Prescribing medicines in pregnancy

Laura M Yates
Simon HL Thomas

Abstract

Prescribing in pregnancy is complex; it needs to take into account the effects that physiological changes associated with pregnancy can have on a drug's pharmacology and the impact of these changes on the benefits and risks of treatment in the mother, as well as the benefits and risks to the developing fetus. Fetal effects are sometimes predictable, given the mechanism of action of a drug, but they can be unpredictable and unexpected. Identifying therapies that are safest for the fetus, yet do not compromise effective treatment of the maternal condition, is essential but challenging. Whereas older drugs may have been used in pregnancy without any signal of fetal harm, often little is known about the fetal risk of newer preparations, which may be preferred for the mother due to improved efficacy or adverse effect profiles. Some drugs essential for the management of long-term maternal conditions are known to have teratogenic properties and there may be no effective alternatives. Weighing up the risks and benefits for mother and fetus in such circumstances is particularly difficult. Teratology information services are established worldwide and provide up-to-date, evidence-based advice to support informed prescribing in pregnancy. Information designed for use by pregnant women is also increasingly available to help inform their choices.

Keywords Congenital malformation; pregnancy; prescribing; teratogen; Teratology Information Service

Key points

- Prescribing in pregnancy should take into account the risk to the mother and fetus of inadequate maternal treatment, as well as the known or theoretical risks to the fetus from use of the medicine
- Teratology information services are available worldwide to support healthcare providers and/or women by providing up-to-date, evidence-based information and expertise
- Pre-pregnancy counselling and early specialist involvement during pregnant is advised for women with pre-existing medical conditions such as epilepsy
- Reporting of exposures to teratology information services and pregnancy registries enables follow-up of pregnancy outcome to inform the use of medicines in human pregnancy

Introduction

Most women take medicines at some stage during pregnancy; this may be for treatment of acute illnesses, including those associated with pregnancy (e.g. heartburn, morning sickness) or for management of chronic illness predating or developing during pregnancy (e.g. epilepsy, asthma, depression, psychosis, chronic hypertension). Occasionally, a medication is prescribed to the mother to treat a fetal condition (e.g. flecainide for fetal dysrhythmia).

Much drug use during pregnancy involves preparations available over the counter, but there is also considerable use of prescribed medicines, with around 80% of pregnant women being given at least one prescription. In an internet-based survey of pregnant women in four European countries, 83% reported using at least one medication (range 1–16) during pregnancy or in the month preceding conception, excluding fertility medications, iron tablets, multivitamins and folic acid.[1] Exposure in early pregnancy is also common: in an Irish study, 39% of women reported using a prescription drug (excluding folic acid) at their booking interview. Medications commonly prescribed during pregnancy include analgesics, antibiotics, vitamins (not just folic acid) and antiemetics; for most of these, there is considerable experience of use in pregnancy without evidence of harm to the fetus, although systematic study of particular adverse outcomes is generally lacking. There is also appreciable use of medicines for which risk to the fetus remains uncertain, for example antidepressants, the use of which has been increasing in pregnancy. In a small but important proportion of women (approximately 1–4%), medicines are prescribed that are known to have harmful fetal effects when used in pregnancy (e.g. antiepileptics).

Pregnant women, and the health professionals who care for them, are rightly concerned about the risk of drug-induced congenital malformations, and increasingly about the possibility of longer term persistent neurobehavioral teratogenicity. However, these concerns need to be put in the context of the potential benefits of therapy to the mother and the risks to the fetus from inadequate treatment of maternal illness. Information on the risks and benefits of drug treatment in pregnancy is often limited, and this presents particular challenges to safe prescribing during pregnancy.

Laura M Yates *MB ChB DRCOG MRPCH PhD is a Consultant in Clinical Genetics at the Institute of Genetic Medicine in the Newcastle Hospitals NHS Foundation Trust, and Head of Teratology for the UK Teratology Information Service (UKTIS), Newcastle upon Tyne, UK. Her research interests are in developmental genetics and teratology. Competing interests: none declared.*

Simon HL Thomas *MD FRCP FRCPE is a Consultant Physician in the Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK, Professor of Clinical Pharmacology and Therapeutics at Newcastle University and Director of the National Poisons Information Service (Newcastle Unit). His research interests are adverse drug reactions and poisoning. Competing interests: none declared.*

Pharmacology during pregnancy

Physiological changes associated with pregnancy have effects upon pharmacokinetics. Drug absorption can be affected by the increase in gastric pH during pregnancy, and the progesterone-related slowing of gastric emptying can delay peak drug concentrations after oral ingestion. Major changes in bioavailability are unlikely, although vomiting, which is common in early pregnancy, can have a substantial impact.

Increased cardiac output, which is established in the first trimester,[2] enhances the speed of distribution of drugs. Total body water and plasma volume increase by about 20% and 50%, respectively, affecting the volume of distribution and steady-state plasma concentration of water-soluble drugs. Reduction of plasma albumin, by around 10 g/litre at term, coupled with reduced binding affinity, affects the total concentration of albumin-bound drugs such as sodium valproate or phenytoin. This in turn affects interpretation of plasma total drug concentrations; free drug concentrations are unaffected, so lower total drug concentrations are associated with equivalent clinical effects. Distribution can also be influenced by the increase in body fat associated with pregnancy, which contributes to an increased total body weight, although enhanced distribution to fat is unlikely to have substantial effects on plasma drug concentrations.

Metabolism of drugs is altered in pregnancy as a result of increased hepatic blood flow and variable effects on hepatic enzymes (Table 1). A prominent mechanism is induction of cytochrome P450 isoenzymes by oestradiol (e.g. CYP2A6, CYP3A4) or progesterone (e.g. CYP2A6, CYP2B6, CYP2C8, CYP3A4, CYP3A5).[3] The overall effects on drug metabolism can be difficult to predict, especially as some drugs are metabolized by several cytochrome P450 isoenzymes.

The 40–65% increase in glomerular filtration rate in pregnancy results in enhanced clearance of renally excreted drugs (e.g. penicillins, atenolol, digoxin, metformin, lithium) and active metabolites (e.g. morphine glucuronides). Renal tubular secretion of drugs via P-glycoprotein (P-gp) is also enhanced in late pregnancy, further enhancing elimination of P-gp substrates (e.g. digoxin).

These pharmacokinetic changes can have substantial effects on plasma drug concentrations, which are especially important for drugs with a low therapeutic index. However, evidence is limited for many drugs because of the difficulties of performing clinical research during pregnancy. Much available data relates to antiepileptic drugs: total blood concentrations of phenytoin and valproate can fall by up to 50% in pregnancy, although concentrations of free drug are changed to a smaller extent. Lamotrigine concentrations are reduced as a result of enhanced glucuronidation, and there is evidence suggesting that this change is associated with an increase in seizure frequency. Lower plasma concentrations for equivalent doses of the antidepressants citalopram, escitalopram and sertraline are achieved from week 20 of pregnancy as a result of enhanced metabolism.

Pharmacodynamic changes in pregnancy are less well studied. Corticosteroid-induced increases in blood pressure and blood glucose may be more common in pregnancy, and impairment of cell-mediated immunity can alter the efficacy of vaccination, especially in the third trimester. There is evidence of increased sensitivity to the heart rate-lowering effects of β-adrenoceptor blockade. These changes and their clinical implications are poorly understood.

For drugs with a low therapeutic index, the complex pharmacological changes of pregnancy may require adjustment of drug dosage. For drugs subject to therapeutic drug monitoring, doses can be adjusted according to plasma concentration, taking into account the effects of plasma albumin concentrations for drugs subject to binding. For other drugs, specific dosing recommendations for pregnancy are often unavailable and prescribers have to rely on dose recommendations for non-pregnant patients, adjusting dosage according to response.

Placental transfer

Movement of drugs from maternal to fetal blood is most marked for drugs with a low molecular weight (e.g. <600 Da) and high lipid solubility, while plasma protein binding reduces placental transfer because the plasma albumin concentration is higher in the mother than the fetus. The ionization constant of a drug

Change in hepatic enzyme function during pregnancy

Enzyme	Effect of pregnancy	Substrates (examples)
Cytochrome P450 isoenzymes		
CYP1A2	Decreased (all trimesters)	Paracetamol, theophylline, caffeine
CYP2A6	Increased	Sodium valproate, nicotine
CYP2C9	Increased (third trimester)	Warfarin, NSAIDs, ACE inhibitors, phenytoin
CYP2C19	Decreased (second and third trimesters)	Proguanil, citalopram
CYP2D6	Increased	Metoprolol, tricyclic antidepressants, SSRIs, venlafaxine, methadone
CYP3A4	Increased	Nifedipine, carbamazepine Protease inhibitors (e.g. nelfinavir)
Uridine diphosphoglucuronosyltransferases	Increased (all trimesters)	Lamotrigine, morphine
N-Acetyltransferase 2	Decreased	Isoniazid, hydralazine

ACE, angiotensin-converting enzyme; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors.

Table 1