a comprehensive reference source.
- ☐ Reprotox and Teris are specialist areas within Micromedex, which require paid subscription (www.thomsonhc.com).

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