Prescribing in Pregnancy

Identifying abnormalities

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Drugs taken during pregnancy create concern whether they are self administered or medically prescribed. The number of mothers who take drugs during pregnancy is not known, but a survey in the United States showed that about 45% of women may use at least one drug on prescription, and many more use drugs bought over the counter.¹ A recent prospective study in the United Kingdom, however, suggested that only about 10% of women took drugs in early pregnancy.²

Defects occur in about 2% to 3% of babies at birth, of which about 25% are of genetic origin and 65% are of unknown aetiology. Only 2% to 3% of defects are thought to arise in association with drug treatment.³ The effect of a particular drug on the developing fetus depends on several features, including the type of agent and the gestational age at which it was taken.

The aim of this article is to provide a guide for doctors treating pregnant women who have taken, or who are currently taking, drugs. Advice depends on the following: (a) knowledge of the timing of embryonic and fetal development because preparations taken outside the critical phases are unlikely to be teratogenic; (b) the precise nature of the drug so that the teratogenic effect may be determined (table); and (c) whether the teratogenic effect is likely to be sufficiently apparent to make prenatal diagnosis feasible.

Teratogenic effects of drugs

Drug	Effect	Incidence	Prenatal diagnosis
Lithium	Cardiac defects (Ebstein's complex)	10-12%	Feasible
	Chondrodysplasia punctata		
	Facial anomalies	5%	Unlikely
	Severe anomalies of the central nervous system		
Phenytoin	Craniofacial	30%	Feasible
	Limb		
	Growth deficiencies		
	Facial clefting		
Primidone and phenobarbitone	Cardiac anomalies	Unknown	Feasible
Sodium valproate	Central nervous system	2-3%	Feasible
Sex hormones	Cardiac defects	Unknown	Feasible
	Multiple anomalies		

Timing of embryonic and fetal development

Several important phases in human development are recognised (fig 1).

During the pre-embryonic phase, from conception until 17 days, implantation, blastocyst formation, and gastrulation take place.

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During this time the result of an insult to the developing organism is either death and abortion (or resorption) or survival intact through multiplication of the still totipotent cells to replace those which have been lost.

FIG 1—Timing of embryonic and fetal development.

Embryonic development, from 18 to 55 days after conception, is when the basic steps in organogenesis occur. This is the period of maximum sensitivity since not only are tissues differentiating rapidly but damage to them becomes irreparable. The earlier in this period the insult occurs the greater the likely effect.

During the fetal phase, from 56 days to term, the effects of drugs are usually limited to defects of growth and functional loss rather than gross structural abnormalities.

Drugs and their teratogenic effects

Extensive reviews on the teratogenic effects of drugs have recently been published.^{4,5} The teratogenicity of some more commonly used drugs is briefly described here and covered more comprehensively in later articles.

ANTIBIOTICS

Commonly used drugs, such as penicillins and cephalosporins, do not appear to be teratogenic.⁵ In the case of antituberculous drugs ethambutol and isoniazid have a good safety record. Streptomycin causes deafness. Rifampicin, which causes neural tube defects and facial clefting in mice is associated with a human fetal abnormality rate two to three times higher than ethambutol or isoniazid⁶ and should be avoided if possible in the first trimester. Ethionamide has been associated with exomphalos and exencephaly and should also be avoided.

PSYCHOTROPICS DRUGS

The benzodiazepines have been incriminated in the formation of oral clefts, though their teratogenicity has been disputed.⁷ Tricyclic antidepressants and phenothiazines are not associated with fetal abnormality.⁵

Lithium, which is used in the treatment of affective disorders, is associated with an incidence of fetal abnormality of about 12%.⁸ The cardiovascular system is more often affected with coarctation, patent ductus arteriosus, and mitral and tricuspid atresias being reported. The rare condition of Ebstein's anomaly, in which the tricuspid valve is distorted and displaced, occurred in a third of the affected babies and overall is about 500 times more common in the babies of women who take lithium.

ANTICOAGULANTS

Oral anticoagulants have been recognised as teratogens for several years⁹ and are associated with three main types of abnormality.¹⁰ Firstly, the abortion rate is increased by up to 50%. Secondly, anticoagulants can cause a well defined embryopathy, which includes bone stippling (chondrodysplasia punctata) and nasal hypoplasia. Both of these abnormalities occur more commonly, though not exclusively, with treatment during the first trimester. The overall incidence of the embryopathy is about 5%. Finally, there is a risk of serious abnormalities of the central nervous system, thought to result from dorsal midline dysplasia, which include absence of the corpus callosum, Dandy-Walker syndrome, and encephaloceles.

ANTICONSULSANTS

A twofold to fourfold increase in the incidence of malformations has been found among the babies of epileptic mothers. These include orofacial clefts and cardiac malformations (for example, septal defects), skeletal anomalies (talipes and hip dislocations), microcephaly, and neural tube defects.

The phenytoin syndrome, which occurs in up to 30% of exposed babies, comprises craniofacial abnormalities (depressed nasal ridge, hypertelorism, clefts), limb defects (hypoplasia of distal phalanges, digital thumb, hip dislocation), and intrauterine and postnatal growth deficiencies as well as neck and rib defects and umbilical hernias.¹²

Primidone and phenobarbitone may be teratogenic when combined with phenytoin,¹³ though the evidence for their teratogenicity when used alone is not strong. Both have been associated with facial clefting and cardiac defects.

Sodium valproate, introduced as a useful alternative to other anticonvulsants, seems to be an important teratogen and is particularly likely to produce neural tube defects, with an incidence of about 2.5%.¹⁴ It appears to cause spina bifida much more often than anencephaly the ratio being 5:1 with sodium valproate compared with a normal ratio of 1:25-2:25:1.

Carbamazepine does not appear to be teratogenic, although problems might arise when it is combined with other agents; it should therefore be used alone whenever possible.¹³

IMMUNOSUPPRESSIVE DRUGS

Pregnancy in women who have undergone renal transplantation and who are taking drugs such as azathioprine and prednisolone is becoming increasingly common. Studies on patients with ulcerative colitis and Crohn's disease, however, show little evidence that either agent is teratogenic in humans.¹⁵

SEX HORMONES

Hormone preparations taken in early pregnancy include the oral contraceptive pill and those used in threatened abortion and, unusually now, the hormone pregnancy test. Despite numerous studies, the teratogenic effects of hormones remain uncertain. Three main groups of abnormalities may occur: limb reductions; cardiac defects, especially transposition of the great vessels; and central nervous system defects such as hydrocephaly and neural tube lesions. The constellation of disorders termed VACTERAL (vertebral, anal atresia, cardiac, tracheo-oesophageal atresia, renal and limb defects) has been significantly associated with ingestion of hormones in early pregnancy in some studies.¹⁶

Management of pregnancy and potential teratogenesis

Teratogenesis concerns two main groups of patients: women already taking drugs for a chronic underlying illness and those who have taken a single course of treatment unaware of an early pregnancy. Undoubtedly, women in the former group should be counselled before their pregnancy so that they are fully aware of the risks of teratogenesis and how the risk of fetal malformation may be reduced. Such an approach demands close cooperation between physicians, general practitioners, and the prenatal diagnostic team. Regrettably, all too often the patient first presents in pregnancy. Under these circumstances we suggest the following scheme, which aims to establish accurately gestational age at the time of exposure to the drugs and the potential of prenatal diagnosis (fig 2).

HISTORY

Menstruation—A careful record of the recent dates of periods and the menstrual cycle should always be sought. Gestational age is more likely to be correct if the first day of the last period has been noted and the preceding cycles were regular (every 28 days), although even then up to 15% of calculations will be wrong by 14 days or more.¹⁷

Conception—It is always worth inquiring whether the woman knows when conception occurred; occasionally, remarkably accurate calculations are made.

Treatment—Once the gestational age has been established the exact time of exposure to the drugs must be determined. This may require a review of the patient's notes either from the general practitioner or the hospital. Careful identification of the drugs taken is vital, not just by group—"I think it was something for my nerves"—but by name. The possibility that more than one drug was taken should also be considered. The patient may forget to mention the most important drug, and taking several drugs together may result in a higher incidence of teratogenesis. Patients should also be asked about self medication as they may report only medically prescribed preparations.

Other medical conditions—Conditions such as epilepsy or diabetes increase the background incidence of fetal anomaly and this should be taken into account when assessing possible effects of drugs.

INVESTIGATION

Establishing gestational age

Accurate estimation of gestational age is essential. Although a good history will help, dating by ultrasound scanning using fetal

FIG 2—Outline of procedure to follow in cases of drug use in pregnancy.

crown-rump length or, between 12 and 20 weeks, the biparietal diameter should allow the dates to be calculated to within about a week. With these data the exact stage in pregnancy at which treatment was given can be established. Quite often it can be shown that the mother was either not even pregnant at the time of exposure or had passed the time at which teratogenesis would be likely to occur.

Prenatal diagnosis

If drugs were taken at a critical gestational age the most effective method of excluding fetal anomaly is by high resolution ultrasound scanning. In optimal conditions this provides extraordinarily good images of the fetal brain and spine, the heart, the arms, legs, and hands, and the face (fig 3).

Fetal anomalies associated with teratogens may be broadly grouped into: defects of the central nervous system, cardiovascular system, and arms and legs; facial clefting; and multisystem defects. Most structural anomalies should be detectable by about 20 to 22 weeks, although this depends on several different factors, and it is not possible to provide exact rates of detection.

Central nervous system—One of the commonest indications for ultrasound examination in pregnancy is to exclude neural tube defects. Anencephaly can usually be identified about 12 weeks after the last period, but spina bifida is often more subtle and is best detected at 16 to 18 weeks. The predictive ability of ultrasound examination depends on good equipment, a high level of training, good fetal position, and a mother who is not excessively obese. In one series of neural tube defects all cases of anencephaly were

FIG 3—Ultrasound scans of (a) fetal brain (me=midline echo, bs=brain stem, c=cerebellum); (b) fetal spine (s); (c) fetal heart, showing the four chambers (rv=right ventricle, lv=left ventricle, ivs=intraventricular septum, fo=foramen ovale); (d) fetal hand (h=hand, t=thumb); (e) fetal face (e=eyelid, p=philtrum, h=hand); and (f) leg (t=tibia, fi=fibula, f=foot).

detected as well as 96 of 102 cases of spina bifida. In two cases spina bifida was wrongly diagnosed.¹⁸

The value of measuring maternal serum α fetoprotein concentration and performing amniocentesis is debatable in patients already referred for a detailed scan, when a lesion would be unlikely to be missed. If fetal views are poor, however, amniocentesis would be indicated in the presence of increased serum α fetoprotein concentrations. The high incidence of spina bifida in the babies of patients taking sodium valproate would certainly indicate the need for amniocentesis if views were unsatisfactory.¹⁹

Cardiovascular system—Fetal cardiology is a relatively recent development reflecting the vast improvements in the quality of imaging. Most serious heart defects, particularly those of connection, should be detectable by 16 to 18 weeks.²⁰ The basic requirement in cardiac scanning is to obtain a four chamber view, which, if normal, will exclude many important abnormalities. Gross defects, such as Ebstein's complex associated with lithium, have been detected by scan.²¹

Deformities of the arms and legs—Although it is relatively easy to measure the fetal limbs, abnormalities of growth may not become apparent until later in pregnancy.²² Gross deformities of the type associated with thalidomide should, however, be detected by 16 weeks. Abnormalities of the hands and even equinus deformities of the feet may well be seen given optimal conditions.

Facial clefting—This appears to be a common feature of teratogenesis, and, although not usually in itself an indication for terminating pregnancy, the display of normality may be some comfort to anxious parents. Fig 3e shows the clarity with which the fetal face can be seen.

Multiple anomalies—This group of anomalies can often be detected early in pregnancy and usually by 16 weeks. In the VACTERAL complex features of the arms, legs, kidneys, and heart should be detectable by 18 to 20 weeks. Vertebral defects may be seen earlier, but tracheo-oesophageal fistula and anal atresia may not be diagnosed until delivery.

Conclusions

The exact role of drugs in producing fetal abnormalities remains

uncertain, and some apparently unexplained fetal anomalies may be the result of a forgotten toxic insult. We hope that this article will be a useful guide to practitioners consulted about possible teratogenesis. In general terms we recommend the formation of a team, comprising a clinical pharmacologist and members of a prenatal diagnostic unit, which could provide rapid and effective advice.

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Medicine and the Media

MILLIONS OF viewers will be following Dennis Potter's new television serial *The Singing Detective* (BBC 1, Sunday evenings). It has already stimulated predictably enthusiastic reviews in the "quality" papers and equally predictable puzzlement and dismay in the popular press. What it has also done is to provoke considerable anxiety, even fear, among those who have the misfortune either to suffer from "ordinary" psoriasis or to have a close relative, especially a child, with the condition.

Potter's detective, Philip Marlow, is in hospital for the treatment of a particularly nasty acute attack of his psoriatic arthritis. His whole skin is inflamed, suppurating, breaking open, and fulminating. Temperature control is in consequence being lost. He finds it difficult to move, and his hands are close to useless. Marlow is all too evidently a very sick man. He is in a mess and looks it. The make up artists have made an excellent job of him, providing an all too accurate portrayal of psoriasis at its terrifying worst.

Potter himself has suffered from psoriatic arthritis for over 25 years and has referred to his experience of it in numerous interviews. He has, too, already put it into fictional form in visiting the disorder upon his character Daniel Miller in the novel *Hide and Seek*. His semiautobiographical endeavours can be contrasted in an

interesting way with those of the American novelist, John Updike. Updike introduced his own experience of psoriasis in the young man Cauldwell in his novel *The Centaur* and has brilliantly described and analysed the experience of psoriasis under treatment in two articles in the *New Yorker*, one of which was tellingly entitled "Journal of a leper."

Updike's writing deals with psoriasis as it afflicts the mass of chronic sufferers. It at once informs and expresses their understanding of what it is like to have an extensive chronic skin disorder and be subject to the treatments currently available for it, which can impose almost as many problems as they solve. Potter, however, deals with the even more bitter experience of psoriasis gone into one of its rarer complications. While psoriasis is common, psoriatic arthropathy affects only perhaps one in a thousand sufferers.

Having watched the first episode of *The Singing Detective* (16 November), hundreds of worried sufferers and parents have phoned the Psoriasis Association seeking information, advice, and reassurance. They have also pleaded that, "It should be stopped!"—an impossibility, of course. Many have responded with great alarm to the view expressed by doctors at Marlow's bedside—that his currently awful fate may well be iatrogenic—with the naming of