**Principles of drug therapy in pregnancy**

Physiological changes in pregnancy During the 40 weeks of pregnancy total body water is increased by approximately 8 litres, leading to altered drug distribution. Pregnancy also increases cardiac output, the rate of liver metabolism, plasma volume, glomerular filtration and fat stores. These physiological changes cause drug concentrations to be reduced in pregnancy through a combination of haemodilution and increased distribution, metabolism and excretion.

It is therefore important that medications and their effects are monitored carefully during pregnancy to ensure that the doses used are as low as possible but provide an adequate therapeutic response.

Placental transfer

The rate of placental transfer is affected by metabolism and gestational age, and the protein binding, ionisation, lipid solubility and molecular weight of the drug. There is a misconception that there is a placental barrier providing protection to the fetus; however, almost all drugs are able to pass freely through the placenta, with only those with a molecular weight of >1000Da being unable to do so, eg insulin and heparin.

Teratogenicity

A drug is identified as a teratogen if exposure in utero causes, directly or indirectly, structural or functional abnormalities in the fetus or in the child after birth. . The most obvious forms of teratogenicity are structural malformations, for example the effects of thalidomide, which were first recognised in the 1960s. Other drugs that do not appear to be associated with an increased risk of structural anomalies can produce other forms of fetal toxicity. One example is the beta-blockers (most notably atenolol), which have been associated with intrauterine growth retardation (IUGR), probably due to increased fetal and uteroplacental peripheral vascular resistance and reduced placental blood flow. Diethylstilbestrol, which was used to prevent recurrent miscarriages, is now known to cause transplacental carcinogenicity; in-utero exposure is associated with problems in later life such as infertility in both male and female offspring and a rare form of vaginal cancer. Neuropsychological and behavioural abnormalities may also occur after drug exposure. Some antiepileptic drugs and drugs of abuse have been associated with learning and behavioural problems following in-utero exposure; however, the potential confounding effects of social factors and maternal illness can make ascertainment of causality difficult.

Timing of exposure

During the preimplantation stage, in very early pregnancy, exposure to a drug is unlikely to produce a teratogenic effect due to an inbuilt ‘recovery process’ in the conceptus. If a teratogenic insult occurs and there is damage to only a small number of cells then ‘compensation’ occurs whereby the remaining viable cells continue to divide to replace any that were damaged. However, if a large number of cells are damaged then implantation will not occur and the pregnancy will be lost. This is known as the ‘all or nothing’ or totipotent period. The 10 weeks following implantation are the most sensitive as this is the time during which major structural changes and organogenesis are taking place. For example, it is during this period that the neural tube closes and major organs and limbs develop. While the first trimester is the most sensitive period to structural malformations, some drugs may affect the fetus in the later stages of pregnancy, so care should be taken when prescribing throughout pregnancy. For example, exposure to ACE inhibitors in the second and third trimesters can cause serious adverse effects such as oligohydramnios, growth retardation, lung and kidney hypoplasia and hypocalvaria. It is important to carry out an individual risk assessment when considering prescription of a drug in pregnancy. It is not possible to produce lists of ‘safe’ drugs and drugs that must always be avoided. In certain cases it may be necessary to prescribe a suspected teratogen, as the benefit may outweigh the risk due to, for example, the severity of the maternal condition, or stage of pregnancy.

Route of exposure

Though concern in pregnancy mostly centres around the use of orally administered drugs, there may also be risk from some topical medications. For example, chloramphenicol eye drops carry theoretical risks and should be substituted for safer alternatives wherever possible.

General considerations when prescribing in pregnancy

The risk posed by drug use in pregnancy can be minimised through prepregnancy counselling. Folic acid supplementation can be initiated and treatment optimised to ensure that the safest medications are used. However, as many pregnancies are unplanned, this opportunity is often lost. When prescribing for a patient planning a pregnancy, or a patient who has become pregnant, consideration should be given to whether medication is absolutely necessary. Often nondrug measures may be sufficient, eg dietary measures may alleviate common conditions such as nausea and constipation, and behavioural therapy and counselling may be adequate in the management of anxiety and mild depression. When prescribing for pregnant women it is important to balance the (often poorly defined) risk of drug treatment to the fetus against the risks to both mother and fetus from failing to treat the maternal condition. The case for each drug should be assessed on an individual patient basis. For some women drugs associated with some risk of adverse fetal effects may be required to control a condition that, if left untreated, would prove detrimental to the mother and/or fetus. If there is no alternative option then medication must not be withheld. Together with their prescriber, pregnant women or women planning a pregnancy need to ensure that they can make informed choices regarding the optimum treatment to minimise risks to her pregnancy. All drugs in pregnancy should be prescribed in the lowest effective dose for the shortest possible time. Drugs may act synergistically in terms of teratogenic potential and for this reason monotherapy is desirable when possible. Evidence has, for example, demonstrated that polytherapy with antiepileptic drugs poses a higher risk to the fetus than monotherapy.