Pregnancy and medicines

Introduction

Agents or factors that cross the placenta to cause congenital malformations are termed **teratogens** (from the Greek *teratos* meaning monster). This strict definition is often relaxed to include any agent that, directly or indirectly, causes structural or functional abnormalities in the fetus or child after birth when administered to a pregnant woman. Teratogens do not cause abnormalities in all fetuses exposed at the critical period. For example thalidomide, which is a highly teratogenic drug, caused abnormalities in less than half of all fetuses exposed during the critical period.

The **incidence of major congenital malformations** in the UK general population is estimated to be between 2-3%.

A high proportion of these malformations are of unknown aetiology; only 1-2% are thought to be due to drugs.

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There are diagrams illustrating when teratogens might be more likely to adversely affect specific aspects of fetal development, including this example.

The embryo is most vulnerable to teratogens during the **embryonic phase**, from days 18 to 55, when the cells differentiate and the major organs are formed. If differentiated cells are damaged they are unlikely to be replaced resulting in permanent malformations. During the **fetal period**, from day 56 until birth, organs such as the cerebral cortex and the renal glomeruli continue to develop and remain particularly susceptible to damage. Functional abnormalities such as deafness may also occur.

Teratogenicity is usually **dose-dependent** and there is normally a threshold dose below which a drug does not exert any teratogenic effects. For example the incidence of neural tube defects with sodium valproate may be dose-related. The risk of teratogenicity may also be increased if the **number** of concomitant drugs is increased. This has been studied especially in women with epilepsy: the incidence of malformations increases with the number of anti-epileptic drugs taken.

Teratogenicity is not the only risk posed by medicines. They can, for example, trigger **spontaneous miscarriage** (also known as spontaneous abortion). The background incidence of spontaneous miscarriage is about 10-20% of all pregnancies.

Animal studies

Although rodents are normally used to evaluate the safety of drugs in pregnancy during pre-clinical studies, their physiology, metabolism and development are very different to humans. It cannot be assumed that a drug that does not cause embryotoxicity, fetotoxicity or teratogenicity in animal studies can be used 'safely' in human pregnancies. However, if a drug does cause fetal toxicity in several animal species, this is an indicator that the same effects may occur in man.

Potential harm

A drug does not need to cross the placenta to cause fetal toxicity. For example, any drug that causes vasoconstriction of the placental vasculature can harm the fetus. However, almost all drugs do cross the placenta, mostly by simple diffusion. The extent to which compounds will cross the placenta depends upon their molecular size, degree of ionisation, protein binding and lipid solubility:

- Non-ionised, lipid-soluble, drugs will cross in preference to polar, ionised, hydrophilic compounds (e.g. the more lipid soluble labetalol will cross the placenta to a greater extent than the more hydrophilic atenolol).

- Drugs with a high molecular weight tend not to cross the placenta (e.g. insulin, heparin).

Although fetal malformations are the most obvious adverse pregnancy outcome that medicines can cause, there are others including the following:

- Spontaneous abortions (e.g. isotretinoin)
- Intra-uterine growth retardation or 'IUGR' (e.g. many street drugs have been associated with IUGR although other factors may be responsible)
- Prematurity (e.g. warfarin)
- Stillbirths (e.g. warfarin)
- Obstetric complications (e.g. NSAIDs can cause excessive maternal bleeding)
- Neonatal side effects (e.g. CNS depression due to sedatives)
- Withdrawal reactions in the neonate (e.g. opioid or benzodiazepine withdrawal)
- Mental impairment (e.g. phenytoin, sodium valproate)
- Cancer (e.g. cervical adenocarcinoma caused by stilboestrol)

Reducing risk

Strategies to reduce risks to the fetus when prescribing to a pregnant woman include:

- Consider **non-drug treatments** and only prescribe drugs if essential.
- Consider the period of gestation and, if possible, **avoid all drugs during the first trimester**.

- **Avoid known human teratogens**, unless absolutely unavoidable.
- **Do not use new drugs** because usually there is little information on their effects in pregnancy.
- **Avoid polypharmacy**.
- Where appropriate, use the **lowest effective dose** for **as short a period** as possible.

No drug has been demonstrated to be completely safe in pregnancy because it would not be ethical to conduct studies to prove the point. However, the drugs below are generally considered to carry **minimal risk** of adverse effects in pregnancy at normal therapeutic doses:

- Antacids
- Paracetamol
- Pencilllins
- Laxatives
- Cephalosporins
- Inhalers for asthma

Conversely, the following medicines are known to carry a **higher risk** in pregnancy. Refer to your Information Sources to find out what common malformations or complications are associated with the following higher risk drugs:

- ACE inhibitors
- Phenytoin
- Isotretinoin
- Alcohol
- Tetracyclines
- Warfarin

Other considerations

It is easy to focus solely on the potential harm to the fetus when advising on the use of medicines in pregnancy, but there are other important aspects of prescribing in pregnancy to be aware of. Monitoring of any chronic medical condition should be intensified during pregnancy because the pattern of disease may change (improve, worsen) as well as the response to medicines.

In particular, **drug pharmacokinetics** will change in the mother. For example increases in plasma volume result in lower serum concentrations of drugs that are predominantly held in the plasma, that is those with a low volume of distribution (e.g. aspirin, phenytoin). A reduction in serum albumin concentrations may result in higher levels of the free fractions of some protein bound drugs (e.g. phenytoin, diazepam). Increases in renal function may affect the clearance of drugs excreted by the kidney (e.g. ampicillin, gentamicin).

It is important to remember that some of these parameters will quickly revert back to their pre-pregnancy levels and that dose adjustments may be required soon after delivery. For example the changes in drug metabolism that require lamotrigine doses to be significantly increased during pregnancy rapidly return to normal postpartum, requiring close monitoring and prompt dose reductions to avoid toxicity.

Also note that mothers may become **poor compliers** if they believe that there is a risk that medication may harm their baby. It is important to explain the benefits and risks of drug treatment in a balanced way, which sometimes can be challenging.

When advising on a medicine for use in pregnancy don't forget the normal' **contraindications and precautions** as they apply to the mother (e.g. avoid recommending labetalol for hypertension in a pregnant patient with asthma). Preventable side effects from medication can reduce maternal compliance, but major side effects might also threaten the fetus.

Finally, note that all women should take **folate supplements** from the time pregnancy is planned and for the first 12 weeks of pregnancy to reduce the risks of neural tube defects in the fetus. Most women should take 400 micrograms daily, but there are exceptions. For example, women taking antiepileptic medication, those on proguanil for malaria prophylaxis, and women who have previously had a child with neural tube defects should take 5mg daily.

You can read more about folic acid use in pregnancy on the bumps website and read about other dietary advice in pregnancy on NHS choices.

Paternal exposure to medicines

You may be asked about paternal exposure to medicines and the risks this may pose to conception or the development of the embryo or fetus. Common scenarios include the time to wait before conception or the risks to an unplanned pregnancy if the father is taking a particular medicine.

There are several key points to consider, including:

- Does the medicine have the potential to alter the number or structure of chromosomes?
- Can the medicine affect spermatogenesis, sperm viability, motility or morphology?
- Can the medicine cause sexual dysfunction such as erectile dysfunction or loss of libido?

Most medicines probably don't pose a significant risk but there are exceptions including cytotoxic agents. If a patient has been exposed to such a medicine then in theory he should wait 6 months (2 spermatogenic cycles) before conception is planned.

Suggested questions

They may not apply to every situation you come across, but here are some questions you should be thinking about in practice.

The Medicine

- How long has the medicine been taken for, and what is the expected duration of treatment?
- Has the woman taken the drug in question during a previous pregnancy?
- What medication has the woman taken during previous pregnancies for any similar condition?

The Mother and Fetus

- Is the woman actually pregnant now, or planning to become pregnant? (i.e. prospective or retrospective exposure).
- How many weeks pregnant is she now?
- Has the woman had any previous pregnancies and what were the outcomes?
- Is there a family history of malformations or history of recurrent abortions?

Going Forward

- Is treatment essential? Can it be delayed?
- Would non-drug alternatives be appropriate?
- Have any alternative medicines been tried, or could they be considered?
- Have any investigations been performed or are they planned (e.g. ultrasound scans)?

Information sources

An obvious point perhaps, but ensure that the information you use is relevant to the trimester you have been asked about. A great deal of information in this field relates to the first trimester, which is interesting but not relevant if you've been asked about exposure in the later stages of pregnancy.

Check the **UK Teratology Information Service** pregnancy monographs for which you will need your organisation's user name and password to log in. You can ring the service for advice too, but make sure you've conducted a thorough search of your resources first. There is an online guide to the information that UKTIS will require when you ring them. Their website for patients (called 'bumps') has lots of helpful information leaflets that correspond to the monographs for professionals.

What do the experts say? After an initial search for information, it is often helpful to look for guidelines, written by expert clinical bodies. Most guidelines on the management of chronic conditions will include a section on pregnancy. These can often be found by via NICE Evidence, limiting your search to 'guidance'.

Depending upon the nature of the question asked, try **Drugs in Pregnancy and Lactation** by Briggs et al. which is kept by most MI centres. Although the book is available online and in a paper format, updates are only issued online. Another well-respected resource is **Drugs During Pregnancy and Lactation** by Schaefer et al. which is available in paper form and electronically, and many MI centres have access.

UKMi has published a number of **Medicines Q&As** for a range of common problems in pregnancy. These are published on the SPS website.

If you need to search the literature then try **Embase** first followed by **Medline**; choose your terms carefully.

SPCs usually contraindicate drug use in pregnancy yet occasionally helpful information is

given. **Manufacturers' medical information departments** may be able to offer more information particularly on very new drugs where published literature is often lacking.

For enquiries relating to specific therapeutic areas such as depression in pregnancy, then specialist resources in that field such as Bazire's **Psychotropic Drug Directory** or **The Maudsley Hospital Prescribing Guidelines** may be helpful.

Be careful about conducting a general internet search on this subject. If you do, you may like to look at our brief guide to evaluating websites about medicines.

Next steps in learning...

There is a description of the stages of development of the human fetus, week by week, here. The NHS Choices site also has a series of images showing the appearance of the fetus as a pregnancy develops.

The physiological changes that affect mothers during pregnancy are covered in some detail by the Merck Manual online.