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Drugs in Pregnancy

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Many physicians, family doctors, and most pregnant women are under the misconception that most drugs are harmful in pregnancy. Many obstetricians also remain very cautious about the use of drugs in pregnancy. This caution stems from the tragic fetal malformations which occurred following the use of thalidomide for nausea, vomiting and hyperemesis in early pregnancy in the late 1950's and early 1960's Thalidomide use resulted in a number of fetal malformations, specifically phocomelia where limbs either do not develop at all, or are shortened and malformed. The drug was eventually banned from use in pregnant women in 1962.

The consequences of thalidomide were that drug companies did not license drugs for use in pregnancy unless they have been specifically studied and found to be safe. However, drug companies rarely do trials in pregnancy and hence most data on safety in pregnancy comes from case series, exposure registries and clinical trials. When a new drug is introduced to the market, in due course a number of women who take the medication will fall pregnant. There will be a proportion of these women who continue taking the new drug in pregnancy and this allows for review of any harmful sequelae of drug use. Various databases and exposure registries have been set up across the world including the UK Teratology Information Service which is updated regularly and provides important information on harmful effects of drugs used in pregnancy. There are valid concerns about the safety profile of a number of medications, but most commonly used drugs have good safety data and can continue to be taken in pregnancy.

There are several principles that it is wise to follow when prescribing drugs in pregnancy:

- No drug should be used in pregnancy without a reasonable indication
- The indication for using the drug in pregnancy and the benefit to the mother of its use should be balanced against any known harm to the fetus
- Use the smallest effective dose of any drug
- Switch agents if there is a similar drug with a better safety profile
- The first trimester is a period that warrants special consideration
- Known teratogens: there are a number of drugs known to have a risk of teratogenicity, however, the consequences of discontinuing them may be worse than the effects of taking it, justifying continuation of therapy (e.g. anti-epileptic drugs).
- Try to avoid using newly introduced medications - many important drug toxicities in pregnancy have only been picked up in post marketing surveillance. It is preferable to prescribe drugs which have been used for a number of years in pregnancy which appear to be safe
- Absence of information about a drug does not imply safety

Many women stop taking medications as soon as they realise they are pregnant. This risks a flare of their medical disease, which may cause harm to them and their babies. Interestingly they freely use herbal and homeopathy treatments with unknown side effects as they consider them to be natural and hence "safe". Women with medical diseases on drug treatment should have a discussion regarding the safety profile of the medications in pregnancy, ideally prior to conception.

Drugs which are known to cause harm may only do so at specific periods in pregnancy. These drugs should be avoided at those times, but may be used at a different stage in pregnancy when they may have no effect on the fetus.

- Pre-embryonic stage (0–14 days after conception): methotrexate, thalidomide, retinoids, misoprostol, mifepristone, can result in miscarriage. Misoprostol and mifepristone are both used as abortifactants, however, misoprostol is used in the third trimester to induce labour.
- Organogenesis (generally regarded as first trimester, until 10 weeks gestation): a number of drugs are teratogenic i.e. they affect organogenesis and result in congenital malformation. These drugs include antiepileptic drugs, angiotensin enzyme converting (ACE) inhibitors, retinoids, and warfarin.
- Growth and functional development (second and third trimester): some drugs can cause fetal growth restriction, affect functional development, neuropsychological behaviour (e.g. high-dose sodium valproate), have a toxic effect on fetal tissues (e.g. ACE inhibitors, tetracycline) or cause fetal bleeding (e.g. warfarin). The effects of some drugs are only apparent later on in life e.g. adenocarcinoma of the vagina after puberty in the

Table 1: Drug safety in pregnancy	
Drugs that can be used in pregnancy	**Drugs considered unsafe to use in pregnancy**
Analgesics (paracetamol, codeine, NSAIDs <32 weeks gestation, opiates)	NSAIDs >32 weeks gestation
Antiemetics e.g. cyclizine, promethazine, metoclopramide, prochlorperazine, ondansetron	Thalidomide
All antacids, H2 blockers and proton pump inhibitors	Warfarin*
Most laxatives e.g. lactulose, fybogel, senna	Codanthramer, paraffin
Antihistamines including chlorpheniramine, cetirizine, loratidine	Statins
NSAIDs under 32 weeks gestation	Cyclophosphamide
Oral antiglycaemic drugs e.g. metformin glargine	Methotrexate
Calcium channel blockers e.g. nifedipine, amlodipine	Mycophenolate mofetil
Beta blockers e.g. labetolol, propranolol, sotalol, bisoprolol	ACE inhibitors, angiotensin receptor blockers
Alpha blockers e.g. prazocin, doxazocin	Alendronate
Methyldopa, nitrates	Leflunamide
Most antidepressants (tricyclic antidepressants, SSRIs except prazocin)	Paroxetine
Most antibiotics: Penicillins, cephalosporins, metronidazole, gentamicin, rifampicin, macroglides	Tetracycline, doxycycline
Beta agonists	
Steroids: inhaled, oral, intravenous	
Hormones e.g. insulin, thyroxine	
Low dose aspirin	
Low molecular weight heparins	
Ursodeoxycholic acid	
Hydroxychloroquine, azathioprine, cyclosporin	
Sulfasalazine, 5 ASAs	
Intravenous immunoglobulin (IVIG)	
Some biologics** (etanercept, infliximab, rituximab, adalimumab, certolizumab, golimumab)	

*used in some circumstances e.g. two metal heart valves where maternal benefit outweighs fetal risk; **usually stopped in late 2nd to early 3rd trimester to prevent neonatal immunosuppression (must not have live vaccines for 6 months postnatal)

female when exposed to diethylstilbestrol whilst in-utero.

Table 1 shows the safety profile of various categories of drugs in pregnancy.

SPECIFIC DRUGS

Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non steroidal anti-inflammatory drugs (NSAIDs) can be used in pregnancy until approximately 32 weeks gestation. Use is avoided following this gestation as they can cause premature closure of the fetal ductus arteriosus. NSAID use may be required for women with migraines in pregnancy and for women with ankylosing spondilitis who do not respond well to other types of analgesia.

Beta Blockers

Beta blockers are commonly used in pregnancy for a variety of indications including hypertension (labetolol), migraine prophylaxis (propranolol), symptomatic control of tachycardia in thyrotoxicosis (propranolol), and a variety of cardiac conditions including mitral stenosis, dilated aortic root, coarctation of the aorta and arrhythmias (metoprolol, bisoprolol, sotalol and atenolol). Beta blockers have been shown to be associated with smaller babies, but this is from studies in women with hypertension who are prone to have fetal growth restriction due to hypertension irrespective of the antihypertensive agent they are on. Labetolol is recommended as the first line drug treatment for hypertension in pregnancy according to the National Institute for Heath and Care Excellence in the UK. Women on beta blockers are safe to breastfeed.

Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)

ACE inhibitors and ARBs are avoided in pregnancy at all gestations. First trimester use is associated with a doubling in the background risk of congenital malformations and second and third trimester use is associated with a

Table 2: Anti Xa levels for maintenance of effective anticoagulation with LMWH

Indication for therapeutic LMWH	Peak anti Xa level recommended (i.u./ml)
Venothromboembolism	0.6-0.9
Aortic metal valves	0.8-1.0
Mitral metal valves	1.0-1.2

reduction in development of nephrons leading to renal dysfunction and oligohydramnios and skull ossification defects. Pregnant women should be advised to stop ACE inhibitors and ARBs pre-conception. In some instances it is recommended to stop these treatments as soon as they fall pregnant so as not to spend an indefinite time off treatment whilst trying to conceive e.g. when they are used for the treatment of proteinuric nephropathy. ACE inhibitors can be used postnatally. The most studied drug is enalapril which is commonly used postpartum for the treatment of hypertension and cardiomyopathy.

Corticosteroids

Steroids in inhaled, oral and intravenous forms are commonly used for a variety of conditions in pregnancy. Only minimal amounts of the small inhaled steroid doses are absorbed into the systemic circulation. Prednisolone is metabolised into an inactive form by the placenta and only 10% crosses to the fetus. There are no adverse fetal effects from oral steroids and meta-analyses have shown that initial concerns regarding orofacial clefts are unsubstantiated in humans. Oral steroids are associated with maternal gestational diabetes which needs to be controlled with metformin or insulin. Women on steroids are safe to breastfeed.

Antiepileptic Drugs (AEDs)

Most antiepileptic drugs (AEDs) are associated with major congenital malformations (MCMs). The background risk of MCMs is 2-3%. With most of the antiepileptic drugs, this risk is increased to 4-6%. Combinations of AEDs have higher risks of MCMs. Levetiracetam appears to have very low rates of MCM (reported as less than background), followed by lamotrigine. The risk of MCMs is much higher with sodium valproate and increases significantly with the doses at 600mg/day, with the largest risk in doses over 1000 mg/day with MCM rates of 20.3% at this level. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) prospective study showed that offspring of women taking Sodium Valproate at any stage in pregnancy had lower IQs aged 6 years compared to children exposed to other AEDs, with a difference in IQ of 8-11 points. This effect is also dose related with worse IQ outcomes in women receiving higher doses of valproate. It is therefore recommended that women considering pregnancy be changed to a less harmful AED pre-pregnancy, such as levetiracetam or lamotrigine. Lamotrigine levels need to be checked regularly in pregnancy and the dose increased as metabolism can increase by 300% by the third trimester resulting in low blood levels. All women on AEDs should be prescribed 5mg folic acid to take preconception and for 3 months into the pregnancy to protect the fetus from neural tube defects. Women on AEDs are safe to breastfeed.

Anticoagulants

Indications for therapeutic anticoagulation in pregnancy include:

- Metal heart valves
- Atrial fibrillation
- Venothromboembolism (VTE) in pregnancy
- Multiple previous VTE with a highly thrombogenic thrombophilia

Low molecular weight heparin (LMWH) has largely replaced warfarin for anticoagulation in pregnancy. Warfarin is a teratogen causing chondrodysplasia punctate in 6% with exposure between 6-12 weeks gestation. It also crosses the placenta and anticoagulates the fetus which is therefore vulnerable to miscarriage, intracerebral bleeding and stillbirth. LMWH does not cross the placenta and is therefore safe to use for the fetus. Dosing in pregnancy differs from outwith pregnancy and depends on the agent used e.g. enoxaparin dose is 1 mg/kg bd antenatally changing to 1.5 mg/kg od postnatally. Doses should be adjusted to maintain peak anti Xa levels (4 hours post dose and measured monthly) at the levels shown in Table 2.

LMWH it is not as good an anticoagulant as warfarin: there are more cases of metal valve thrombosis occurring with LMWH compared to warfarin. This is primarily due to suboptimal anticoagulation and non-adherence to the advised anti-Xa levels. Women with metal heart valves should also be on aspirin 75 mg daily. Those with two metal valves or a highly thrombogenic metal valve in the mitral position should remain on warfarin in pregnancy, converting to therapeutic LMWH or unfractionated heparin close to delivery. Warfarin should also be used in women who have had venothromboembolism despite treatment doses of low molecular weight heparin (LMWH). Women on LMWH and warfarin are safe to breastfeed.

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