Drugs in pregnancy

GPs are likely to be the first point of contact for advice about safety or otherwise of drugs during pregnancy. Some medications appear to be safer for use in pregnancy than others but this aspect has to be considered alongside their relative effectiveness.

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One legacy of the thalidomide tragedy 40 years ago is the general perception that all drug, chemical and environmental (xenobiotic) exposures during early pregnancy are potentially harmful to the fetus. In reality, there are relatively few proven human teratogens and an increasing number of agents are being shown to be safe for use during human pregnancy.

More than half of all pregnancies are unplanned and thus many women may be exposed to various agents that can have harmful effects on the fetus during the critical first few weeks of gestation before they know that they are pregnant. These agents include prescribed and over-the-counter medications, alcohol, cigarettes, illicit drugs, herbal preparations, radiation, occupational chemicals and infectious agents.

Women with chronic illnesses such as epilepsy, inflammatory bowel disease, autoimmune disorders and depression are now able to contemplate pregnancy because of improved medical management of the underlying disease. Such women may be counselled, often on spurious grounds, to cease necessary medications because of perceived risks of the medications to the fetus, without consideration of the mother's own medical needs and the often greater risks to the mother's health in ceasing treatment. These women require up-to-date information and balanced counselling about the safety of their medications during pregnancy and lactation.

This article considers the basic principles regarding the use of drugs in pregnancy and outlines some of the important issues that need to be addressed when counselling women about the risks of exposures during pregnancy.

IN SUMMARY

- **Contrary to popular belief, there are relatively few proven human teratogens. Increasing numbers of prescribed medications are being shown to be safe for use during pregnancy.**
- **The risk of adverse pregnancy outcomes related to an exposure to drugs, chemicals and other environmental agents during pregnancy must always be given in the context of the background risk of major malformations (3% of live births) and the risk of spontaneous miscarriage (15% of recognised pregnancies).**
- **The Australian Drug Evaluation Committee's categorisation of risk of drug use in pregnancy is useful as a guide for doctors but should not be regarded as definitive. In some situations the risks and benefits to both mother and fetus of using a particular drug in pregnancy must be weighed up and appropriate counselling given.**
- **There are some drugs that appear to be safer than others for use in pregnancy. In general, the lowest effective dose of a single agent should be used, and older 'tried and true' rather than newer drugs should be used if clinically appropriate.**
- **Ideally, women should be counselled about chronic medication use prior to pregnancy and drug regimens optimised at this time. Other important issues such as folic acid supplementation and rubella immune status, as well as general health and lifestyle modifications, should also be discussed and implemented before conception.**

Agents with fetal effects

Teratogens

Agents introduced during pregnancy that interfere with the development of the fetus such that they induce or increase the incidence of congenital structural malformations are called teratogens. The word teratogen is derived from the Greek word *teratos*, meaning monster. Not all teratogens are drugs; some illnesses are teratogenic and one of the earliest known of these was rubella, congenital rubella syndrome first being recognised by Sir Norman Gregg at the Royal Alexandra Hospital for Children in Sydney in 1941. Various drugs and other agents that have been shown to have teratogenic effects are listed in Table 1.[1]

Developmental teratogens

Developmental teratogens, also known as hadegens, interfere with the maturation and development of the fetus, resulting in functional impairments such as deafness, visual loss or neurodevelopmental delay, without obvious structural abnormalities. The word hadegen is derived from Hades, god of the underworld, and possessor of a helmet of invisibility – the defects caused by hadegens are less visible than the structural defects caused by other teratogens.

Alcohol, phenytoin and sodium valproate are examples of agents that can have hadegenic effects.

Fetotoxic agents

Some agents induce growth restriction and death of the fetus without malformations and are regarded as fetotoxic (or embryotoxic) rather than teratogenic. In many instances these toxic effects are due to the drug's recognised pharmacological actions. Examples include NSAIDs in the third trimester and ACE inhibitors in the second and third trimesters.

Multiple effects

A given agent or disease state may have different harmful effects, depending when in pregnancy the exposure occurs. For example, rubella is teratogenic, hadegenic and fetotoxic in the first trimester, but after 16 weeks of pregnancy is only hadegenic.

Determining drug safety in pregnancy

When a new medication comes onto the market there are always concerns about its use in pregnancy and the possibility of teratogenic effects. Methodological and ethical difficulties in testing new drugs in pregnant women mean that information about possible adverse effects must be gained from other sources, including animal studies (although data from these cannot be extrapolated to humans), as well as from case reports and epidemiological studies following use in human pregnancy. It is difficult to categorically 'prove' that an agent is a true human teratogen,

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Figure 1. A GP is often the first person to be asked about the safety or otherwise of drugs during pregnancy and lactation.

Table 1. Examples of human teratogens

Drugs[1]	Other teratogenic agents and disease states
Aminopterin (not available in Australia)	Alcohol
Androgens	Cocaine
Busulfan	Cytomegalovirus
Carbamazepine	Hyperthermia
Cyclophosphamide	Hypothyroidism/iodine deficiency
Diethylstilboestrol	Maternal diabetes
Isotretinoin	Maternal phenylketonuria
Lithium	Methyl mercury
Methotrexate	Radiation
Misoprostol	Rubella
Phenytoin	Syphilis
Tetracyclines	Toxoplasmosis
Thalidomide (limited indication in Australia)	Varicella
Troxidone (not available in Australia)	
Sodium valproate	
Warfarin	

Categorisation of risk of drug use in pregnancy

The Medicines in Pregnancy Working Party of the Australian Drug Evaluation Committee (ADEC) has classified drugs with regard to their safety in pregnancy according to the categories listed below.[2]

Category A

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Category C

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Category B1

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.

Category B2

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased incidence of fetal damage.

Category B3

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Category D

Drugs which have caused, are suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

Category X

Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Note

For drugs in the B1, B2 and B3 categories, human data are lacking or inadequate and subcategorisation is therefore based on available animal data. The allocation of a B category does not imply greater safety than the C category. Drugs in category D are not absolutely contraindicated in pregnancy (e.g. anticonvulsants). Moreover, in some cases the D category has been assigned on the basis of 'suspicion'.

and no single approach can definitively establish the safety or otherwise of drugs in human pregnancy.

Categorisation of drugs

In Australia, drugs are classified with regard to their safety in pregnancy by the Medicines in Pregnancy Working Party of the Australian Drug Evaluation Committee (ADEC). The drugs are categorised on the basis of critical evaluation of the available data (both human and animal) by ADEC and a booklet is published every few years with updated information (see the box on this page).[2]

This categorisation is a useful guide for GPs and pharmacists but it is not always clearcut and therefore may need further interpretation to fully convey the balance of risks and benefits of taking or not taking a particular medication in pregnancy.

The booklet does not cover infectious or environmental agents, herbal preparations and street drugs, and information about these substances must be gained from other sources.

Counselling and perception of risk

In their role as primary care physicians, it is most often general practitioners who prescribe drugs for women of childbearing age and who are therefore the first people to be asked about the safety or otherwise of drugs during pregnancy and lactation.

It is important to ensure that women maintain adequate contraception to prevent pregnancy for the duration of therapy with major teratogenic agents such as isotretinoin and warfarin. Longer term contraceptive methods may be required (such as an IUD or Implanon Implant), rather than relying on standard methods.

The woman and her partner must be given the necessary information and counselled in a nondirective way so that they can understand the risks and make an informed decision based on the best

available data. Accurate information and sensitive counselling will, in most cases, alleviate fears and misconceptions, improve patient compliance and ultimately lead to improved management and obstetric and perinatal outcomes.

Differences between the man and the woman of a couple and between couples (ethnic, religious and other issues) can influence beliefs and decision making with regard to pregnancy and issues such as prenatal testing and termination of pregnancy.

Counselling with regard to the safety of drugs during pregnancy may take place before conception, during the pregnancy or retrospectively. Each situation requires a different approach.

Risk perception

A GP should ensure that a woman and her partner understand the concept of a baseline, or background, risk of having a miscarriage (up to 15% of recognised pregnancies) or a baby with a major malformation (approximately 3% of live births). For example, a risk of neural tube defect of 1% associated with maternal use of carbamazepine may appear high when quoted in isolation but seems more reasonable in the context of the baseline risk for congenital malformations of about 3%.

It is also important to note that very few teratogens have a 100% chance of causing abnormality in the fetus. In most cases, a couple's perceived risk of having a baby with a problem is far greater than their actual risk – which is usually not significantly greater than the baseline risk.

Counselling before pregnancy

Counselling before the woman becomes pregnant is the ideal situation and general practitioners are perfectly placed to perform this important role. For women with chronic medical conditions such counselling allows adjustment of their drug therapy and optimisation of their health status before pregnancy. Treatment of epilepsy is a good example as it may be possible to change medications to reduce fetal risks while still effectively controlling the mother's seizures.

Prepregnancy counselling also allows discussion about other aspects of general health and lifestyle, including smoking and the use of alcohol, street drugs, herbal preparations and natural remedies. The woman's occupation should be discussed as modification may be necessary to avoid occupational exposure to harmful agents.

A careful family history should be obtained so that a realistic risk estimate for any pregnancy can be given, including factors such as genetic risks and advanced maternal age in addition to the underlying medical condition and its treatment.

Counselling should include discussion about the benefits of folic acid supplementation before conception. Recommended doses of folic acid are 0.5 mg daily, or 5 mg daily for high risk women such as those taking carbamazepine or sodium valproate, or those with a previous pregnancy with a neural tube defect or a family history of the condition. Folic acid supplementation should begin when contraception is stopped.

Rubella serology should also be checked at the prepregnancy counselling visit. If the woman is not immune and requires immunisation, the recommendation is to wait three months after immunisation before trying to conceive. Varicella serology should also be checked in women with no history of chickenpox, and immunisation should be considered.

Counselling during pregnancy

Pregnant women tend to seek advice about past or ongoing exposure to drugs, chemicals or other environmental agents. The fact that exposure has already occurred often means that there is a high level of anxiety and some women may already have been counselled (often on the basis of misleading data) to terminate the pregnancy because of concerns about fetal safety. Despite the fact that there are relatively few proven human teratogens, many women will consider terminating otherwise wanted pregnancies for this reason.

A study from Canada has shown that women who sought counselling from a specialised medications in pregnancy service following exposure to known nonteratogens perceived before counselling that their risk of having a baby with a major malformation was around 25% (in the range of the risk associated with thalidomide exposure). Following counselling the women's perception of risk was considerably reduced, and most continued their pregnancies.[3]

Appropriate counselling and information can only be given after a thorough history has been obtained. This should include the dates of the last menstrual period and the exact timing and dosage of the exposure, as well as other potentially confounding risk factors such as the mother's underlying medical condition and her exposure to agents such as alcohol, street drugs, over-the-counter medications and herbal preparations.

Ultrasound is useful in accurately dating the pregnancy and in some cases may completely alleviate anxiety by demonstrating that exposure occurred either before pregnancy or during the 'all or none' or preimplantation period (during which exposure to teratogens is not believed to cause congenital malformation). In many cases a normal fetal morphology ultrasound scan at 18 weeks' gestation will also be reassuring. Follow up ultrasound studies may be indicated with agents such as NSAIDs because fetal effects may only become apparent in the second or third trimesters.

If appropriate, referral to services such as drug and alcohol services or to medical subspecialists should be arranged. In cases of new or rare exposures, the issue of follow up should be raised with the

continued

Table 2. Examples of drug choices during pregnancy[4]

Indication	Drugs of choice	Alternative drugs	Comments
Analgesia	Paracetamol Codeine	Aspirin NSAIDs	Aspirin and NSAIDs should be avoided in the third trimester
Anticoagulation	Low dose aspirin (Cardiprin 100, Cartia) Low molecular weight heparins: dalteparin (Fragmin), enoxaparin (Clexane)	Heparin Aspirin plus dipyridamole (Asasantin SR)	Warfarin should be avoided, particularly between weeks six and nine
Asthma	Inhaled beta agonists Corticosteroids Sodium cromoglycate (Cromese Sterinebs, Intal, Opticrom, Rynacrom)	Systemic corticosteroids Theophylline (Nuelin)	
Constipation	Stool softeners and osmotic agents like glycerin, lactulose (Actilax, Duphalac, Genlac, Lac-Dol), sorbitol (Sorbilax)	Gastrointestinal stimulants should only be used as second-line treatment	
Depression	Tricyclic antidepressants Fluoxetine	Newer SSRIs – paroxetine (Aropax, Paxtine), sertraline (Zoloft), fluvoxamine (Faverin, Luvox), citalopram (Cipramil, Talohexal) MAO inhibitors are probably safe but often poorly tolerated	Little information available about long term developmental outcomes with newer SSRI drugs
Infections (bacterial)	Penicillins Cephalosporins Erythromycin Nitrofurantoin (Furadantin, Macrodantin, Ralodantin)	Aminoglycosides Metronidazole (Flagyl, Metrogyl, Metronide, Rosex) Ciprofloxacin (CiloQuin, Ciloxan, Ciproxin)	Avoid tetracyclines after 16 weeks of pregnancy Avoid sulfonamides in the last trimester
Infections (fungal)	Nystatin – oral, topical, vaginal (Mycostatin, Nilstat) Miconazole – topical, vaginal (Daktarin Oral Gel, Fungo Powder and Solution, Leuko Fungex, Monistat) Clotrimazole – topical, vaginal Ketoconazole – topical (DaktaGOLD, Nizoral Cream)	Low dose fluconazole (Diflucan)	Best to avoid oral ketoconazole High dose fluconazole has been associated with birth defects
Nausea/ vomiting	Antiemetics, metoclopramide (Maxolon, Pramin), dimenhydrinate (Dramamine), prochlorperazine (Stemetil, Stemzine), promethazine (Phenergan) Pyridoxine (vitamin B_6) Antihistamines including diphenhydramine (Nytol, Unisom Sleepgels), doxylamine (Dozile, Restavit)	Ondansetron (little information available)	
Pruritus	Topical moisturising creams, wet dressings, calamine lotion Corticosteroids – topical, systemic Systemic antihistamines	Topical local anaesthetic agents	
Hypertension	Methyldopa (Aldomet, Hydopa) Labetalol (Presolol, Trandate)	Other beta blockers Prazosin Hydralazine (Alphapress, Apresoline) Calcium channel blockers also appear to be safe (most studies are on older drugs like nifedipine and verapamil)	ACE inhibitors should be avoided, particularly after the first trimester because of risks of fetal renal impairment

mother so that prospective pregnancy outcome data may be obtained.

Retrospective counselling

Retrospective evaluation after an adverse pregnancy outcome leads to a different form of risk assessment and counselling. If an association between the exposure in question and the abnormality is plausible, then it is important to also look for other likely causes. A clinical geneticist should be consulted because many more congenital malformations occur due to genetic and chromosomal causes than to exposure to teratogens.

Drugs of choice in pregnancy

Some medications appear to be safer for use in pregnancy than others. In general, the following principles should guide the selection of appropriate drugs for the management of medical conditions during pregnancy:

- use the lowest effective dose
- avoid polytherapy where possible
- use older drugs rather than newer drugs
- avoid over-the-counter preparations where possible.

Although newer drugs may be safer and have fewer maternal side effects, their fetal safety is less likely to be known and, therefore, their use should not be recommended unless there is no therapeutic alternative. For example, there is far more evidence available about the fetal effects (including long term follow up) of fluoxetine than the newer SSRI drugs such as paroxetine and citalopram.

The benefits of using certain agents must always be weighed up against the risks of using other possibly 'less safe' medications – if the 'safer' drug is not efficacious then there is no point in switching a woman to this drug even if it is perceived as being 'safer in pregnancy'. This is particularly relevant in treating conditions such as epilepsy and depression.

Some examples of drugs that I recommend for various conditions during pregnancy are given in Table 2.[4]

Obstetric drug information services

Over the past 15 years, most States and Provinces in North America and many European and other countries have established some form of service providing information on teratogens to address the increasing number of questions from patients and their healthcare providers about maternal exposures during pregnancy. Much useful prospective data regarding exposures and pregnancy outcome has been obtained from these services.

MotherSafe was established in January 2000 at the Royal Hospital for Women in Sydney to provide a designated drugs in pregnancy and lactation service for the women of NSW. MotherSafe provides access to telephone information and counselling for women in the whole State (see the box on this page for contact details). Face-to-face counselling services are available at the Royal Hospital for Women in Sydney and in major rural centres via an outreach counselling network for the approximately 5% of callers who require such services.

A multidisciplinary referral service means that subspecialists (such as psychiatrists, infectious disease physicians, drug and alcohol workers and pharmacologists) can be involved in counselling and follow up where appropriate.

In other Australian States and Territories, queries relating to exposures in pregnancy are generally handled over the telephone by the pharmacy departments of large obstetric hospitals in capital cities (see the box on this page for contact details). The services are available to doctors, other healthcare professionals, and, in most cases, the general public. MT

Obstetric drug information services in Australia

NSW
MotherSafe
Telephone: (02) 9382 6539 or
1800 647 848 (nonmetropolitan NSW)

ACT
Telephone: (02) 6244 3333

Victoria
Telephone: (03) 9344 2277 or
(03) 9594 2361

South Australia
Telephone: (08) 8204 7555

Queensland
Telephone: (07) 3253 7300

Western Australia
Telephone: (08) 9340 2723

Tasmania
Telephone: (03) 6238 8737

Northern Territory
Telephone: (08) 8922 8424

References

1. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation. 5th ed. Baltimore: Williams & Wilkins, 1998.
2. Australian Drug Evaluation Committee (Therapeutic Goods Administration). Prescribing medicines in pregnancy. An Australian categorisation of risk of drug use in pregnancy. 4th ed. Canberra: AusInfo, 1999.
3. Koren G, Bologa M, Long D, Feldman Y, Shear NH. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. Am J Obstet Gynecol 1989; 160: 1190-1194.
4. Smith J, Taddio A, Koren G. Drugs of choice for pregnant women. In: Koren G, ed. Maternal–fetal toxicology: a clinician's guide. 2nd ed. New York: Marcel Dekker, 1994: 115-128.

Further reading

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