Appendix 2: Pregnancy

During pregnancy the mother and the fetus form a non-separable functional unit. Maternal well-being is an absolute prerequisite for the optimal functioning and development of both parts of this unit. Consequently, it is important to treat the mother whenever needed while protecting the unborn to the greatest possible extent.

Drugs can have harmful effects on the fetus at any time during pregnancy. It is important to remember this when prescribing for a woman of childbearing age. However, irrational fear of using drugs during pregnancy can also result in harm. This includes untreated illness, impaired maternal compliance, suboptimal treatment and treatment failures.

Such approaches may impose risk to maternal well-being, and may also affect the unborn child. It is important to know the 'background risk' in the context of the prevalence of drug-induced adverse pregnancy outcomes. Major congenital malformations occur in 2–4% of all live births. Up to 15% of all diagnosed pregnancies will result in fetal loss. The cause of these adverse pregnancy outcomes is understood in only a minority of the incidents.

During the *first trimester* drugs may produce congenital malformations (teratogenesis), and the greater risk is from third to the eleventh week of pregnancy. During the *second* and *third trimester* drugs may affect the growth and functional development of the fetus or have toxic effects on fetal tissues. Drugs given shortly before term or during labour may have adverse effects on labour or on the neonate after delivery. Few drugs have been shown conclusively to be teratogenic in man but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available where there is a known risk of certain defects.

Prescribing in pregnancy

If possible counselling of women before a planned pregnancy should be carried out including discussion of risks associated with specific therapeutic agents, traditional medicines and abuse of substances such as smoking and alcohol. Folic acid supplements should be given during pregnancy planning because periconceptual use of folic acid reduces neural tube defects.

Drugs should be prescribed in pregnancy only if the expected benefits to the mother are thought to be greater than the risk to the fetus. All drugs should be avoided if possible during the first trimester. Drugs which have been used extensively in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs and the smallest effective dose should be used. Well known single component drugs should usually be preferred to multi-component drugs.

The following list includes drugs which may have harmful effects in pregnancy and indicates the trimester of risk. It is based on human data but information on *animal* studies has been included for some newer drugs when its omission might be misleading.

Absence of a drug from the list does not imply safety .

Table of drugs to be avoided or used with caution in pregnancy

Drug	Comment
Abacavir	Toxicity in *animal* studies; *see* section 6.5.2
Acetazolamide	Not used to treat hypertension in pregnancy First trimester: Avoid (toxicity in *animal* studies)
Acetylsalicylic acid	Third trimester: Impaired platelet function and risk of haemorrhage; delayed onset and increased duration of labour with increased blood loss; avoid analgesic doses if possible in last few weeks (low doses probably not harmful); with high doses, closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension of newborn; kernicterus in jaundiced neonates
Aciclovir	Not known to be harmful; limited absorption from topical preparations
Albendazole	Contraindicated in cestode infections; *see* section 6.1.1.1 First trimester: avoid in nematode infections; *see* section 6.1.1.2
Alcohol	First, second trimesters: Regular daily drinking is teratogenic (fetal alcohol syndrome) and may cause growth retardation; occasional single drinks are probably safe Third trimester: Withdrawal may occur in babies of alcoholic mothers
Alcuronium	Does not cross placenta in significant amounts; use only if potential benefit outweighs risk
Allopurinol	Toxicity not reported; use only if no safer alternative and disease carries risk for mother or child
Amiloride	Not used to treat hypertension in pregnancy
Aminophylline	Third trimester: Neonatal irritability and apnoea have been reported
Amitriptyline	Manufacturer advises avoid unless essential, particularly during first and third trimesters
Amodiaquine	Use only if no safer alternative
Amoxicillin	Not known to be harmful
Amoxicillin + Clavulanic acid	Not known to be harmful
Amphotericin B	Not known to be harmful but use only if potential benefit outweighs risk
Ampicillin	Not known to be harmful
Artemether	First trimester: Avoid
Artemether + Lumefantrine	Avoid. Toxicity in *animal* studies with artemether
Artesunate	First trimester: Avoid
Asparaginase	Avoid; *see also* section 8.2
Atenolol	May cause intrauterine growth restriction, neonatal hypoglycaemia, and bradycardia; risk greater in severe hypertension; *see also* section 12.3
Atropine	Not known to be harmful

Azathioprine	Transplant patients should not discontinue azathioprine on becoming pregnant; use in pregnancy should be supervised in specialist units; there is no evidence that azathioprine is teratogenic
Azithromycin	Use only if potential benefit outweighs risk
Beclometasone	Benefit of treatment, for example in asthma, outweighs risk
Benzathine benzylpenicillin	Not known to be harmful
Benznidazole	First trimester: avoid
Benzylpenicillin	Not known to be harmful
Betamethasone	Benefit of treatment, for example in asthma, outweighs risk
Bleomycin	Avoid (teratogenic and carcinogenic in *animal* studies); *see also* section 8.2
Bupivacaine	Third trimester: With large doses, neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block
Calcium folinate	Manufacturer advises use only if potential benefit outweighs risk
Carbamazepine	First trimester: Risk of teratogenesis including increased risk of neural tube defects (counselling and screening and adequate folate supplements advised, for example 5 mg daily); risk of teratogenicity greater if more than one antiepileptic used; *see also* section 5.1 Third trimester: May possibly cause vitamin K deficiency and risk of neonatal bleeding; if vitamin K not given at birth, neonate should be monitored closely for signs of bleeding
Ceftazidime	Not known to be harmful
Ceftriaxone	Not known to be harmful
Chlorambucil	Avoid; use effective contraception during administration to men or women; *see also* section 8.2
Chloramphenicol	Third trimester: Neonatal ‘grey’ syndrome
Chlormethine	Avoid; *see also* section 8.2
Chloroquine	First, third trimesters: Benefit of prophylaxis and treatment in malaria outweighs risk; important: *see also* section 6.4.3
Chlorphenamine	No evidence of teratogenicity
Chlorpromazine	Third trimester: Extrapyramidal effects in neonate occasionally reported
Ciclosporin	There is less experience of ciclosporin in pregnancy but it does not appear to be any more harmful than azathioprine; use in pregnancy should be supervised in specialist units
Ciprofloxacin	All trimesters: Avoid—arthropathy in *animal* studies; safer alternatives available
Cisplatin	Avoid (teratogenic and toxic in *animal* studies); *see also* section 8.2
Clindamycin	Not known to be harmful
Clomifene	Possible effects on fetal development

Clomipramine	Manufacturer advises avoid unless essential, particularly during first and third trimester
Clonazepam	Avoid regular use (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia and respiratory depression)
Cloxacillin	Not known to be harmful
Codeine	Third trimester: Depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour
Contraceptives, oral	Epidemiological evidence suggests no harmful effects on fetus
Cromoglicic acid	*see* Sodium cromoglicate
Cyclophosphamide	Avoid (use effective contraception during and for at least 3 months after administration to men or women); *see also* section 8.2
Cytarabine	Avoid (teratogenic in *animal* studies); *see also* section 8.2
Dacarbazine	Avoid (carcinogenic and teratogenic in *animal* studies); ensure effective contraception during and for at least 6 months after administration to men or women; *see also* section 8.2
Dactinomycin	Avoid (teratogenic in *animal* studies); *see also* section 8.2
Dapsone	Third trimester: Neonatal haemolysis and methaemoglobinaemia; folic acid 5 mg daily should be given to mother
Daunorubicin	Avoid (teratogenic and carcinogenic in *animal* studies); *see also* section 8.2
Deferoxamine	Teratogenic in *animal* studies; manufacturer advises use only if potential benefit outweighs risk
Dexamethasone	Benefit of treatment, for example in asthma, outweighs risk; risk of intrauterine growth retardation on prolonged or repeated systemic treatment; corticosteroid cover required by mother during labour; monitor closely if fluid retention
Diazepam	Avoid regular use (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia and respiratory depression)
Didanosine	Avoid if possible in first trimester; increased risk of lactic acidosis and hepatic steatosis; *see* section 6.5.2
Diethylcarbamazine	Avoid: Delay treatment until after delivery
Digoxin	May need dosage adjustment
Diloxanide	Defer treatment until after first trimester
Doxorubicin	Avoid (teratogenic and toxic in *animal* studies); with liposomal product use effective contraception during and for at least 6 months after administration to men or women; *see also* section 8.2
Doxycycline	First trimester: Effects on skeletal development in *animal* studies

	Second, third trimesters: Dental discoloration; maternal hepatotoxicity with large doses
Efavirenz	Avoid (potential teratogenic effects); *see* section 6.5.2
Eflornithine	All trimesters: avoid
Enalapril	All trimesters: Avoid; may adversely affect fetal and neonatal blood pressure control and renal function; also possible skull defects and oligohydramnios; toxicity in *animal* studies
Ephedrine	Increased fetal heart rate reported with parenteral ephedrine
Ergocalciferol	High doses teratogenic in *animals* but therapeutic doses unlikely to be harmful
Ergotamine	All trimesters: Oxytocic effects on the pregnant uterus
Erythromycin	Not known to be harmful
Ethambutol	Not known to be harmful
Ether, anaesthetic	Third trimester: Depresses neonatal respiration
Ethinylestradiol	Epidemiological evidence suggests no harmful effects on fetus
Ethosuximide	First trimester: May possibly be teratogenic; risk of teratogenicity greater if more than one antiepileptic used; *see also* section 5.1
Etoposide	Avoid (teratogenic in *animal* studies); *see also* section 8.2
Fluconazole	Avoid (multiple congenital abnormalities reported with long-term high doses)
Flucytosine	Teratogenic in *animal* studies; manufacturer advises use only if potential benefit outweighs risk
Fluorouracil	Avoid (teratogenic); *see also* section 8.2
Fluphenazine	Third trimester: Extrapyramidal effects in neonate occasionally reported
Furosemide	Not used to treat hypertension in pregnancy
Gentamicin	Second, third trimesters: Auditory or vestibular nerve damage, risk probably very small with gentamicin, but avoid unless essential (if given, serum-gentamicin concentration monitoring essential)
Glibenclamide	Third trimester: Neonatal hypoglycaemia; insulin is normally substituted in all diabetics; if oral drugs are used therapy should be stopped at least 2 days before delivery
Griseofulvin	Avoid (fetotoxicity and teratogenicity in *animals*); effective contraception required during and for at least 1 month after administration (**important:** effectiveness of oral contraceptives reduced, *see* Appendix 1); also men should avoid fathering a child during and for at least 6 months after administration
Haloperidol	Third trimester: Extrapyramidal effects in neonate occasionally reported
Halothane	Third trimester: Depresses neonatal respiration
Heparin	All trimesters: Osteoporosis has been reported after prolonged use; multidose vials may contain benzyl

	alcohol—some manufacturers advise avoid
Hydralazine	Avoid during first and second trimesters; no reports of serious harm following use in third trimester
Hydrochlorothiazide	Not used to treat hypertension in pregnancy Third trimester: May cause neonatal thrombocytopenia
Hydrocortisone	Benefit of treatment, for example in asthma, outweighs risk; risk of intrauterine growth retardation on prolonged or repeated systemic treatment; corticosteroid cover required by mother during labour; monitor closely if fluid retention
Ibuprofen	Avoid unless potential benefit outweighs risk Third trimester: With regular use closure of fetal ductus arteriosus *in utero* and possibly persistent pulmonary hypertension of the newborn. Delayed onset and increased duration of labour
Idoxuridine	Teratogenic in *animal* studies
Imipenem+Cilastatin	Use only if potential benefit outweighs risk (toxicity in *animal* studies)
Indinavir	Avoid if possible in first trimester; theoretical risk of hyperbilirubinaemia and renal stones in neonate if used at term; *see* section 6.5.2
Insulin	All trimesters: Insulin requirements should be assessed frequently by an experienced diabetic clinician
Iodine	Second, third trimesters: Neonatal goitre and hypothyroidism
Isoniazid	Not known to be harmful
Ivermectin	Delay treatment until after delivery; *see also* section 6.1.2.3
Ketamine	Third trimester: Depresses neonatal respiration
Lamivudine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters; *see* section 6.5.2
Levamisole	Third trimester: Avoid
Levodopa + Carbidopa	Toxicity in *animal* studies
Levonorgestrel	In oral contraceptives, epidemiological evidence suggests no harmful effects on fetus
Levothyroxine	Monitor maternal serum-thyrotrophin concentration—dosage adjustment may be necessary
Lidocaine	Third trimester: With large doses, neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block
Lithium	First trimester: Avoid if possible (risk of teratogenicity including cardiac abnormalities) Second and third trimesters: Dose requirements increased (but on delivery return to normal abruptly); close monitoring of serum-lithium concentration advised (risk of toxicity in neonate)
Lopinavir + Ritonavir	Avoid if possible in first trimester; avoid oral solution due to high propylene glycol content; *see* section 6.5.2
Magnesium sulfate	Third trimester: not known to be harmful for short-term

	intravenous administration in eclampsia but excessive doses may cause neonatal respiratory depression
Mebendazole	Toxicity in *animal* studies. Contraindicated in cestode infections; *see* section 6.1.1.1 First trimester: Avoid in nematode infections; *see* section 6.1.1.2
Medroxyprogesterone	Avoid (genital malformations and cardiac defects reported in male and female fetuses); inadvertent use of depot-medroxyprogesterone acetate contraceptive injection in pregnancy unlikely to harm fetus
Mefloquine	Use only if other antimalarials inappropriate, *see also* Prophylaxis and Treatment of Malaria, section 6.4.3
Melarsoprol	All trimesters: Avoid
Mercaptopurine	Avoid (teratogenic); *see also* section 8.2
Metformin	All trimesters: Avoid; insulin is normally substituted in all diabetics
Methotrexate	Avoid (teratogenic; fertility may be reduced during therapy but this may be reversible); use effective contraception during and for at least 6 months after administration to men or women; *see also* section 8.2
Methyldopa	Not known to be harmful
Metoclopramide	Not known to be harmful
Metronidazole	Avoid high-dose regimens
Morphine	Third trimester: Depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour
Nalidixic acid	All trimesters: Avoid—arthropathy in *animal* studies; safer alternatives available
Naloxone	Use only if potential benefit outweighs risk
Nelfinavir	Avoid if possible in first trimester; potential benefit of treatment considered to outweigh risk in second and third trimesters; *see* section 6.5.2
Neostigmine	Third trimester: Neonatal myasthenia with large doses
Nevirapine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters; *see* section 6.5.2
Niclosamide	*T. solium* infections in pregnancy should be treated immediately; *see* section 6.1.1.1
Nifedipine	May inhibit labour; some dihydropyridines are teratogenic in *animals* , but risk to fetus should be balanced against risk of uncontrolled maternal hypertension
Nifurtimox	First trimester: Avoid
Nitrofurantoin	Third trimester: May produce neonatal haemolysis if used at term
Nitrous oxide	Third trimester: Depresses neonatal respiration
Norethisterone	In oral contraceptives, epidemiological evidence suggests no harmful effects on fetus In higher doses masculinization of female fetuses and other

	defects reported
Nystatin	No information available, but absorption from gastrointestinal tract negligible
Ofloxacin	All trimesters: Avoid—arthropathy in *animal* studies; safer alternatives available
Oxamniquine	If immediate treatment not required schistosomiasis treatment should be delayed until after delivery; *see* section 6.1.3.1
Paracetamol	Not known to be harmful
Penicillamine	All trimesters: Fetal abnormalities reported rarely; avoid if possible
Pentamidine isetionate	Potentially fatal visceral leishmaniasis must be treated without delay. Should not be withheld in trypanosomiasis even if evidence of meningoencephalitic involvement. Potentially fatal *P. carinii* pneumonia must be treated without delay
Pentavalent antimony compounds	Potentially fatal visceral leishmaniasis must be treated without delay
Phenobarbital	First, third trimesters: Congenital malformations; risk of teratogenicity greater if more than one antiepileptic used. May possibly cause vitamin K deficiency and risk of neonatal bleeding; if vitamin K not given at birth, neonate should be monitored closely for signs of bleeding; *see* section 5.1
Phenoxymethylpenicillin	Not known to be harmful
Phenytoin	First, third trimesters: Congenital malformations (screening advised); adequate folate supplements should be given to mother (for example folic acid 5 mg daily); risk of teratogenicity greater if more than one antiepileptic used. May possibly cause vitamin K deficiency and risk of neonatal bleeding; if vitamin K not given at birth, neonate should be monitored closely for signs of bleeding. Caution in interpreting plasma concentrations—bound may be reduced but free (or effective) unchanged; *see also* section 5.1
Phytomenadione	Use only if potential benefit outweighs risk—no specific information available
Podophyllum resin	All trimesters: Avoid—neonatal death and teratogenesis have been reported
Polyvidone–iodine	Second, third trimesters: Sufficient iodine may be absorbed to affect the fetal thyroid
Potassium iodide	Second, third trimesters: Neonatal goitre and hypothyroidism
Praziquantel	*T. solium* infections in pregnancy should be treated immediately; *see* section 6.1.1.1. Benefit of treatment in schistosomiasis outweighs risk If immediate treatment not considered essential for fluke

	infections, treatment should be delayed until after delivery
Prednisolone	Benefit of treatment, for example in asthma, outweighs risk; risk of intrauterine growth retardation on prolonged or repeated systemic treatment; corticosteroid cover required by mother during labour; monitor closely if fluid retention
Primaquine	Third trimester: Neonatal haemolysis and methaemoglobinaemia. Delay treatment until after delivery
Procarbazine	Avoid (teratogenic in *animal* studies and isolated reports in humans); *see also* section 8.2
Proguanil	Benefit of prophylaxis and of treatment outweighs risk. Adequate folate supplements should be given to mother
Promethazine	No evidence of teratogenicity
Propranolol	May cause intrauterine growth restriction, neonatal hypoglycaemia, and bradycardia; risk greater in severe hypertension; *see also* section 12.3
Propylthiouracil	Second, third trimesters: Neonatal goitre and hypothyroidism
Pyrazinamide	Use only if potential benefit outweighs risk
Pyridostigmine	Third trimester: Neonatal myasthenia with large doses
Pyrimethamine	First trimester: Theoretical teratogenic risk (folate antagonist); adequate folate supplements should be given to the mother. First trimester: avoid in Pneumocystosis and toxoplasmosis; *see also* Sulfadiazine
Quinine	First trimester: High doses are teratogenic; but in malaria benefit of treatment outweighs risk
Ranitidine	Not known to be harmful
Retinol	First trimester: Excessive doses may be teratogenic; *see also* section 27.1 [text]
Rifampicin	First trimester: Very high doses teratogenic in *animal* studies Third trimester: Risk of neonatal bleeding may be increased
Ritonavir	*See* Lopinavir with Ritonavir
Salbutamol	For use in asthma *see* section 25.1 [text] Third trimester: For use in premature labour *see* section 22.1
Saquinavir	Avoid if possible in first trimester; potential benefit of treatment considered to outweigh risk in second and third trimesters; *see* section 6.5.2
Silver sulfadiazine	Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded
Sodium cromoglicate	Not known to be harmful; *see also* section 25.1 [text]
Sodium valproate	*see* Valproic acid
Spironolactone	Toxicity in *animal* studies
Stavudine	Avoid if possible in first trimester; increased risk of lactic acidosis and hepatic steatosis; *see* section 6.5.2

Streptokinase	All trimesters: Possibility of premature separation of placenta in first 18 weeks; theoretical possibility of fetal haemorrhage throughout pregnancy; risk of maternal haemorrhage on postpartum use
Streptomycin	Second, third trimesters: Auditory or vestibular nerve damage; avoid unless essential (if given, serum-streptomycin concentration monitoring essential)
Sulfadiazine	Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded In toxoplasmosis, avoid in first trimester, but may be given in second and third trimester if danger of congenital transmission
Sulfadoxine + Pyrimethamine	In malaria, benefit of prophylaxis and treatment outweigh risk. First trimester: Possible teratogenic risk (pyrimethamine a folate antagonist) Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded *See also* section 6.4.3
Sulfamethoxazole + Trimethoprim	First trimester: Teratogenic risk (trimethoprim a folate antagonist) Third trimester: Neonatal haemolysis and methaemoglobinaemia; fear of increased risk of kernicterus in neonates appears to be unfounded
Sulfasalazine	Third trimester: Theoretical risk of neonatal haemolysis; adequate folate supplements should be given to mother
Suramin sodium	In onchocerciasis, delay treatment until after delivery. In *T. b. rhodesiense* treatment should be given even if evidence of meningoencephalopathic involvement
Suxamethonium	Mildly prolonged maternal paralysis may occur
Tamoxifen	Avoid—possible effects on fetal development; effective contraception must be used during treatment and for 2 months after stopping
Testosterone	All trimesters: Masculinization of female fetus
Tetracycline	First trimester: Effects on skeletal development in *animal* studies Second, third trimesters: Dental discoloration; maternal hepatotoxicity with large doses
Theophylline	Third trimester: Neonatal irritability and apnoea have been reported
Thiopental	Third trimester: Depresses neonatal respiration
Trimethoprim	First trimester: Teratogenic risk (folate antagonist)
Vaccine, BCG	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus (*see also* section 19.3 [contraindications and precautions])

Vaccine, Measles	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus (*see also* section 19.3 [contraindications and precautions]); avoid MMR
Vaccine, MMR	Avoid; pregnancy should be avoided for 1 month after immunization
Vaccine, Poliomyelitis, live	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus (*see also* section 19.3 [contraindications and precautions])
Vaccine, Rubella	Avoid; pregnancy should be avoided for 1 month after immunization
Vaccine, Yellow fever	First trimester: Theoretical risk of congenital malformations, but need for vaccination may outweigh possible risk to fetus (*see also* section 19.3 [contraindications and precautions])
Valproic acid	First, third trimesters: Increased risk of neural tube defects (counselling and screening advised—folic acid supplement may reduce risk); risk of teratogenicity greater if more than one antiepileptic used; neonatal bleeding (related to hypofibrinaemia) and neonatal hepatotoxicity also reported; *see also* section 5.1 (sodium valproate)
Vancomycin	Use only if potential benefit outweighs risk—plasma-vancomycin concentration monitoring essential to reduce risk of fetal toxicity
Vecuronium	Use only if potential benefit outweighs risk—no information available
Verapamil	*Animal* studies have not shown teratogenic effect; possibility that verapamil can relax uterine muscles should be considered at term; risk to fetus should be balanced against risk of uncontrolled maternal hypertension
Vinblastine	Avoid (limited experience suggests fetal harm; teratogenic in *animal* studies); *see also* section 8.2
Vincristine	Avoid (teratogenicity and fetal loss in *animal* studies); *see also* section 8.2
Warfarin	All trimesters: Congenital malformations; fetal and neonatal haemorrhage *See also* section 10.2
Zidovudine	Avoid if possible in first trimester; benefit of treatment considered to outweigh risk in second and third trimesters; *see* section 6.5.2