

Drugs

Drugs to avoid in pregnancy

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Drugs given in pregnancy can adversely affect the fetus in many ways. Anxiety about birth defects is a major parental concern during pregnancy. Doctors and their patients often seek information about the potential teratogenicity of drugs that are taken by or prescribed for the pregnant woman. Because no drug is entirely without side effects, great caution should be taken when prescribing in pregnancy. The development of knowledge in understanding the use of drugs during pregnancy has been in stalemate in comparison to other areas of therapeutics, mainly due to difficulties in testing new products in pregnant women and paucity of good quality research. In this article, we aim to review current knowledge of the epidemiology of drug use among pregnant women, drug metabolism in pregnancy, adverse fetal and neonatal effects of drugs and specific effects of drugs that are relatively or absolutely contraindicated in pregnancy. © 2000 Harcourt Publishers Ltd

DRUG EPIDEMIOLOGY

Despite a growing awareness of the need to avoid drugs, pregnant women take many medications. The typical pregnant woman takes one to three drugs, besides vitamin supplements or iron.¹ About a third of women in the United Kingdom take drugs at least once during pregnancy, but only 6% take a drug during the first trimester.²

There has been a considerable reduction in drugs used in pregnancy since the last major survey (mid-1960s) in the United Kingdom, with total use falling from 80 to 35% and self-administered drugs from 64 to 9%.³ This reduction could largely be due to the continued media focus on drug-induced fetal abnormalities.

In the puerperium the use of drugs increases substantially with no difference in the pattern of prescribing between mothers who breast-feed and those who bottle-feed.⁴

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DRUG METABOLISM

The practical view to take when prescribing drugs in pregnancy is that transfer of drugs to the fetus is inevitable. The placenta is essentially a lipid barrier between the maternal and fetal circulation and drugs cross the placenta by passive diffusion. Low molecular weight, lipid soluble, un-ionised drugs cross the placenta more readily than more polar drugs. However, eventually most drugs achieve roughly equal concentrations on each side of the placenta.³ There are several physiological changes with marked impact on pharmacokinetics⁵ and, therefore, some established therapeutic ranges might be inappropriate.

HUMAN TERATOGENESIS

Teratogenesis is defined as structural or functional (e.g. renal failure) dysgenesis of the fetal organs.⁶ Typical manifestations of teratogenesis include congenital malformations with varying severity, intra-uterine growth restriction, carcinogenesis and fetal demise. Lack of understanding of the mechanisms of teratogenicity makes it difficult to predict on pharmacological grounds that a certain drug will produce

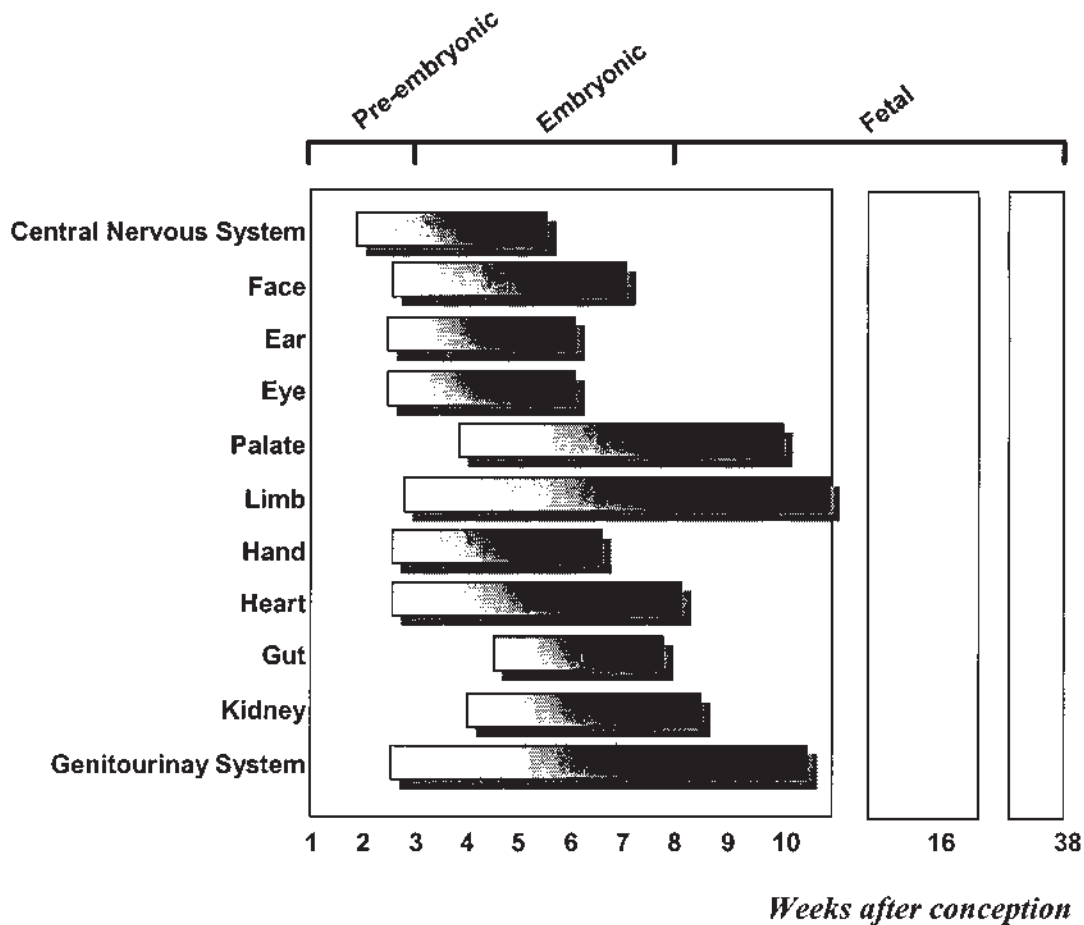


Fig. 1 Timing of the development of major body structures in the embryo and fetus. Used with permission of BMJ Publishing⁶⁵

congenital malformations. The period of highest sensitivity to teratogens is early organogenesis. Later in fetal development, exposure to a teratogen is far less likely to be the cause of a structural defect, but can cause serious functional abnormalities, notably of the neurobehavioral type.

ORGANOGENESIS

The major body structures are formed in about the first 12 weeks after conception (Fig. 1). Interference in this process causes a teratogenic effect. If a drug is given after this time it will not produce a major anatomical defect, but possibly a functional one.

The overall incidence of major congenital malformations is around 2–3% of all births,⁷ and of minor malformations is 9%.⁸ The part played by drugs is probably small. It has been estimated that 25% are due to genetic or chromosomal abnormalities, 10% due to environmental causes including drugs, and 65% of unknown aetiology.⁹ Even known teratogens do not invariably cause anatomical defects, and the mechanism of drug-induced teratogenicity remains unclear. The genetic composition of the fetus, the timing of the insult, maternal age, nutritional condition,

disease status and the dose of the drug may play a role.

CONTRAINDICATED DRUGS

Some of the drugs to be avoided during pregnancy are shown in Table 1. Selected drugs are discussed in detail below.

Absolute

Cytotoxic drugs

These drugs exert their effects mainly on rapidly dividing cell, and hence are most dangerous in the organogenesis stage. The alkylating agents cyclophosphamide and chlorambucil, and the folic acid antagonist methotrexate are all teratogenic and are contraindicated in pregnancy.^{10,11} The risk of congenital abnormalities in cyclophosphamide-exposed children has been estimated to be in the range of 16–22%, but its use may be contemplated later in pregnancy if the mother's disease is life threatening.¹⁰ Methotrexate should be discontinued at least 3 months prior to conception and folic acid (5 mg) supplementation given pre-conceptually.¹⁰

Table 1 Contraindicated drugs

Absolute	Relative
<i>Cytotoxic drugs</i> Busulphan, Cyclophosphamide Methotrexate	<i>Psychotropic drugs</i> Antipsychotic drugs – Lithium
<i>Vitamin A analogues</i> Etretinate, Isotretinoin	<i>Anticoagulants</i> Warfarin
<i>Thalidomide</i>	<i>Anticonvulsants</i> Carbamazepine Phenytoin Sodium valproate
<i>Cardiovascular drugs</i> Angiotensin-converting enzyme inhibitors Angiotensin II inhibitors – Losartan Spironolactone	<i>Endocrinological drugs</i> Carbimazole Propylthiouracil Chlopropamide, Sulphonylureas
<i>Antifungal drugs</i> Griseofulvin Ketoconazole Triazoles – Fluconazole, Itraconazole Terbinafine	<i>Cardiovascular drugs</i> Beta-blockers Minoxidil
<i>Anti-inflammatory drugs</i> NSAIDs (3rd trimester)	<i>Antibiotics</i> Tetracycline Ciprofloxacin Aminoglycosides Chloramphenicol Nitrofurantion Vancomycin
<i>Endocrinological drugs</i> Radioactive iodine Sex hormones Octreotide	<i>Anti-inflammatory drugs</i> Colchicine
<i>Anthelmintic drugs</i> Mebendazole	<i>Others</i> Dapsone (3rd trimester)
<i>Others</i> Misoprostol Mefloquine Statins Biphosphonates	

Vitamin A analogues

Retinoids–Acitretin and Isotretinoin

Acitretin and isotretinoin are synthetic vitamin A derivatives. Acitretin, a metabolite of etretinate, is an oral preparation used for the treatment of severe resistant or complicated psoriasis and some of the congenital disorders of keratinization. Isotretinoin reduces sebum secretion and is used in its oral form for the treatment of nodulo-cystic and conglobate acne and severe antibiotic-resistant acne.

The introduction of retinoids in the early 1980s has resulted in a new teratogenic spectrum. After the thalidomide experience, it was naively thought that appropriate labelling of teratogenic drugs like isotretinoin would be effective in preventing fetal exposure to the drug. Such warnings are not sufficient and, in addition, some women and men are functionally illiterate or some women taking isotretinoin may conceive due to contraception failure.¹²

The teratogenic effects of retinoids on animals were known for years before their clinical use.¹³ Despite explicit warning labels, scores of children with retinoid embryopathy were born in the years after the drug was introduced in North America. These teratogenic effects are seen in up to 25% of babies born to

mothers who took retinoids.¹⁴ The embryopathy¹² includes CNS, craniofacial, cardiovascular, thymic and miscellaneous defects such as limb reduction, decreased muscle tone, spontaneous miscarriage, and behavioural abnormalities.^{15,16}

Contraceptive measures must be taken at least 1 month before and during treatment. Isotretinoin is eliminated from the body within 4 weeks of stopping treatment but acitretin is eliminated slowly and pregnancy should be avoided for two years after a course of the drug. After thorough counselling and before taking the drug, patients are asked to sign a written consent, explaining all possible complications and advice of termination of pregnancy should they get pregnant. Fetal abnormalities have not been associated with topical retinoids but it is advisable to avoid their use in pregnancy and ensure women use adequate contraception.

Thalidomide

The thalidomide disaster drastically changed our perception of drugs' effects on the fetus. Fetal exposure to thalidomide caused high rates of abnormalities (20–30%).¹⁷ These included severe limb shortening

defects (phocomelia), loss of hearing, abducens and facial paralysis, anotia, microtia, renal malformations and congenital heart disease.¹² The mechanism of action is thought to be partly due to antiangiogenesis.¹⁸ Thalidomide is no longer used as an antiemetic but is used for a variety of other diseases, in particular drug-resistant multiple myeloma,¹⁹ cutaneous lupus erythematosus,²⁰ erythema nodosum leprosum, Behcet's disease,²¹ and in the treatment of Kaposi's sarcoma²² and mouth ulcers in patients with acquired immuno-deficiency syndrome. As with retinoids, the drug is only prescribed after proper counselling and a documented consent.

Cardiovascular drugs

Angiotensin-converting enzyme inhibitors

These drugs are orally active inhibitors of angiotensin-converting enzyme, which is responsible for conversion of inactive angiotensin I to the potent pressor peptide angiotensin II. These drugs have been associated with prolonged renal failure and hypotension in the newborn, decreased skull ossification, hypocalcaemia, and renal tubular dysgenesis.²³ In addition, there are several case reports of intrauterine growth restriction, oligohydramnios, patent ductus arteriosus and neonatal hypotension.

The use of these drugs in the first trimester is not thought to produce structural malformations, so it is acceptable to cease treatment early in pregnancy and not necessarily preconception.^{24,25}

Spironolactone

Spironolactone is a competitive antagonist of aldosterone at receptor sites in the distal renal tubules. It acts to augment renal tubular re-absorption of potassium and to increase sodium and chloride excretion. Its use in pregnancy is contraindicated and if diuretics are necessary at that time, another agent is preferable. It is also used for the treatment of hyperaldosteronism.

Spironolactone has anti-androgenic effects, probably through competitive inhibition at the level of testosterone, dihydrotestosterone and androstenedione receptors. It has therefore been used successfully in the treatment of idiopathic hirsutism. These anti-androgenic effects were observed in spironolactone-exposed male animal fetuses born with anomalies of external genitalia.²⁶ This was not reproduced in other studies.²⁷

Anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs)

Aspirin and NSAIDs do not produce structural defects,^{10,28} but salicylates (in analgesic doses) and NSAIDs may increase the risk of neonatal haemorrhage via inhibition of platelet function.²⁹ NSAIDs may also lead to oligohydramnios via effects on the fetal kidney.³⁰ They are usually avoided in the last

trimester as they may cause premature closure of the ductus arteriosus,¹⁰ with neonatal pulmonary hypertension due to prostaglandin synthetase inhibition. However, the risk has been exaggerated since premature closure of the ductus has not been encountered when indomethacin is used for the treatment of premature labour.³¹ Both the ductus premature closure, and the oligohydramnios are reversible.²⁸ If used during pregnancy, they should be discontinued at least 6–8 weeks prior to delivery.^{10,28}

Antifungal drugs

Griseofulvin

Griseofulvin is a systemic agent used to treat fungal infections of the skin, hair and nails. It is a known teratogen in laboratory animals and has been demonstrated to cross the human placenta. Griseofulvin use is contraindicated during pregnancy, and pregnancy should be avoided for 1 month after treatment. Men should not attempt to father children within 6 months of treatment.

Ketoconazole

Ketoconazole is used in systemic mycoses, serious chronic resistant mucocutaneous candidiasis, gastrointestinal mycoses, chronic resistant vaginal candidiasis and resistant dermatophyte infections of skin or fingernails. It inhibits placental microsomal aromatase and cytochrome P-450.³² Although it has been used in some pregnant women without complications,³³ it should be avoided during pregnancy as there is not enough information to confirm its safety.

Triazoles – fluconazole and itraconazole

These triazole antifungal agents attack the fungal cell wall causing leakage of cellular contents. The main indications for their use are vaginal candidiasis, dermatophyte infections and oral or intestinal candidiasis. If treatment of these conditions is clinically indicated, other safer antifungal agents should be used.

Terbinafine

Oral terbinafine was first introduced in the UK in February 1991 and was approved for the treatment of onychomycosis in the US in May 1996. It is estimated that 4 million patients worldwide have been treated with oral terbinafine. The adverse-effects profile of oral terbinafine in pregnancy is limited³⁴ and should therefore be avoided.

Endocrinological drugs

Radioactive iodine

Radioactive iodine therapy is contraindicated in pregnancy since it is taken up by the fetal thyroid, resulting in thyroid ablation and hypothyroidism. Pregnancy should be avoided for at least 4 months after treatment with radioactive iodine therapy and investigations

using ^{131}I in view of the theoretical risk of chromosomal damage and genetic abnormalities.³⁵

The teratogenic potential of the sex steroids is less well established and the literature is contradictory and confusing. Although many of the progestogens used as contraceptive agents, such as norethistrone and levonorgestrel, are 19-nortestosterone derivatives and have mild androgenic properties, with a potential to produce virilization of a female fetus, they are unlikely to do so due to the small amounts present.

Danazol is a testosterone derivative and a weak androgen, used for the treatment of endometriosis, menstrual disturbances, immune thrombocytopenic purpura, classic haemophilia, Christmas disease and alpha-1 antitrypsin deficiency. Reports suggest virilization of the external genitalia of female fetuses exposed to the drug during pregnancy producing fused labia and clitoral hypertrophy,³⁶ and therefore it should be avoided.

Antihelminthics

Mebendazole

Mebendazole is a broad-spectrum antihelminthic agent effective in the treatment of ascariasis, enterobiasis, trichuriasis and hookworm disease. It has been found to be embryotoxic and teratogenic in rats and is therefore not recommended for use during pregnancy.

Relative

Psychotropic drugs

Antipsychotic drugs-Lithium

Lithium carbonate may rarely be indicated for treatment of the manic phase of manic-depressive psychosis during pregnancy. The precise mechanism of action is unknown, but it is thought to be due to altered ion transport or inhibition of adenyl cyclase, influencing nerve excitation, synaptic transmission, and neuronal metabolism in the CNS.

Lithium is associated with an increased incidence of fetal abnormalities.^{37,38} Since the 1960s, an international Register of Lithium Babies has collected information about lithium-exposed children in the first trimester of pregnancy.³⁹ It is estimated that 7.8% of lithium-exposed embryos develop abnormalities.⁴⁰ Early data showed that the cardiovascular system is the most affected, with mitral and tricuspid atresias, aorta coarctation and patent ductus arteriosus being reported. The disorder known as Ebstein anomaly (tricuspid valve distortion and displacement) occurs excessively among lithium-exposed infants, affecting a third of the malformed babies. There have been reports suggesting an association between maternal lithium therapy and premature delivery, with the recommendation that women receiving lithium therapy

during pregnancy should be closely monitored for the onset of premature labour.³⁸

If lithium is used for prophylaxis, it is advisable to discontinue it during the first trimester, unless its withdrawal would jeopardize the woman or the pregnancy. During pregnancy, the smallest dose possible for acceptable therapeutic effects should be used.

While initial information regarding the teratogenic risk of lithium treatment was derived from biased retrospective reports, more recent epidemiological data indicate that the teratogenic risk of first trimester lithium exposure is lower than previously suggested.⁴¹ The clinical management of women with bipolar disorder who have childbearing potential should be modified with this revised risk estimate.

Anticoagulants

Warfarin

Warfarin is a form of coumarin with vitamin K antagonist action. Its use in pregnancy is associated with a high incidence of fetal loss, congenital malformations and physical disability.⁴² Exposure to the drug between the sixth and ninth weeks of gestation is associated with defective ossification of bone, resulting in nasal hypoplasia and chondrodysplasia punctata. On a molecular level, vitamin K inhibitors may alter calcium binding for several proteins, affecting bone ossification and thus causing the characteristic bony abnormalities of the 'fetal warfarin' syndrome. The syndrome constitutes skeletal defects (nasal hypoplasia and stippled epiphyses), limb hypoplasia (particularly distal digits), low birth weight (<10th percentile), hearing loss and ophthalmic anomalies.⁴²

The use of warfarin in the second and third trimester is not without serious complications. The effects are mainly CNS abnormalities and are thought to be due to microhaemorrhages in the brain. The defects include dorsal midline dysplasia (agenesis of corpus callosum and Dandy-Walker malformations) or ventral midline dysplasia (optic atrophy),¹⁷ mental retardation, delayed development, seizures and microcephaly.⁴³

In a recent study of pregnant women on warfarin (INR 2.5–3.5), there was a substantially increased incidence of fetal complications with high doses of the drug, independent of the INR.⁴⁴ Women whose warfarin doses were >5 mg had significantly more fetal complications than those taking a dose ≤5 mg.

The risk of teratogenicity with warfarin has led to the recommendation that heparin should be substituted for the treatment and prophylaxis of venous thromboembolism. However, heparin is not as effective as warfarin in preventing arterial thromboembolism in women with artificial heart valves, mitral disease or atrial fibrillation. In these situations, the risk of thrombosis may exceed the risks of warfarin use, and warfarin use may be justified. It should be used with great caution and close monitoring of both the mother and fetus.

Anticonvulsants

Epilepsy is the commonest chronic neurological disorder to complicate pregnancy, affecting approximately 0.5% of pregnancies,⁴⁵ and many women need to continue taking an anticonvulsant throughout pregnancy. The main concern in pregnancies complicated by epilepsy stems from the increased risk of congenital abnormalities. Even epileptics who are not taking any anticonvulsants have a slightly increased risk (4%) compared to the general population (3%).⁴⁶ The risk of the child itself developing epilepsy is also increased (4% compared to 1% background) if either parent has epilepsy. If there is a previously affected sibling the risk is 10%. If both parents have epilepsy the risk is 15–20%. It is possible that these are not entirely due to anticonvulsant therapy and that genetic factors associated with epilepsy are partly responsible, as suggested by the evidence of increased malformation rate in the children of epileptic fathers.⁴⁷

Phenytoin, primidone, phenobarbitone, carbamazepine and sodium valproate all cross the placenta and are teratogenic. The major abnormalities produced by anticonvulsants are neural tube, orofacial and congenital heart defects. The neural tube defects are mainly caused by sodium valproate (1–2%),^{48,49} and carbamazepine (0.5–1%).⁵⁰ Orofacial defects, the fetal hydantoin syndrome,⁵¹ impaired neurodevelopment and low performance scores on tests of intelligence⁵² are produced by phenytoin. Heart defects are produced by phenytoin and sodium valproate.

The teratogenic risk for any one drug is about 6–7% (i.e. double to three times the background level). The risk increases with the number of drugs, so for those taking 2 or more anticonvulsants the risk is 15%, and for those taking the combination of valproate, carbamazepine, and phenytoin the risk is as high as 50%.⁵³ One mechanism for teratogenesis is thought to be folate deficiency. Phenytoin and phenobarbitone particularly, but also carbamazepine and valproate, interfere with folate metabolism. The risk of, particularly, neural tube defects can be decreased by the use of pre-conceptual and first trimester folic acid (5 mg).⁵⁴

There are not yet enough data on the newer anticonvulsant drugs such as vigabatrin, lamotrigine, topiramate and gabapentin to ascertain the teratogenic risk of these drugs in isolation. The benzodiazepines (e.g. clonazepam) are not teratogenic. Lamotrigine and gabapentin are not teratogenic in animals and although lamotrigine carries a theoretical risk because it may interfere with folate metabolism, in practice it seems to carry a low risk of teratogenesis. Whether this risk is low enough to justify replacement of an older anticonvulsant for lamotrigine pre-pregnancy is not yet known.

Endocrinological drugs

Antithyroid drugs – Carbimazole and Propylthiouracil
These are the most commonly used antithyroid drugs in the UK. Both drugs cross the placenta,

propylthiouracil less than carbimazole. Gross teratogenesis is not a feature with these drugs, although carbimazole occasionally causes a scalp defect known as aplasia cutis. In high doses they may cause fetal hypothyroidism and goitre,³⁵ but doses of propylthiouracil at or below 150 mg/day and carbimazole 15 mg/day are unlikely to cause problems in the fetus.⁵⁵ The lowest possible dose to maintain the free thyroxine (FT4) level within the normal range should be used. There is no place for 'block-and-replace regimens' in the management of thyrotoxicosis in pregnancy as high doses of antithyroid drugs are required and thyroxine replacement does not cross the placenta in sufficient doses to protect the fetus from hypothyroidism.³⁵

Cardiovascular drugs

Beta-adrenergic antagonists

Beta-adrenergic antagonists have fewer side effects than many antihypertensives, but their safety in pregnancy is not so well established. Some studies have found no adverse effects on the outcome of pregnancy while others have described a variety of fetal and neonatal complications.⁵⁶ The concern is that if these drugs are used throughout pregnancy, they may produce adverse fetal and neonatal effects. These complications include bradycardia, hypotension, hypoglycaemia, intrauterine growth restriction and respiratory distress. However, many studies suggest that they are safe antihypertensives for use in the third trimester.⁵⁷ If treatment of hypertension is required before 28 weeks, methyldopa should be the first drug of choice. Guidelines of the International Society for the Study of Hypertension in Pregnancy (ISSHP) do not recommend the use of oral beta-adrenergic antagonists for mild hypertension in pregnancy.

Antibiotics

Tetracycline

Tetracycline is contraindicated during pregnancy. This broad-spectrum antibiotic crosses the placenta, chelates with calcium and is deposited in the developing teeth and bones of the fetus. The effects on bone are minimal, but discoloration of the teeth and enamel hypoplasia can occur from the end of the first trimester. The deciduous teeth begin to mineralize at approximately 14 weeks gestation and the process continues until 2–3 months after birth. Staining of the permanent teeth is most likely when tetracyclines are administered after 24 weeks gestation.

Maternal hepatotoxicity in the form of acute fatty liver, leading to death in some cases, has been reported in pregnant women treated with tetracycline in high doses or chronic use.^{58,59}

Ciprofloxacin

Quinolone antibiotics are extensively utilized in antimicrobial therapy. However, quinolone treatment in

developing adolescents of several animal species is associated with acute arthropathy of the weight-bearing joints. Although arthropathy has rarely been observed following quinolone therapy in man, the toxicity observed in immature animals has resulted in restricted use of these drugs in children and pregnant women.^{60,61}

A recent study investigating the effect on the fetus of intrauterine exposure to quinolones in terms of teratogenicity, concluded that the use of the ciprofloxacin during the first trimester of pregnancy does not appear to be associated with an increased risk of malformations or musculoskeletal problems.⁶² However, they suggested longer follow-up and magnetic resonance imaging of the joints to exclude subtle cartilage and bone damage.

These results indicate that caution must be taken when quinolones are to be used during pregnancy, and suggest the need for more studies.

Aminoglycosides

These antibiotics penetrate the cell wall and cytoplasmic membrane of susceptible microorganisms and act on the bacterial ribosomes, leading ultimately to cell death. All aminoglycosides are ototoxic in adults, and streptomycin is definitely toxic to the fetal ear causing eighth nerve damage with auditory impairment more common than vestibular defects. Streptomycin should not be used as a first line for the treatment of tuberculosis. There is little information about the use of other aminoglycosides during pregnancy, although gentamycin should not be withheld if clinically indicated. Levels should be checked regularly to avoid toxicity.

Chloramphenicol

Chloramphenicol inhibits protein synthesis in bacteria and rickettsiae, primarily by preventing peptide-bond synthesis in ribosomes. It should be avoided in late pregnancy and during labour because of the potential for the "grey syndrome" in the newborn infant. The syndrome usually starts 2–9 days after therapy has begun, causing vomiting, suck refusal, rapid irregular respiration, abdominal distension, followed by flaccidity, an ashen grey colour and hypothermia. About 40% of these neonates die from circulatory collapse on about the fifth day. Therefore, it should only be used in pregnancy in life-threatening conditions, when no alternative is available.

Nitrofurantoin

The exact mechanism of action of nitrofurantoin is unknown. Nitrofurantoin may be administered in pregnancy, but should be avoided near term. Low levels of glutathione may predispose the fetus to haemolytic anaemia if it is exposed to nitrofurantoin shortly before birth.

Vancomycin

Vancomycin is a bactericidal antibiotic with a fetal ototoxic effect. It acts primarily by inhibiting cell wall

synthesis and inhibiting RNA synthesis in bacterial cytoplasmic membranes. Avoid unless benefit outweighs potential risk.

Anti-inflammatory drugs

Colchicine

Colchicine reduces the inflammatory response to deposition of monosodium urate crystals in joint tissue, in part by inhibiting polymorphonuclear leukocyte metabolism, mobility, and chemotaxis. It also inhibits cell division in metaphase by interfering with the mitotic spindle. It is used to relieve the pain of acute gouty arthritis attacks and prophylaxis of recurrent gout attacks. It is also used in familial Mediterranean fever, Behcet's disease and amyloidosis. It is embryocidal in mice and rabbits but the risk of teratogenesis in humans is unknown.

There is anxiety that colchicine given around conception may result in an increased frequency of trisomy 21 by causing chromosomal non-disjunction.⁶³ If it is used, fetal karyotyping can be recommended.⁶⁴ Colchicine ingestion by either parent should be discontinued 3 months before conception.

CONCLUSION

The decision to use any potentially harmful drug in pregnancy should be made on a case-by-case basis. There should be thorough counselling with active involvement of the patient in the informed consent process, during which the risks and benefits are discussed and documented.

The evidence discussed in this review suggests that few drugs have been shown definitely to be teratogenic in humans. However, it is equally true that no drug is completely safe.

The use of drugs during pregnancy requires maintenance of a fine balance. Before prescribing a drug, consideration must be given to any potentially harmful effects on the fetus. Equally, no harm must come to the mother or baby because a disease is being inadequately treated. To minimize the fetal risks, the lowest possible effective dose should be used.

In addition to the dangers associated with fetal exposure to teratogenic drugs, there are risks associated with misinformation about the teratogenicity of drugs. This can lead to unnecessary abortions or the avoidance of essential treatment. The drug manufacturers and medical community should make every effort possible to protect women and their unborn babies from both risks. Implicit in this statement is the need to counsel pregnant women about the safety as well as the dangers of drug use in pregnancy.

To receive up-to-date, evidence-based information on the safety of drugs during pregnancy, clinicians can consult a teratogen-information service. Table 2

Table 2 Teratogen Information Services

United Kingdom	
National Teratology Information Service (NTIS)	
Newcastle (191) 232 1525	
United States	
Organization of Teratology Information Services	
Utah (801) 328-2229 (for referral to nearest service)	
World Wide Web address: http://orpheus-1.ucsd.edu/otis/index.html	
Canada	
Motherisk Program	
Toronto (416) 813-6780	
World Wide Web address: http://www.motherisk.org	

lists some World Wide Web addresses and telephone numbers of teratogen services.

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