Prescribing medicines in pregnancy

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Abstract

Prescribing in pregnancy is complex; it needs to take into account the effects that physiological changes associated with pregnancy may have on the 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 often may 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.

Experience of safe use in pregnancy is available for many older drugs used in the treatment of common conditions, but often little is known about the fetal risk of the newer preparations increasingly preferred due to improved efficacy or adverse effect profiles. Some drugs essential for 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 now well-established worldwide and provide up-to-date, evidence-based advice to support safe and informed prescribing in pregnancy.

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

What's new?

- An increasing number of drugs have been recognized as teratogens (e.g. mycophenolate mofetil)
- Epidemiological studies have demonstrated an increased prevalence of chronic medical conditions requiring treatment during pregnancy as a result of women delaying motherhood
- There is improved understanding of the pharmacodynamic changes associated with pregnancy
- There is increasing recognition of the role of membrane transporters in transplacental drug transfer

Introduction

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

Much of 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 receiving at least one prescription.[1] Medications commonly involved include analgesics, antibiotics, vitamins (including folic acid) and anti-emetics; for most of these there is considerable experience of safety in pregnancy. However, there is also appreciable use of medicines for which less safety information is available, for example antidepressants, the use of which appears to be increasing in pregnancy.[2] 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.[3]

Pregnant women and the health professionals who care for them are rightly concerned about the potential adverse effects of drug therapy upon the fetus, especially the risk of drug-induced congenital malformations, but 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 risks and benefits of drug treatment in pregnancy is often limited and this presents particular challenges to safe prescribing during pregnancy.

Pharmacology during pregnancy

Physiological changes associated with pregnancy have effects upon the pharmacokinetic properties of drugs.[4] Drug absorption may be affected by the increase in gastric pH during pregnancy and the progesterone-related slowing of gastric emptying may 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 enhances the speed of distribution of drugs. Total body water and plasma volume increase by about 20% and 50% respectively, affecting distribution volumes and steady-state plasma concentrations 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

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phenytoin. This affects interpretation of plasma total drug concentrations; free drug concentrations are unaffected so lower total drug concentrations are associated with equivalent clinical effects. Distribution may also be affected 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).[5–8] 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, but evidence is limited for many drugs because of the difficulties in performing clinical research during pregnancy. Much available data relates to antiepileptic drugs: total blood concentrations of phenytoin and valproate may 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.[9] 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.[10]

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 may 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.[11] 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 plasma albumin concentration is higher in the mother than the fetus. The ionization constant (pKa) of a drug affects lipid solubility at physiological pH and weak bases may become trapped in the more acidic fetal circulation.

Placental transfer of drugs is also affected by the actions of the many placental membrane transporters, such as the adenosine triphosphate-binding (ATP-binding) cassette (ABC) transporter P-glycoprotein (P-gp), sometimes termed the multidrug resistance protein 1 (MDR1) or ABCB1. Effects on placental transfer depend on location: those in the apical surface of the syncytiotrophoblast, adjacent to the maternal circulation, act as efflux transporters and prevent drugs reaching the fetal circulation, while those located in the basolateral aspect, facing the fetal circulation, have the opposite effect.[12,13] The clinical implications of placental transporter activity are not well studied as yet, although inhibition of P-gp has been shown to increase transplacental movement of the P-gp substrates, indinavir[14] and lopinavir.[15] Membrane transporter polymorphisms may also have an important effect.

A further complication is that placental transfer of drugs is probably not uniform over the course of pregnancy. Maternofetal diffusion distance reduces as pregnancy progresses,

Change in hepatic enzyme function during pregnancy[5–8]

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 trimester)	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 (NAT2)	Decreased	Isoniazid, hydralazine

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

Table 1