Principles of prescribing in pregnancy

Tarek El Shamy

Onnig Tamizian

Abstract

Medication use (both over the counter and prescribed) is common during pregnancy and lactation. However, prescribing in pregnancy can be challenging for several reasons. First, the physiological changes associated with pregnancy and its impact on the pharmacokinetics of medications. Second, the lack of information regarding potential adverse fetal effects of new medications. Adherence to the safe principles of prescribing together with patient involvement in decision making is essential when prescribing in pregnancy. In this article, we review the principles of safe prescribing in pregnancy and review commonly used medications and their potential teratogenic effects. Finally, we discuss the management of pregnancy complicated with potential teratogenicity.

Keywords congenital malformation; drug safety; pharmacokinetics; pregnancy; prescribing; teratogen

Overview of problem

In the UK, approximately 1 in every 3 pregnant women takes medication, other than vitamins and iron, at least on one occasion during pregnancy. Recent studies in the UK estimated 65% of pregnant women had been prescribed at least one medication and that one in every 164 women had received a US FDA category X drug in early pregnancy.

Certain factors contribute to fetal exposure to prescription drugs including the fact that least half the pregnancies in North America are unplanned. Another important factor is that with the increasing maternal age, more women are already on long-term medication for chronic conditions at the time they embark on a pregnancy.

Women suffering from certain medical conditions that were previously considered to be incompatible with pregnancy (SLE, certain types of heart disease, transplant recipients), now are amenable to motherhood due to dramatic improvement in maternal medicine leading to successful pregnancy outcomes. Another contributing factor is the increased risk in older mothers of pregnancy-related problems such as hyperemesis gravidarum, gestational diabetes, obstetric cholestasis and pre-eclampsia.

Tarek El Shamy ***MBBCH MSc MRCOG*** *Clinical Research Fellow, Derby Teaching Hospitals NHS Foundation Trust, Derby, UK. Conflicts of interest: none declared.*

Onnig Tamizian ***FRCOG LLM (Medical Law)*** *Consultant Obstetrician Gynaecologist, Royal Derby Hospital, Derby, UK. Conflicts of interest: none declared.*

Pregnancy outcome in relation to timing of exposure

Congenital defects are present in 2–3% of babies at birth with approximately 1–2% of the total associated with drug treatment. Teratogenesis is defined as dysgenesis of fetal organs, in terms of either structural integrity or function. It may take the form of malformations that occur during the period of organogenesis or at a later stage by altering the structure or function of organ systems involved.

The fetal response is influenced by several factors including genetic factors, the dose of the teratogenic agent, the route and timing of exposure.

The timing of exposure to a drug is a critical factor in determining the nature and extent of any adverse effects. The three important phases in human development are:

1. Pre-embryonic phase: This extends from conception to 17 days post conception. During this period any adverse effect is an 'all or none phenomenon' and the result of an insult will be either fetal death or intact survival through multiplication of the totipotent cells.
2. Embryonic phase: This extends from day 18 to day 55. It is the period of greatest vulnerability for the embryo due to rapidly differentiating tissues. The following lesions have been identified with time of exposure;
   - Anencephaly – day 24,
   - Limb reduction defects – days 12–40,
   - Cleft lip – day 36,
   - Ventricular septal defects – day 42,
   - Hypospadias – day 84.
3. Fetal phase: This runs from gestational age of 8 weeks to term. The cerebral cortex and glomeruli continue to develop and remain susceptible to damage. Functional abnormalities such as deafness may occur and drugs that can cross the placenta may affect fetal growth and development rather than causing structural malformations.

Prescribing principles in pregnancy

It is important to consider the following general principles:

- Drugs should be prescribed only for clear indications where the benefits (usually for the mother) outweigh the potential risks (usually to the fetus).
- Wherever possible try and avoid all drugs in the first trimester.
- Medication should be used in the smallest effective dose for the shortest required duration.
- Prescribe medication that has been widely used in pregnancy and has a good safety track record.
- Most drugs with a molecular weight of less than 1500 Da can cross the placenta and, therefore, potentially can affect the fetus.
- Encourage preconceptual counselling in all patients with chronic medical disorders.

How does pregnancy affect pharmacokinetics?

Pharmacokinetics refers to the absorption, distribution, metabolism and excretion of a drug.

Gastrointestinal transit time is prolonged in pregnancy due to slower emptying of the stomach and reduced gut motility. Molecular distribution of a given drug is affected by its lipid solubility

Please cite this article in press as: El Shamy T, Tamizian O, Principles of prescribing in pregnancy, Obstetrics, Gynaecology and Reproductive Medicine (2018), https://doi.org/10.1016/j.ogrm.2018.03.005

and protein binding. Another physiological adaptation to pregnancy involves increase in the total body water and plasma volume (and hence volume of distribution), along with a fall in plasma proteins such as albumin. Drugs that have low lipid solubility and are predominantly bound to plasma proteins, will thus have a greater plasma concentration of the unbound drug.

Table 1 summarises teratogenic and adverse fetal effects of common medication.

Breastfeeding and maternal pharmacotherapy

Most drugs cross into breast milk. In general terms, the doses of drugs reaching the baby are clinically insignificant when one considers dilution of the drug in the mother and the small volumes of milk the neonate feeds on. Most important factors that determine drug compatibility for a breast-feeding mother are the volume of distribution (between 1 and 20L/kg), percentage of maternal protein binding (>90%) and the molecular weight (>800 Da). Very few drugs are absolutely contraindicated in breastfeeding.

Drugs can be considered in three main categories with respect to breastfeeding:

a. Drugs that cannot be detected in the baby, e.g. warfarin and aminoglycosides,
b. Drugs which are detectable in the baby in clinically insignificant amounts, e.g. NSAIDs, penicillins, cephalosporins, antihypertensive drugs, bronchodilators and anticonvulsants (except barbiturates).
c. Drugs that reach the neonate in sufficient amounts to cause fetal side effects e.g. benzodiazepines, barbiturates, tetracyclines, cytotoxic and immune suppression drugs, and aspirin.

Drugs used in pregnancy

Supplements and vitamins

Folic Acid: Preconceptual folic acid reduces the incidence of NTDs, cleft lip and cleft palate. It is recommended at a dose of 400 μg pre-conceptually and until 12 weeks'gestation in all women. A higher dose of 5 mg/day is recommended in those with a previous pregnancy affected by NTD, or on anticonvulsants or those who suffer from haemolytic anaemias, hyperhomocystinaemia and Crohn's disease.

Vitamin K: Vitamin K is required in the synthesis of clotting factors and prevention of haemorrhagic disease of the newborn. It is required in pregnant women on anticonvulsants, obstetric cholestasis, primary biliary cirrhosis and acute fatty liver of pregnancy at a dose of10 mg per day.

Vitamin B: Thiamine (vitamin B_6) is required in severe hyperemesis gravidarum at a dose of 50 mg three times daily. Vitamin B_{12} is required in Vitamin B_{12} deficiency in pernicious anaemia, or due to malabsorption syndromes e.g. Crohn's disease.

Vitamin D and Calcium: NICE recommends daily supplementation of vitamin D at a dose of 10 mg (400 units) for all pregnant and breastfeeding women.

Drugs with proven teratogenic and fetal effects in humans

Drug	Teratogenic/Adverse effect
ACE inhibitors	decreased skull ossification, renal tubular dysgenesis, oligohydramnios
Aminoglycosides	Deafness, vestibular damage
Androgenic drugs and Danazol	Masculinisation of female fetuses
Anticholinergics	Neonatal meconium ileus
Barbiturates	Neonatal withdrawal symptoms when drugs are taken in late pregnancy
Beta blockers	Growth restriction, neonatal bradycardia and hypoglycaemia
Benzodiazepines	Neonatal withdrawal symptoms when drugs are taken in late pregnancy
Carbamazepine	Neural tube defects
Chloramphenicol	Grey baby syndrome
Cocaine	Growth retardation, placental abruption, uterine rupture
Cyclophosphamide	CNS malformations, secondary cancer
Diethylstilbestrol	Vaginal carcinoma, genitourinary defects in male and female offspring
Ethanol	Fetal alcohol syndrome (pre- and postnatal growth restriction, CNS anomalies, characteristic facial features)
Frusemide	Decreased uterine blood flow, hyperbilirubinemia
Griseofulvin	Fetotoxicity and teratogenicity in animals.
Indomethacin	Premature closure of ductus arteriosus, necrotizing enterocolitis, neonatal pulmonary hypertension
Lithium carbonate	Epstein's anomaly
Methotrexate	CNS and limb malformations
Misoprostol	Moebius syndrome
Opioids	Neonatal withdrawal symptoms when drugs are taken in late pregnancy
Phenothiazines	Neonatal effects of impaired thermoregulation, extrapyramidal effects
Phenytoin	Growth restriction, CNS defects
Propylthiouracil	Fetal and neonatal goitre and hypothyroidism
Quinolones	irreversible arthropathy in animal studies
Retinoids	CNS, craniofacial and cardiovascular defects
Sulphonamides	Hyperbilirubinemia, kernicterus
Tetracycline	Anomalies of teeth and bone
Thalidomide	Phocomelia
Thiazides	Neonatal thrombocytopenia
Tramadol	Embryotoxic in animal studies
Valproic acid	Neural tube defects, dysmorphic features, developmental delay
Verapamil	May reduce uterine blood flow with fetal hypoxia
Warfarin	Skeletal and CNS defects, Dandy Walker syndrome

Table 1

Please cite this article in press as: El Shamy T, Tamizian O, Principles of prescribing in pregnancy, Obstetrics, Gynaecology and Reproductive Medicine (2018), https://doi.org/10.1016/j.ogrm.2018.03.005