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to general practitioners and pharmacists in Wales

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Prescribing in pregnancy

Pregnancy can cause dilemmas in prescribing for several reasons. Certain drugs are known to be harmful to the fetus. Fear of potential teratogenicity of drugs is widespread among patients, prescribers and the public. This causes reluctance both to prescribe and to take prescribed medicines. Nevertheless, pregnant women need medication when the risk of the untreated disease is considered to be greater than the drug risk to the fetus. Most drugs are unlicensed for use during pregnancy because there is no evidence from clinical trials about their use in pregnant women. However, extensive circumstantial evidence of the safe use of several drugs during pregnancy enables many conditions to be treated appropriately.

Summary

- ♦ Drug therapy during pregnancy poses serious challenges to prescribers. Several drugs are known teratogens but the under-treatment of disease can be equally harmful.
- ♦ Women taking teratogenic drugs and who become pregnant or plan pregnancy should be referred for specialist advice without delay. Drug treatment of serious conditions can often be continued with safer alternative drugs.
- ♦ Many conditions can be treated using drugs with a long history of safe use.
- ♦ This bulletin lists factors that should be considered when prescribing for pregnant women, with examples of common illnesses that require continued therapy. Table 1 lists known teratogens and Table 2 lists drugs that have a good safety record in pregnancy. Sources of further information are given.

Teratogens

Teratogens are substances that can cause congenital malformations, spontaneous abortion, or other structural or functional abnormalities in the fetus or the child after birth (see Table 1 on page 4). The incidence of major congenital malformations in developed countries is about 2 to 4% of live births and of these 5% are thought to be caused by environmental factors including drugs and other chemicals.¹ The risk of a drug affecting organogenesis depends on several factors including the drug, time of exposure, dose, genetic composition of the fetus and the mother's previous obstetric history. In the pre-embryonic period (up to 17 days post-conception) a toxic insult is believed to lead to either death of the embryo or

replacement of damaged cells and intact survival (the "all or nothing" principle). From 18 days to 10 weeks post-conception the fetus is most vulnerable to toxins affecting organogenesis. After this period teratogens may interfere with fetal growth and development (see Table 1). Delayed effects are also possible; diethylstilbestrol can cause vaginal adenosis and adenocarcinoma in female offspring at 15 to 20 years of age, after in utero exposure to the drug.

Teratogens are not toxic in all cases of exposure; the risk of birth defects varies from about 1% for carbamazepine to about 38% for isotretinoin.¹

Manufacturers' data sheets and summaries of product characteristics should be consulted for full prescribing information.
For some drugs mentioned in this bulletin, use during pregnancy is not licensed although it may be established medical practice. It is important for doctors to recognise the responsibility that prescribing these drugs entails.

Considerations when prescribing in pregnancy

Almost all drugs cross the placenta. Exceptions are drugs with a high molecular weight such as heparin. In addition, drugs may also affect the fetus indirectly by altering maternal homeostasis. For example, pregnancy may alter insulin requirements and lead to poor control of diabetes; the resulting fetal hyperinsulinaemia may cause organomegaly, hypoxia and possibly congenital abnormalities.²

Some teratogenic drugs may be toxic in the first trimester, but others are more harmful at later stages, such as non-steroidal anti-inflammatory drugs taken after 30 weeks (see Table 1). All pregnant women taking potentially teratogenic drugs need early review at an antenatal clinic.

General principles of prescribing

- ◆ Prescribe drugs only when necessary; in some conditions non-drug approaches may be effective, e.g. changing diet in constipation. Consider topical treatment before systemic treatment.
- ◆ Use the lowest effective dose for the shortest possible time but remember that under-treatment poses risks to maternal well-being and may also affect the fetus.
- ◆ Use the minimum number of drugs as some teratogenic drugs have been shown to act synergistically.³
- ◆ Prescribe older, more established drugs in preference to newer drugs. For instance, use antacids rather than proton pump inhibitors, and older rather than more recently introduced antidepressants (see example on next page).
- ◆ Teratogenic risk should be considered when prescribing for **any** woman who may become pregnant.

Disease management

A pregnant woman who has a serious condition being managed by a specialist should be referred for review.

With some conditions, the risk of acute disease may be greater than the risk of harm to the fetus associated with the drug. Such conditions include asthma, diabetes, epilepsy (see example) and severe hypertension (see example). If travel is unavoidable to an area where malaria is endemic, then the benefit of chemoprophylaxis outweighs the risk of contracting malaria.

Many common conditions can be managed using drugs that have an established record of safe use during pregnancy (see Table 2). Examples include heartburn, urinary tract infection, asthma, constipation, hay fever, pain, nausea and vomiting.

Compliance

Pregnant women may be less compliant than usual through fear of harming the unborn child; in one study half of the pregnant women said they would not take antibiotics prescribed by their doctor.⁴ The risks and benefits of drug therapy (and the risks of not treating the disease) should be thoroughly discussed with the patient.

Effect of pregnancy on illness

Pregnancy may alter the course of an existing illness or it may precipitate one for the first time. Such illnesses include asthma, diabetes, epilepsy, hypertension, migraine and thromboembolic disease (see example).

Effect of pregnancy on drug handling

Pregnancy may affect the pharmacokinetic parameters of drugs, requiring changes in doses. For example, renal blood flow approximately doubles, increasing excretion of renally eliminated drugs such as amoxicillin, digoxin and lithium. An increase in metabolism may result in reduced plasma concentrations of some anti-epileptic drugs.

Other considerations

Pregnant women should be advised to avoid self-medication with herbal remedies and should follow expert advice on over-the-counter drug use. For example, vitamin A in high doses may cause congenital malformations. There is even less information on the safety of herbal remedies in pregnancy than with conventional medicines.

All women considering pregnancy should be advised about the need to take a daily folic acid supplement.

In the UK a doctor is immune from civil liability for the adverse effects on the fetus of a drug prescribed appropriately if it is currently given in pregnancy as established medical practice (Congenital Disabilities (Civil Liability) Act 1977).

Depression

Maternal depression during pregnancy can have deleterious effects on the neonate, because of the potential for poor maternal weight gain or malnutrition, activation of the hypothalamic-pituitary-adrenal axis caused by stress, risk of suicide and adverse psychosocial consequences.⁵ If supportive counselling is not adequate, tricyclic antidepressants and fluoxetine are first-line choices in the management of depression. Tricyclic antidepressants have a long history of use without increasing teratogenic risk in pregnant women.⁶ Fluoxetine has been studied in prospective trials and no evidence for a higher incidence of malformations or other teratogenicity was found.^{5,7}

Doses of tricyclic antidepressants may need to be higher during pregnancy because of physiological changes such as increased hepatic metabolism.⁵

Where appropriate, to avoid withdrawal symptoms in the neonate, antidepressants should be slowly withdrawn or reduced to the minimum dose prior to delivery.⁵

Epilepsy

The incidence of congenital malformations has been found to be higher in untreated epileptic patients than in non-epileptic patients. About 10% of women with epilepsy have an increase in seizure frequency during pregnancy. This is probably caused by decreased plasma concentrations of their anti-epileptic drugs owing to changes in pharmacokinetics such as increased drug clearance. Reduced compliance and persistent vomiting are other potential factors. Repeated maternal seizures have been reported to cause serious effects in the fetus such as hypoxia, bradycardia and antenatal death,⁸ therefore, the benefits of continued treatment are considered to outweigh the risks. Some consultants of pregnant patients may consider preconceptional withdrawal of anti-epileptic drugs if the patient has not had a seizure for at least two years.⁸

Reported incidences of congenital deformities in pregnant women taking one or more anti-epileptic drugs vary from 0.5-1% with a single drug to 20-30% with four drugs.^{3,9,10} The risk is greater with polypharmacy and higher doses of drugs. Less information is available about the newer agents such as gabapentin or lamotrigine but they have not been found to be teratogenic in experimental animals^{11,12} and are used at some centres (Davies NJ, personal communication, 2000).

Preconception counselling is strongly advised in women taking anti-epileptic drugs who wish to become pregnant. Once pregnant, they need early referral to a specialist team or antenatal clinic but a drug regimen that is effective should not be stopped. Monotherapy is preferable in pregnancy but if required for seizure control, a second drug should not be withheld. With sodium valproate, peak plasma concentrations should be reduced by changing dosing from twice daily to three times daily or to the modified-release preparation (before conception if possible). There appears to be no consensus on the need to monitor serum levels of anti-epileptic drugs during pregnancy, probably because of difficulty with interpreting values.^{8,10} If status epilepticus occurs, it should be treated as in non-pregnant patients.

Supplementation in epilepsy

Folic acid deficiency has been implicated in teratogenicity caused by anti-epileptic drugs. Therefore, supplementation with folic acid at a dose of 5 mg daily is recommended, ideally starting 3 months before conception.⁸ Vitamin K deficiency may occur more frequently in neonates prenatally exposed to anti-epileptic drugs that induce liver enzymes. This can be prevented by giving oral vitamin K (as phytomenadione, 10 to 20 mg daily) to the mother during the last month of pregnancy.⁹

It is recommended that all pregnant women with epilepsy are registered with the UK Epilepsy and Pregnancy Register. Information is collated about these patients, their drug use and pregnancy outcomes, and a free telephone advice helpline is provided (tel: 0800 389 1248).

Chronic hypertension

Chronic severe hypertension ($\geq 170/110$ mm Hg) predisposes pregnant women to pre-eclampsia as well as other serious complications,¹³ and should always be treated. Early control of mild-to-moderate hypertension has been found not to affect maternal or fetal outcome.¹³ Mild-to-moderate hypertension does not necessarily require treatment during pregnancy but should be monitored frequently. Maternal blood pressure usually decreases during the first trimester and it may be possible to withdraw drug therapy. In the third trimester hypertension may re-emerge or present for the first time.

The first choice antihypertensive drug for all stages of pregnancy is methyldopa, and most pregnant patients should be switched to this agent. Normal development has been shown in children up to 8 years after exposure to methyldopa in utero.¹⁴ Labetalol and nifedipine are used as second-line treatment after the first trimester,^{1,13} although nifedipine is not licensed for use during pregnancy. Reports of smaller fetuses associated with atenolol¹⁵ have led to advice to limit beta-blocker use to the third trimester.¹⁶

Antihypertensive agents are not known teratogens in the first trimester and, therefore, none need to be changed urgently when a woman becomes

pregnant, but ACE inhibitors should be stopped by the 12th week at the latest.¹⁶

Thromboembolic disease

Pregnancy increases the risk of venous thromboembolism and pulmonary embolism.¹ Any anticoagulant can increase the risk of a haemorrhage in the fetus, but heparin is the preferred drug in most cases because of the teratogenicity of warfarin.¹⁶ Like unfractionated heparin, the low-molecular-weight heparins are too large to cross the placenta. Although experience with these in pregnant women is still limited, they are used for prophylaxis at some centres in Wales.

Table 1: Some drugs shown to be harmful during pregnancy in humans^{1,15-17}

Drugs that may cause congenital malformations

anti-epileptic drugs	lithium
cytotoxic drugs	retinoids (systemic)
danazol	warfarin

Drugs affecting fetal growth and development - *possible effect*

ACE inhibitors (after 12 weeks) - <i>fetal or neonatal renal failure</i>
Barbiturates, benzodiazepines (near term) - <i>drug dependence in the fetus</i>
NSAIDs (after 30 weeks) - <i>constriction of fetal ductus arteriosus</i>
Tetracyclines (after 12 weeks) - <i>abnormalities of teeth and bone</i>
Warfarin - <i>fetal or neonatal haemorrhage</i>

Table 2: Some drugs that have a good safety record in pregnancy^{1,15-17}

Analgesics: paracetamol, codeine
Antacids containing aluminium, calcium or magnesium
Antibiotics: cephalosporins, penicillins, erythromycin, clindamycin, nitrofurantoin (avoid near term)
Anti-emetics: cyclizine, promethazine
Antifungal agents (topical and vaginal): imidazoles (e.g. clotrimazole), nystatin
Antihistamines: chlorphenamine (chlorpheniramine), hydroxyzine
Asthma: bronchodilator and steroid inhalers, a short course of oral corticosteroids
Corticosteroids (topical, including nasal)
Insulin (human)
Laxatives: bulk-forming, lactulose
Levothyroxine
Methyldopa
Oral contraceptives (inadvertent use in early pregnancy)
Ranitidine
Vaccines (inactivated)

Sources of information

- ◆ BNF, Appendix 4: pregnancy.
- ◆ Local drug/medicines information centres.
- ◆ Pharmaceutical company medical information departments.
(For medico-legal reasons these often cannot give recommendations for the use of drugs in pregnancy but may be able to provide information about the outcome of pregnancies during which a drug was taken.)
- ◆ National Teratology Information Service (NTIS), Regional Drug and Therapeutics Centre, Wolfson Unit, Claremont Place, Newcastle-upon-Tyne, NE2 4HH. Tel: 0191 232 1525.
(Telephone enquiry service for all health professionals; monographs on drugs and conditions available on Toxbase, see below.)
- ◆ Useful World Wide Web addresses:
www.spib.axl.co.uk (Toxbase, information on drugs in pregnancy provided by NTIS)
www.motherisk.org (Motherisk Program, Department of Pediatrics, University of Toronto)
- ◆ Specialist textbooks:
Briggs GC, Freeman RK, Yaffe SJ. A reference guide to foetal and neonatal risk: drugs in pregnancy and lactation. 5th edition, Williams & Wilkins, Baltimore, 1998 (cost: £66).
Lee A, Inch S, Finnigan D. Therapeutics in pregnancy and lactation. Radcliffe Medical Press, Abingdon, 2000 (cost: £19.95).

References

1. Theis JGW, Koren G. Maternal and fetal clinical pharmacology. In: Speight TM, Holford NHG, eds. Avery's Drug Treatment, 4th Ed. Auckland: Adis International, 1997: 75-126.
2. Gilmer MD. Management of pre-existing disorders in pregnancy: diabetes mellitus. Prescr J 1996; 36: 159-164.
3. Nakane Y et al. Multi-institutional study on the teratogenicity and fetal toxicity of antiepileptic drugs: a report of a collaborative study group in Japan. Epilepsia 1980; 21: 663-680.
4. Butters L, Howie CA. Awareness among pregnant women of the effect on the fetus of commonly used drugs. Midwifery 1990; 6: 146-154.
5. Wisner KL et al. Pharmacologic treatment of depression during pregnancy. JAMA 1999; 282: 1264-1269.
6. Appleby L et al. Depression in pregnant and postnatal women: an evidence-based approach to treatment in primary care (editorial). Br J Gen Pract 1999; 49: 780-782.
7. Nulman I et al. Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997; 336: 258-262.
8. Nulman I et al. Treatment of epilepsy in pregnancy. Drugs 1999; 57: 535-544.
9. Malone FD, D'Alton ME. Drugs in pregnancy: anticonvulsants. Semin Perinatol 1997; 21: 114-123.
10. Cleland PG. Management of pre-existing disorders in pregnancy: epilepsy. Prescr J 1996; 36: 102-109.
11. Lamictal[®] (lamotrigine) tablets. Summary of Product Characteristics. GlaxoWellcome, 1999.
12. Neurontin[®] (gabapentin) tablets. Summary of Product Characteristics. Parke-Davis, 2000.
13. Teoh TG, Redman CW. Management of pre-existing disorders in pregnancy: hypertension. Prescr J 1996; 36: 28-36.
14. Cockburn J et al. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. Lancet 1982; 1: 647-649.
15. Rubin P. Drug treatment during pregnancy. BMJ 1998; 317: 1503-1506.
16. Shehata HA, Nelson-Piercy C. Drugs to avoid in pregnancy. Curr Obstet Gynaecol 2000; 10: 44-52.
17. Koren G et al. Drugs in pregnancy. N Engl J Med 1998; 338: 1128-1137.