Clinical review

Fortnightly review

Drug treatment during pregnancy

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For most doctors prescribing a drug to a pregnant woman is like taking a journey through uncharted territory; navigation is made no easier by the darkness cast by "thalidomide's long shadow."[1] The usual benchmarks are absent because evidence from large clinical trials doesn't exist for drug treatment during pregnancy. Information on many drugs includes non-specific warnings along the lines of "not to be used in pregnancy unless the benefits outweigh the risks," even though the benefits may not have been confirmed and the risks are not specified. Also, the disease being treated may affect or be affected by pregnancy. Nevertheless, at least a third of all pregnant women in the United Kingdom are prescribed at least one course of drug treatment.[2] The purpose of this review is to summarise some of the important points that should be considered when prescribing drugs for pregnant women.

Summary points

- Evidence about the effects and effectiveness of drug treatment during pregnancy is often circumstantial
- All doctors who prescribe drugs for women of childbearing age must think about potential pregnancies before prescribing
- Counselling before pregnancy is essential for all women receiving long term drug treatment
- A useful treatment should not be stopped without good reason

Methods

For obvious ethical reasons there are few randomised and placebo controlled clinical trials designed to evaluate the safety and efficacy of drugs in pregnancy. Exceptions to this rule include studies of aspirin in the prevention of pre-eclampsia[3 4] and some small studies of antihypertensive agents.[5 6] Studies of drug treatment during pregnancy are usually done as retrospective analyses (performed by reviewing charts or monitoring prescriptions) or case reports. Case reports are important in recording alleged adverse effects but suffer from the weakness of being anecdotal evidence. The problem is that in 1-2% of all pregnancies in developed countries there will be some form of fetal anomaly, and chance associations between these anomalies and drugs are always difficult to refute.[7] Thus, certainty is a rare commodity when trying to provide information on drug treatment during pregnancy. References used in this review are drawn from my own collection which is updated regularly by computerised literature searches.

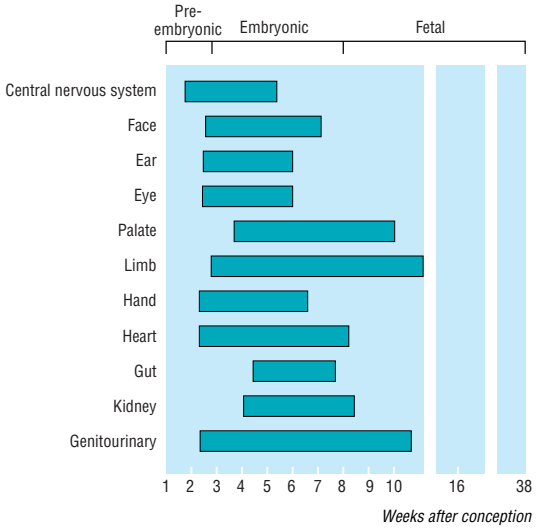
Drugs that harm the fetus

The thought that drugs taken during pregnancy may harm the fetus is what scares patients and their doctors, but of the many drugs in use only a few have been shown definitively to be harmful to the fetus. These drugs may cause anatomical defects, like cleft lip or spina bifida, or physiological problems such as renal failure or growth retardation. The effects depend not only on the drug used but also on the gestation of the fetus when the drug is taken.[8]

Organogenesis

The major body structures are formed in about the first 12 weeks or so after conception (figure). Interference in this process causes a teratogenic effect (from the Greek teratos meaning monster). If a drug is given after this time it will not produce a major anatomical defect—for example, it is not possible to cause a ventricular septal defect after the septum is formed. By the time a woman presents to her doctor she is usually well into, or even beyond, this crucial period. Stopping a useful drug at this point is illogical and may even be harmful if the disease being treated worsens. Similarly, if a teratogen is still in the body during organogenesis, even though the course of treatment was completed before conception—as may happen with retinoids[9]—there is the potential for harm. Commonly used drugs that are known to cause teratogenic effects during the first trimester are shown in the box.

Being a teratogen does not mean that a drug will always cause harm in the first trimester—for example, anticonvulsants are teratogenic in less than 10% of fetuses exposed to the drug. The mechanisms of drug induced teratogenicity have not been elucidated; the



Timing of the development of major body structures in the embryo and fetus. Used with permission of BMJ Publishing[29]

Commonly used drugs that are teratogenic

Phenytoin[10]
Carbamazepine[11]
Sodium valproate[12]
Lithium[13]
Warfarin[14]
Retinoids[9]
Danazol[15]

genetic composition of the fetus, the precise timing of exposure, and the dose may all play a part in producing teratogenic effects.

Drugs later in pregnancy

The growth and development of the fetus may be affected by drug treatment later in pregnancy. Examples of drugs that may affect fetal development are shown in the box. Treatment with anticoagulants is a challenge since not only can warfarin have adverse effects on the fetus but also long term, high dose unfractionated heparin can cause bone demineralisation in the mother. This may be less of a problem with low molecular weight heparins.

There is about a 25% risk of intrauterine growth retardation when atenolol is used to treat essential hypertension throughout pregnancy[16]; other β blockers have not been systematically studied but it should be assumed that this is an effect of this class of drugs. Although babies who have been exposed to atenolol achieve their growth milestones after delivery it is preferable to avoid β blockers for treating hypertension. Methyldopa has a well established record of safe use during pregnancy.

Tetracyclines should not be used during pregnancy because of their ability to discolour teeth and inhibit bone growth. However, it is common for a tetracycline that has been prescribed for acne to have been used inadvertently for a brief time early in the first trimester. In the absence of any other risk factors such an occurrence would not ordinarily justify termination of the pregnancy on medical grounds.[17]

Drugs that can affect fetal growth and development

Drug	Possible effect
Angiotensin converting enzyme inhibitors[19]	Fetal or neonatal renal failure
Antithyroid drugs[20]	Fetal hypothyroidism (if drug used in excessive dose)
Benzodiazepines[21]	Drug dependence in the fetus
β blockers[16]	Growth retardation may occur if used throughout pregnancy (this has been shown for atenolol and inferred for others)
Barbiturates[22]	Drug dependence in the fetus
Non-steroidal anti-inflammatory drugs[23]	Constriction of ductus arteriosus (from second trimester onwards)
Tetracyclines[17]	Tooth discoloration; may inhibit bone growth (brief exposure early in first trimester not shown to be harmful)
Warfarin[24]	Bleeding into fetal brain (even if the mother's international normalised ratio is therapeutic)

Aspirin can cause minor neonatal haemorrhage when used in analgesic doses within a few days before delivery.[18] This effect has not been seen in trials of low dose aspirin.[3]

Drugs and breast feeding

Most drugs do cross over into breast milk but dilution in the mother's body coupled with the amount of milk swallowed usually means that whatever reaches the baby is not sufficient to cause any effects. Examples of drugs that should be avoided by mothers who are breast feeding are shown in the box.

Drugs that should be avoided while breast feeding

Drug	Possible effects on the baby
Amiodarone hydrochloride	Iodine content may cause neonatal hypothyroidism
Aspirin	Theoretical risk of Reye's syndrome
Barbiturates	Drowsiness
Benzodiazepines	Lethargy
Carbimazole	Hypothyroidism (use lowest effective dose)
Combined oral contraceptives	May diminish milk supply and reduce nitrogen and protein content of breast milk
Cytotoxic drugs	Immune suppression and neutropenia
Ephedrine hydrochloride	Irritability
Tetracyclines	Theoretical risk of tooth discoloration

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Misconceptions about drug treatment during pregnancy

Corticosteroids have a reputation for being teratogenic. There is no evidence for this in humans,[25] although in high doses corticosteroids cause oral clefts in rodents. Corticosteroids have been used in thousands of pregnant women for treatment of autoimmune diseases, severe asthma, inflammatory bowel disease and after organ transplantation with no evidence of an excess occurrence of fetal abnormality. In contrast to the steroids used to accelerate lung maturity corticosteroids are metabolised in the placenta, and there is no evidence that they influence the fetal endocrine system.

Warfarin is regarded by some doctors and midwives as being contraindicated in nursing mothers. This is a mistake.[26] Concentrations of warfarin in breast milk have been found to be low, and extensive clinical experience attests to its safety in this context.

Oral contraceptives are commonly taken inadvertently in the early stages of the first trimester. It was initially thought that this posed a risk to the fetus but a meta-analysis of the evidence does not support this view.[27]

There is a widely held view that some anticonvulsant drugs are safer than others during pregnancy. The reported frequency of fetal anomalies associated with anticonvulsant drugs varies widely but there are two points to remember. Firstly, the safest drug is the one that controls the epilepsy; secondly, the early part of pregnancy is not the best time to start trying different treatments, particularly if the existing treatment is working.

Avoiding risk

The best way to avoid harming the fetus as a result of drug treatment is for a patient not to take a drug in the first place. Unfortunately, it seems not to be widely recognised—even among some of my medical colleagues—that having sexual intercourse without using contraception may result in pregnancy. A common scenario is that of a woman and her general practitioner realising that she was pregnant but did not know it when she took a drug a few weeks earlier. All doctors who prescribe drugs for women of childbearing age must remember that pregnancy happens and must think about potential pregnancies when prescribing.

For women who must remain on drug treatment decisions are more complicated. Advice about the risks and benefits of treatment, and the risks of stopping treatment, should be given before pregnancy in a sympathetic and informed manner. In the case of anticonvulsant drugs it is sensible to give folic acid 4 mg/day starting before conception. This has not been shown to prevent fetal abnormalities associated with drug treatment, but theoretically it should.

New drugs

Except in the few instances of drugs being evaluated for use in treating a complication of pregnancy (for example, preterm labour) it is likely that it will be many years before any easily interpreted information will accrue on the risks of using new drugs during pregnancy. Even when such information is available there is the problem of bias because of the selective reporting of fetal abnormalities. Ideally every time a pregnant woman is exposed to a new drug this should be reported to the manufacturers, the drug regulatory authorities, or both, so that both the number of exposures and the number of adverse effects are known.

Drugs with a good safety record during pregnancy

In these litigious times it would be a reckless person who dogmatically stated that anything was absolutely "safe." However, there are many drugs that have been used in pregnancy without apparently harming the fetus. In addition to those mentioned above paracetamol, penicillins, cephalosporins, antacids, and steroid and bronchodilator inhalers should be considered safe. The treatment of morning sickness has been difficult since Debendox (doxylamine, dicyclomine, and pyridoxine), known as Bendectin in the United States, was taken off the market in the early 1980s. No drug has yet been shown to be consistently effective in treating this problem.

Influence of pregnancy on drugs

Drugs may not have their expected therapeutic effect during pregnancy. One important and underrecognised reason is the poor compliance of pregnant women. One study found that 50% of pregnant women would not take a course of drug treatment as prescribed by their doctor.[28] The same study found that magazines, friends, and relatives were a more likely source of information about drugs during pregnancy than doctors or midwives. Fear of harming the fetus is the main concern for mothers, and it is important that the benefits and risks of treatment—and of stopping treatment—are explained in a balanced manner.

Drugs may also be less effective during pregnancy because of pharmacokinetic changes such as increased metabolism (which may affect phenytoin, for example) or excretion (which may affect amoxycillin, for example). Doses of these drugs may need to be increased during pregnancy.[29]

Because of the combined effects of poor compliance and possible changes in clearance, monitoring the therapeutic concentration of drugs during pregnancy may be helpful, especially in conditions such as epilepsy.

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Lesson of the week

Malaria at Christmas: risks of prophylaxis versus risks of malaria

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Health professionals need to educate travellers about the dangers of malaria and the importance of prophylaxis

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There was a large increase in the number of cases of falciparum malaria imported into the United Kingdom and reported to the malaria reference laboratory in the first quarter of 1998.[1] The two factors cited to explain this increase were unusually heavy rains in east Africa and a reduction in the use of the most effective antimalaria drug, mefloquine.[1] At the same time there was an increase in the number of cases of severe malaria in the United Kingdom.[1] During December 1997 and January 1998 this hospital treated five patients for severe malaria and gave advice on a further 20 patients with malaria who had been admitted to intensive care units throughout England. Of the 25 patients, 13 were male (median adult age 50; range 23 to 85) and two were children. Twenty two of those treated were of European origin. Altogether 20 patients had travelled to east Africa (16 to Kenya and at least six of these to Mombasa); five had travelled to west Africa. Median parasitaemia was 16% (range 1.1% to 60%). Ten patients (40%) had taken no prophylaxis; one of these was a Kenyan man of Asian origin who was on holiday in the United Kingdom. Prophylactic drugs had been prescribed for 15 patients: 11 had been prescribed proguanil and chloroquine, two had been prescribed mefloquine, and two had been prescribed other drugs. Nine of the 15 had not taken the drugs as prescribed. Thus 19 of the 25 (76%) had taken either inadequate doses or no prophylactic drugs. The cost to the NHS for intensive care for these patients exceeded £160 000 ($256 000). We report on four cases of severe malaria seen at our hospital.

Case reports

Case 1—A 50 year old woman who thought she had influenza was admitted to an intensive care unit with a parasitaemia of 37%, renal failure, and pulmonary haemorrhage. She had been told by a practice nurse that antimalaria drugs had too many side effects; she had sought alternative prophylaxis from homoeopathy.

Case 2—A 54 year old woman was discouraged by a friend, a community psychiatric nurse, from taking mefloquine. The patient took no prophylaxis because she thought that nothing else was available. She was subsequently admitted to the intensive therapy unit with a parasitaemia of 35% and cerebral, renal, and pulmonary involvement.

Case 3—A 55 year old man working in Nigeria had tolerated mefloquine well but his doctor was concerned about possible long term side effects and stopped the drug after six months. The patient could not tolerate chloroquine and proguanil and so took no prophylaxis. He was admitted to an intensive therapy unit on Christmas Eve with a parasitaemia of 18% and renal failure.

Case 4—A 37 year old Sudanese woman who lived in the United Kingdom was prescribed mefloquine for travel to Sudan but decided not to take it, probably thinking incorrectly that she was immune to malaria. She was admitted on Christmas Day with a fever and perianal abscess. The abscess was drained but the fever did not settle. She was readmitted eight days later with jaundice, shock, and a reduced level of consciousness.