MEDICAL PRACTICE

Prescribing in Pregnancy

General principles

PETER C RUBIN

Understanding of the multifaceted issues concerned in the use of drugs during pregnancy has lagged far behind the development of knowledge in other areas of therapeutics. This is partly because "thalidomide's long shadow" has slowed research that entails giving a drug to a pregnant woman.[1] A further reason is undoubtedly the difficulties (often more imagined than real) in performing interdisciplinary research. None the less, progress is being made, and several monographs on the clinical pharmacology of pregnancy have recently been published.[2-6]

This series is aimed at practising clinicians who prescribe drugs for women who are, or who may become, pregnant. The emphasis is on the clinically relevant aspects of research performed over the past 10 years or so. There are two introductory articles: one on clinical pharmacology relevant to human pregnancy and the other on identifying fetal abnormality. The series will then cover treatment during pregnancy of: minor ailments, bacterial infections, asthma, thromboembolic disease, psychiatric disorders, rheumatoid arthritis, cardiovascular disorders, endocrine diseases, and epilepsy.

Epidemiology of drug use during pregnancy

About 35% of women in the United Kingdom take drugs at least once during pregnancy, although only 6% take a drug during the first trimester.[7] This excludes iron and vitamin supplements and drugs used during delivery. The most commonly used drugs are non-narcotic analgesics, which are taken by 12·9% of women, antibacterial agents, taken by 10·3% of women, and antacids, taken by 7·4% of women. A recent study performed in The Netherlands produced similar findings: analgesics were taken by 12·3% of women, antibacterial agents by 11·6%, and antacids by 7·7%. Drugs such as anticonvulsants and bronchodilators, for which careful monitoring of dose is necessary, are each prescribed in about 1% of pregnancies.

Drug use during pregnancy has decreased considerably since the last major survey in the United Kingdom in the mid-1960s. Total use has fallen from just under 80% to 35%, while the percentage of women taking self administered drugs has fallen from 64% to 9%.[7] This may be due largely to the continued attention paid by the news media to drug induced fetal abnormality.[8]

In the puerperium the use of drugs increases substantially.[9,10] One study showed that more than 99% of women received at least one drug, often an analgesic, during the first week after delivery.[9] This study also found that hypnotics were used by 36% of women in the puerperium. There was no difference in the pattern of prescribing between mothers who were breast feeding and those who were bottle feeding.

Effect of pregnancy on dose requirements

The physiological changes of pregnancy can lead to clinically important reductions in the blood concentrations of certain drugs.

Total body water increases by as much as 8 litres during pregnancy,[11,12] which provides a substantially increased volume within which drugs can be distributed.

Serum proteins relevant to drug binding undergo considerable changes in concentration.[13] Albumin, which binds acidic drugs such as phenytoin, decreases in concentration by up to 10 g/l.[14] The main implication of this change is in the interpretation of drug concentrations, which is discussed below.

Liver metabolism increases during pregnancy,[15] but liver blood flow does not.[16] Drugs with a rate of elimination which depends on the activity of liver enzymes can show large increases in clearance during pregnancy. Phenytoin is cleared at twice the rate found in

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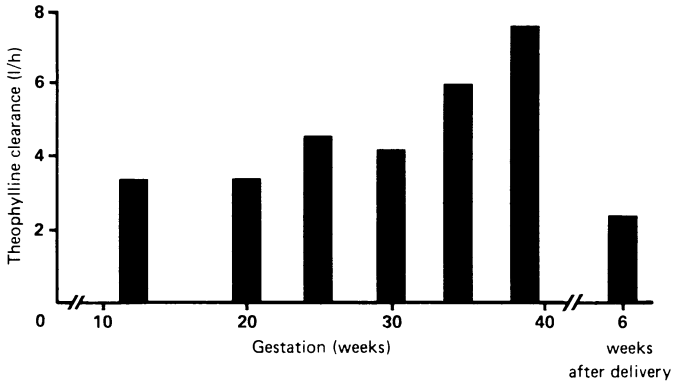
non-pregnant women,[17] and theophylline undergoes similar changes (figure). In contrast, drugs which are eliminated at a rate mainly dependent on liver blood flow, such as propranolol, show no change in clearance during pregnancy.[18]



Theophylline clearance calculated from steady state concentrations in a pregnant woman with asthma. Having been controlled before pregnancy on 250 mg every 12 hours, by the end of pregnancy this patient had subtherapeutic concentrations despite receiving 1500 mg/day.

Renal plasma flow has almost doubled by the last trimester of pregnancy.[19] Drugs which are eliminated unchanged by the kidney are usually eliminated more rapidly, but so far this has been shown to be clinically important in only a few cases. For example, ampicillin clearance doubles during pregnancy[20] and the dose used for systemic infections should be doubled. In urinary infections no change in dose is necessary.

The major consequence of these physiological changes is that some drugs—notably, anticonvulsants and theophylline derivatives—can undergo changes in distribution and elimination which lead to ineffective treatment because of inadequate drug concentrations in the blood.

Therapeutic drug monitoring during pregnancy

Among the drugs for which plasma concentrations would normally be measured those most likely to be encountered during pregnancy are anticonvulsants and theophylline derivatives. Because important changes in concentration may occur drug concentrations should be measured at monthly intervals throughout pregnancy and again one week and four weeks after delivery. The dose required usually increases as gestation progresses, particularly in the third trimester, and decreases in the puerperium. The increase may be large—for example, a patient who is normally well controlled taking 300 mg of phenytoin a day may require 600 mg a day by the end of pregnancy just to stay at the bottom of the therapeutic range.

Two points should be considered when interpreting drug concentrations during pregnancy.

Protein binding—The reduction in albumin concentration during pregnancy leads to a decrease in the measured concentrations of drugs which are highly bound, such as phenytoin. The increased amount of drug which is unbound will, however, be available for both distribution out of the blood and for elimination from the body. The net result of the change in albumin concentration on phenytoin is that the total level falls but the free level is virtually unchanged. Only the free (unbound) drug is pharmacologically active, and so if the laboratory gives drug concentrations as total drug the therapeutic range should be revised downwards. As a rule of thumb, the concentration of the drug should be kept at the bottom of the usual therapeutic range.

Therapeutic range—It is not clear whether pregnancy alters the effects of drugs. This is an important matter, but one which is difficult to study. Apart from the pharmacokinetic considerations detailed above, it is possible that established therapeutic ranges might be inappropriate during pregnancy because of changes in the relation between drug concentration and effect.

Passage of drugs to the fetus

Much of the published work on the transfer of drugs across the placenta is concerned with the rate of transfer, but except in the context of single doses—for example, at the time of delivery—this is not the major issue. The placenta is essentially a lipid barrier between the maternal and fetal circulations. Drugs cross the placenta by passive diffusion. A lipid soluble, un-ionised drug of low molecular weight will cross the placenta more rapidly than a more polar drug. Given time, however, most drugs will achieve roughly equal concentrations on each side of the placenta. For example, after a single dose of indomethacin the ratio of cord to maternal plasma concentration is 0·5:1 at two hours but 1:1 at five hours.[21] A similar example is provided by the β blockers. Researchers thought that a polar drug like atenolol might have limited transfer to the fetus, but on long term dosing this was found not to be the case.[22] Thus the practical view to take when prescribing drugs during pregnancy is that transfer of drugs to the fetus is inevitable. The only notable exception to this rule is heparin, which is so large and so polar that its transfer across the placenta is negligible.

Breast feeding

As with the transfer of drugs across the placenta, much has been written on the theoretical aspects of passage of drugs into breast milk, but the relevance of these publications is equally doubtful. Virtually all drugs cross into breast milk. Previous dilution in the mother's body, however, coupled with the volume of milk consumed usually mean that the dose administered to the baby is clinically unimportant.

There are three main categories of drugs so far as breast feeding is concerned.

(1) Drugs which are undetectable in the baby. These include warfarin, which is so highly bound to maternal proteins that it is undetectable even in breast milk,[23] and aminoglycosides, which are not absorbed from the gastrointestinal tract of normal infants.[24]

(2) Drugs which reach the baby but in an insignificant dose. These include most drugs used in everyday practice: non-narcotic analgesics,[25] non-steroidal anti-inflammatory drugs,[26] penicillin and cephalosporin antibiotics,[27] antihypertensive drugs,[28] bronchodilator inhalers, and anticonvulsants (with the exception of barbiturates).[29] Special mention should be made here of two drugs which often feature in consultation requests to this department. Firstly, oral contraceptives containing low doses of oestrogen do not suppress established lactation and are not harmful to the baby. Secondly, metronidazole appears to be safe for the baby but causes the milk to have a bitter taste, which may impair feeding.

(3) Drugs which reach the baby in sufficient dose to be harmful. These are listed in the table.

Conclusion

The use of drugs during pregnancy and in the puerperium requires that a fine balance should be maintained. No harm should be allowed to befall the baby because of the drug, but equally no

Commonly used drugs which are contraindicated in women who are breast feeding

Laxatives	Lithium
Amiodarone	Opiates
Ephedrine and pseudoephedrine	Carbimazole
Barbiturates	Iodine (propylthiouracil seems to be safe)
Benzodiazepines	Cytotoxics and immunosuppressant drugs
Bromide salts	

harm must come to the mother or baby because a disease is being inadequately treated. The aim of this series is to provide the information on which a clinical decision can be made.

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Personal Paper

Observations on the management of mood in a neurological hospital

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I present my interpretation of aspects of organisation observed during a period as an inpatient, initially in a general hospital but for the most part in a specialist neurological unit, in which some seven weeks were spent in the men's surgical ward interrupted by a brief spell in the intensive care unit. My condition was diagnosed as myelitis, a disease of the spinal cord that causes paralysis and which in my case affected my legs and all functions below the ribs. It gets worse before it gets better, and though recovery was always in prospect, the medical staff were unable or unwilling to predict its rate or degree. All that was certain was that my stay in hospital would be a matter of weeks if not months, and I therefore sought a sociological theme as a way of passing the time.

In a study of religious behaviour I had incurred the wrath of fellow sociologists for my use of covert methods of observation, so I was keen to secure the informed consent of all those whom I observed in the hospital. Even as I lay in intensive care I recalled between moments of self pity that one of my severest critics had been the medical sociologist Robert Dingwall, in whose stamping ground I was now reposing.[1] Accordingly, I made my research purpose explicit at all times, was ostentatious in note taking and questioning, wrote this paper in the hospital, and circulated copies of it within the hospital before submitting it for publication.

In this account I consider mood management under three headings. Morale refers to the attitude of patients towards their condition and the likelihood of recovery. The treatment of dignity refers to a tension between the cure of the body and respect for the person within it. (Other patient observers[2,3] have complained of depersonalisation or dehumanisation, and I have taken the opportunity to reassess this process.) The section on discontent examines the satisfaction of patients as consumers, whether of goods, such as food, or of services, such as the responses of nurses to patients' calls.

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Morale

My medical mentor believed that neurology was inherently less "gloomy" than other branches of medicine, such as chest medicine. The expectation of recovery was supported not only by the vague notions of statistics with which patients cheered themselves but in the systematic practice and policy of the nursing and medical staff.

My bed was in a bay of five which were reserved for patients who were likely to need closer attention than others. The bay adjoined the day room where ambulant patients came for their meals, received their guests, and watched television. While still obliged to lie in bed for my meals, therefore, I was able to observe the celebration of recovery and the daily improvement of those who had been more severely affected than I. The sequence from bed rest to sitting up to wheelchair to walking frame to crutches to sticks was a recognised progression, as were the exercises prescribed by the physiotherapist. I could see new patients going through the motions by which I had been introduced as well as more progressed patients practising the skills that I would rehearse. The visibility of recovery is important to patients receiving treatment for myelitis and related conditions such as the Guillain-Barré syndrome[4]; it affirms the doctors' assurance that deterioration is a normal first stage and that tangible improvement will follow.

Confidence in one's doctors and in the prognosis of improvement is enhanced rather than diminished by a full appraisal of possible consequences. My recovery, I was told, might take two years; that seemed a long