

Pregnancy and medicines

After completing this tutorial, you will be able to:

- Describe the key stages of embryonic and fetal development and the risks that medicines may pose.
- Outline strategies to reduce the risk of harm from medicines during pregnancy.
- Help patients make informed decisions about using medicines during pregnancy.

Why this subject matters...

The number of women needing to take medicines during pregnancy is increasing, in part due to women becoming pregnant at an older age, and requiring treatment for pre-existing medical problems, and/or suffering obstetric complications. It is essential that women can make informed decisions about whether to use a medicine during their pregnancy.

Therefore you need to be familiar with the stages of development of the embryo and the fetus, the potential harm that medicines can pose, and strategies to reduce any risk(s).

Teratogenicity

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 always 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. Some may be due to the mother's health during pregnancy or her lifestyle; only 1-2% are thought to be due to drugs.

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.

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This [example diagram](#) illustrates when teratogens might be more likely to adversely affect specific aspects of fetal development.



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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 major congenital malformations with carbamazepine 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 antiepileptic drugs taken.

A note on nomenclature

As it is difficult to know exactly what date ovulation and conception happens, the stage of a woman's pregnancy is counted from the first day of her last menstrual period (LMP). For example, a woman who misses her period, finds out she is pregnant, and the first day of her LMP was four weeks ago, is described as '**4 weeks pregnant**'. This is despite conception only happening about 2 weeks ago.

Another term that is used is the '**gestational age**' which is also counted from the first day of the last menstrual period. It is essential to use this nomenclature accurately, and seek clarity if necessary.

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 humans.

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) but there are exceptions (e.g. adalimumab, infliximab).

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. beta-blockers)
- Prematurity (e.g. statins)
- Stillbirths (e.g. warfarin)
- Obstetric complications (e.g. NSAIDs can cause excessive maternal bleeding used near term)
- Neonatal side effects (e.g. CNS depression due to sedatives)
- Withdrawal reactions in the neonate (e.g. opioid or benzodiazepine withdrawal)
- Impaired neurodevelopment (e.g. sodium valproate)
- Cancer (e.g. cervical adenocarcinoma caused by diethylstilbestrol)

Reducing risk

When giving advice about prescribing medicines for a woman who is pregnant:

- Consider **non-pharmacological 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**.
- **Avoid newer 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.

However these strategies cannot be applied in every case, and the potential risk(s) of the medicine must always be carefully balanced against the potential benefit(s). For example, a woman stabilised on a newer antidepressant in her first trimester of pregnancy, may on balance benefit more from continuing with treatment rather than swapping to an older antidepressant with more safety information, or discontinuing treatment.

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
- Penicillins
- Laxatives
- Cephalosporins

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.



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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 the [NHS](#) website.

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 between stopping a drug and trying to conceive or the risks to an unplanned pregnancy if the father is taking a particular medicine.



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There are several key points to consider, including:

- Does the medicine have the potential to alter the number or structure of chromosomes, the genetic sequence or cause epigenetic modification of the DNA?
- 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.

It is theoretically possible that fetal exposure to a drug or its active metabolites may occur through transfer via semen to the pregnant mother. The drug or its metabolites may have a direct effect on the uterus, or the fetus may be exposed through the systemic circulation if the drug is absorbed through the vaginal mucosa. However, studies suggest that transfer of an agent through the cervix is unlikely and any uptake via the vaginal mucosa is expected to be extremely low and below clinically meaningful levels.

Talking to patients

Communicating the risk of medicines in pregnancy isn't a situation you are likely to face often as a foundation pharmacist, but it is important to be prepared. You may be asked to counsel a patient who is planning a pregnancy and needs to start a medicine, or perhaps the patient has conceived whilst taking a medicine for a long-term condition.

Either situation will demand a careful, tailored explanation of the potential risks to the child and the likely benefits of treating the maternal condition in language the woman can understand. It is important that the woman knows that not treating her medical condition may cause more harm than any potential risk(s) posed by a medicine. For example, epileptic seizures in pregnancy can have significant adverse effects on pregnancy outcome and some patients with depression may experience a deterioration in their condition if not treated. For patients who are likely to require a medicine throughout their pregnancy and postnatally, it may be appropriate to offer advice about safety whilst breastfeeding too.



Courtesy of Angela Badiani

If written information is available such as that on the [bumps](#) website, then this should be used to supplement your consultation. Remember that manufacturers' patient information leaflets will usually warn against the use of a medicine in pregnancy, and it may be helpful to provide reassurance on this point during the consultation.

A helpful framework to follow is to explain;

- The potential **consequences** of using a medicine during pregnancy
- How **likely** the woman and her unborn child are to be affected
- What can be done to **manage any risk(s)**

Consequences

It may be helpful to start by explaining that pregnant women are generally not included in clinical trials of medicines, and so often evidence for a medicine's safety is limited. You may

also like to add that it is sometimes difficult to separate out any effect of the maternal disease state on the unborn child and the medicine itself. Explain the known risks clearly, taking into account the stage of the pregnancy that has been, or will be exposed. For example, if a medicine has been associated with causing a cleft palate, but the woman is now 16 weeks post-conception, which is after the palate has formed, then this will not affect her pregnancy. For newer medicines there may be unknown risks.

Likelihood

Firstly, offer an estimate of the **background risks** of adverse pregnancy outcomes in the general population to help the woman put any potential risk(s) from a medicine into context. Sensitively explain that as many as 1 in every 5 pregnancies may end in a miscarriage, and up to 1 in 40 babies are born with a birth defect.

Try to convey whether any potential risk(s) is:

- **Theoretical** – such as with a new folic acid antagonist, for example. Although what we know about other folic acid antagonists such as phenytoin would predict the potential for neural tube defects if early exposure has occurred, evidence for the new medicine is completely lacking.
- **Uncertain at present** – for example if different studies have produced conflicting results, or if the evidence base is made up of only one or two small studies, or some individual case reports, such as with pregabalin and the risk of CNS anomalies.
- **Suspected** – if multiple studies have produced similar results, such as fluoxetine and cardiovascular defects.
- **Likely or certain** – if a medicine has been confirmed as being responsible for a particular adverse effect ('a causal association'). For example isotretinoin and CNS and facial abnormalities.

Quantify any risk in absolute rather than relative terms. For example you could say *"Fluoxetine may increase the risk of your baby developing an uncommon lung condition after they are born called persistent pulmonary hypertension of the newborn. The chance of this problem happening may increase from 1 or 2 cases in every 1000 newborn babies, to around 5 in every 1000"* rather than *'Fluoxetine may double or triple your risk of...'*

Mitigation

Once you have explained the potential consequences and the likelihood of them occurring, it is important to describe how they will be managed to reduce their impact upon your patient's pregnancy. For example, in a woman planning a pregnancy, her medicines should be optimised to only include essential medicines at the lowest effective doses. In some cases maybe non-drug treatment such as cognitive behavioural therapy for mild depression may be appropriate.

Older medicines with more safety data may also be preferred such as methyldopa for hypertension, but this isn't always the case. Any known teratogens should be changed to safer alternatives such as changing warfarin to enoxaparin for the treatment of a deep vein thrombosis.

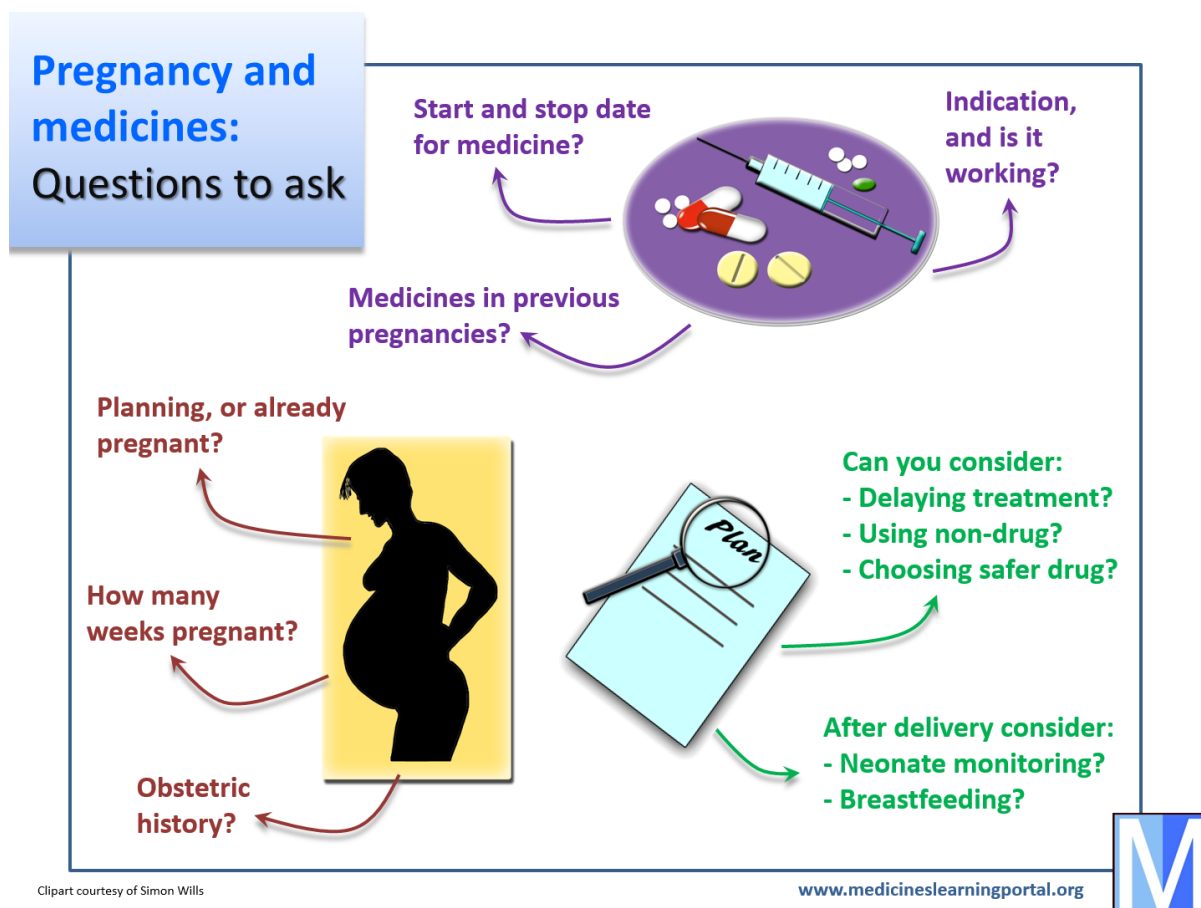
In a woman who presents after taking a medicine, consider whether the medicine can be stopped, or if it needs to be continued or swapped to a safer option. Explain whether extra monitoring and investigations may be required.



Suggested questions

The questions below cover a range of scenarios depending, for example, on whether the patient is currently pregnant and whether they have already been exposed to a drug. Not all the questions may be appropriate to the clinical situation you are dealing with.

Nonetheless, here are some questions you should be thinking about in practice:



There's more detail on these questions and why they are important, on the next page.

The Medicine

- When did the medicine start and has it been stopped? *Don't just ask what trimester the medicine was taken in because it doesn't tell you about the duration of exposure. Was it started before pregnancy or during it? If it is to continue, how long will the medicine be taken for?*
- Indication, and is it working? *If treatment is to continue, you have to know the indication in case you need to recommend a safer alternative. You also need to balance the risk to the mother and the risk to the fetus. If the medicine is very effective and for a serious medical condition, then this may make you more inclined to continue with the treatment depending upon the risk to the fetus.*
- Medicines in previous pregnancies? *Has the woman taken the drug in question during a previous pregnancy, and was it effective? What other medication has the woman taken during previous pregnancies for any similar condition? Taking the same medicine in a previous pregnancy doesn't guarantee safety but is evidence of efficacy.*

The Mother and Fetus

- Is the woman planning a pregnancy or actually pregnant now? *Are you being asked for advice about prospective or retrospective exposure? You have scope to recommend a safer treatment from the beginning if the woman is not yet pregnant.*
- How many weeks pregnant is she now? *This will define the period of expected fetal exposure to the medicine, which is often crucial in determining safety.*
- Obstetric history? *Has the woman had any previous pregnancies and what were the outcomes? Is there a family history of malformations or history of recurrent miscarriage?*

Going Forward

- Can you consider alternative approaches to limit the exposure to this medicine?
 - *Is treatment essential? Can it be **delayed** until after delivery, or a safer period in the pregnancy?*
 - *Would **non-drug** alternatives be appropriate? They may carry less risk.*
 - *Are there medicines **with better evidence of safety** that can be used? Have any different medicines been tried, or could they be considered?*
- Have you planned for after delivery? *Plan early, if applicable. Will the newborn need to be monitored (for e.g. sedation, withdrawal effects) and who will do this? If mum intends to breastfeed, will the medicine be safe in this situation? If not, what should be done? (See [breastfeeding tutorial](#))*

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.

SPCs usually contraindicate or caution against drug use in pregnancy. **Manufacturers' medical information departments** may be able to offer more information particularly on very new drugs where published literature is often lacking.

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.



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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 and is available as a book and 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](#).

What do the clinical 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 via [NICE Evidence](#), limiting your search to 'guidance'.

If you need to search the literature then try **Embase** first followed by **Medline**; choose your terms carefully - ask for help if you are unsure.

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 website 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](#).