

with a beaming, knowing smile by a ward sister whom I recognised as having been one of Cecilia's favourite pupils. This time the Koplik's spots were there.

#### Single but not slighted

Cecilia was graded "nurse in charge," never "sister." Why? She had never sat any examinations—she was "too busy for that sort of nonsense"—but they could not upgrade her to sister—or so it seemed—without the examinations. Not for the first or last time various of her admirers petitioned the matron and superintendent and begged them to find a way round the regulations.

"There's no ward like ward 20," I argued. "I go in there at night to do my final ward round and every child is asleep. Where else in this hospital is that true?"

"Ah!" said the matron, "but have you ever really examined how much brandy you sign for?" Cecilia was never made "sister" but she was designated "nurse in charge" of various wards where nursing of babies was specially important. She had health problems but they were never allowed to hinder her work. I recall our farewell.

"You never married," I said to Cecilia.

"No," she answered, "I never had the notion or the time. I will go single to the grave; but you might like to know: I have not been neglected."

## Prescribing in Pregnancy

### Treatment of cardiovascular diseases

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Drugs required in pregnancy for cardiovascular disorders fall into two major categories: antiarrhythmic and antihypertensive agents. Antihypertensive agents have been widely used, and both controlled and uncontrolled trials have been performed with these drugs in pregnancy. Experience of their use in the first trimester is limited, however, so the absence of reports of malformation cannot be equated with safety. The rarity of cardiac arrhythmias during pregnancy means that most information is anecdotal or retrospective. Further information on the use of drugs for cardiovascular disorders during pregnancy is contained in recent detailed reviews.<sup>1,6</sup>

#### Antiarrhythmic drugs

The indications for starting antiarrhythmic treatment in pregnancy are the same as in non-obstetric practice. Most experience has been gained with digoxin, quinidine, and the  $\beta$  blockers.

#### DIGOXIN

There have been no reports of digoxin causing malformation. Digoxin crosses the human placenta, and toxic maternal concentrations can be fatal to the fetus. At therapeutic concentrations, however, digoxin does not appear to have an adverse effect on the fetus. There is some evidence that digoxin increases myometrial tone,<sup>7</sup> resulting in shorter pregnancy and labour.<sup>8</sup> Digoxin is found in human breast milk in concentrations similar to those in maternal

serum. Thus the daily dose to a breast fed infant may be about 1-2  $\mu$ g; one report showed no detectable digoxin in the infant's blood during breast feeding.<sup>9</sup> Digoxin is safe to use throughout pregnancy and the puerperium provided that maternal serum concentrations do not rise above the therapeutic range. Digoxin clearance by the kidney increases during pregnancy. If the dosage remains unchanged, by the end of pregnancy the serum concentration will have fallen to about half the value before pregnancy. It is therefore important to measure the digoxin concentration at intervals during and after pregnancy.

Digoxin is the drug of choice for control of atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia in pregnancy. Like all antiarrhythmic drugs it is indicated as a prophylactic agent only when the arrhythmia to be treated has been shown to be recurrent, sustained, and poorly tolerated.

#### QUINIDINE

Teratogenesis has not been reported with quinidine. At therapeutic concentrations it appears to be safe, and the drug has only mild oxytocic activity.<sup>10</sup> Some quinidine is found in human breast milk but at concentrations below those of maternal plasma. Quinidine is normally 80% protein bound. Changes in plasma protein concentrations during pregnancy cause total plasma quinidine concentrations to fall and free concentrations to be underestimated. This must be taken into account when interpreting drug monitoring data. After delivery total concentrations of quinidine increase by half.

Quinidine is the drug of choice for the treatment during pregnancy of premature extrasystoles, Wolff-Parkinson-White syndrome, and ventricular arrhythmias and for treatment after cardioversion of supraventricular tachycardia.

#### PROCAINAMIDE

Procainamide has not been associated with teratogenesis. The drug crosses the placenta but does not appear to have any adverse

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effects. In view of the association with the lupus syndrome procainamide should be reserved for patients who failed to respond to quinidine.

#### LIGNOCAINE

There is no evidence to suggest that lignocaine is teratogenic. Later in pregnancy moderate doses over short periods appear to be safe. Fetal blood concentrations are about half of the maternal values, and the fetus is capable of metabolising lignocaine by term. The use of lignocaine in the presence of fetal hypoxia may be dangerous, however, since ion trapping may cause concentration of lignocaine in the fetal circulation. No information is available on the effects of pregnancy on lignocaine disposition.

#### DISOPYRAMIDE

Disopyramide has not yet been widely studied in pregnancy. It crosses the placenta, resulting in fetal concentrations which are about 40% of the maternal values, and is also found in breast milk. One report suggested that it may cause uterine contractions.<sup>11</sup> Experience with this drug in pregnancy is too limited to draw conclusions about the effect of pregnancy on its disposition.

#### VERAPAMIL

There is little experience in the use of verapamil in pregnancy. One group reported no teratogenic or adverse effects in pregnancy.<sup>12</sup> It is known to cross the placenta, resulting in fetal concentrations about 40% of maternal values. The effects of pregnancy on verapamil disposition have not been described.

In summary, present experience is greatest with digoxin, quinidine, and lignocaine. Most arrhythmias occurring in pregnancy may be treated by one of these three drugs.

#### Antihypertensive drugs

Although the risks of maternal hypertension during pregnancy are clearly recognised, the benefits to the fetus of pharmacological intervention remain controversial. Results of controlled studies suggest that treatment of both chronic hypertension and pregnancy induced hypertension is beneficial to the fetus, but the size of these studies limits the ability to draw definitive conclusions.<sup>13 14</sup> Redman *et al* studied 247 women with chronic hypertension and reported nine miscarriages or perinatal deaths in their control group and only one in the treated group.<sup>13</sup> In a study of women who developed hypertension during pregnancy Rubin *et al* showed a reduction in both maternal blood pressure and neonatal morbidity in the treatment group compared with the control group.<sup>14</sup> Recommendations about the level of blood pressure which warrants treatment during pregnancy are controversial, particularly since blood pressure is normally expected to fall to a nadir in the mid-trimester. Our own, admittedly aggressive, policy is to treat chronic hypertension at a pressure above 140/90 mm Hg after the first trimester and to treat hypertension which develops during pregnancy if there has been a rise of 30 mm Hg systolic or 15 mm Hg diastolic above the values before pregnancy or during the first trimester.

#### FIRST LINE AGENTS IN MILD TO MODERATE HYPERTENSION

##### *Methyldopa*

Methyldopa has been used for many years in pregnancy, but there have been no reports of serious adverse effects on the fetus. It crosses the placenta and is found in the amniotic fluid. The largest reported study showed no adverse effect on the fetus,<sup>15</sup> and follow

up studies of the children for over seven years have confirmed the safety of the drug.<sup>15</sup> When given near term methyldopa was associated with a reduction in systolic blood pressure in neonates, but their stress response was normal.<sup>16</sup>

Methyldopa is effective in controlling chronic hypertension during pregnancy. It does not, however, reduce the incidence of superimposed pre-eclampsia. Although unwanted side effects (sedation, depression, and postural hypotension) may necessitate discontinuation of the drug in about 15% of women, its good safety record makes methyldopa the drug of choice in treating chronic hypertension in pregnancy.

##### *β Blockers*

There is no evidence of a teratogenic effect of β blockers. There have been a few reports of fetal abnormality, but these must be viewed in the light of the background incidence of deformities.

Several studies have assessed the effects of β blockers later in pregnancy. All of these drugs cross the placenta, producing fetal concentrations similar to those in maternal plasma. There was initially some concern that propranolol might inhibit fetal growth, but subsequent studies suggest that growth is at most only slightly retarded.<sup>14 17-21</sup> Some reports have implicated propranolol in the reduction of fetal heart rate variability, an effect not confirmed with atenolol. Various β blockers have been linked with serious neonatal morbidity, particularly hypotension and hypoglycaemia. These anecdotal observations have not been confirmed by placebo controlled prospective trials with atenolol<sup>14</sup> or metoprolol,<sup>22</sup> however, and almost certainly reflect the complications of the disease rather than the actions of the drugs.

All of the β blockers are found in breast milk in varying concentrations, but the dose to the neonate is clinically insignificant. Pregnancy has no clinically important effects on the disposition of β blockers.

Good blood pressure control has been achieved with metoprolol, oxprenolol, labetalol, atenolol, acebutolol, and propranolol in both chronic hypertension and pregnancy induced hypertension. There is little to choose between the various β blockers.

Both β blockers and methyldopa are effective antihypertensive agents. Comparative studies have shown little difference between them in the outcome of pregnancy.<sup>17 23-25</sup> A β blocker may be better tolerated by the mother, but methyldopa has the advantage of a reassuring long term follow up for the infant.

#### SECOND LINE AGENTS IN MODERATE TO SEVERE HYPERTENSION

##### *Hydralazine*

Hydralazine has not been widely used in the first trimester. Blood pressure is lowered without any reduction in uteroplacental blood flow.<sup>26</sup>

It is known to cross the placenta, but the only recorded problem in neonates exposed to hydralazine during late pregnancy has been occasional thrombocytopenia,<sup>27</sup> which may take up to three weeks to reverse. Only low concentrations of hydralazine are found in breast milk. It is not known whether pregnancy alters the disposition of hydralazine.

Except in the acute management of hypertensive emergencies, when it is given parenterally, hydralazine should be given as second line treatment to poorly controlled patients after failure to respond to methyldopa or a β blocker.

##### *Prazosin*

There have been no reports of teratogenesis with prazosin, and the available evidence suggests that it is safe later in pregnancy. Satisfactory control of blood pressure and fetal growth were recorded in 25 patients with pregnancy induced hypertension

treated with prazosin combined with oxprenolol.<sup>28</sup> Small doses are usually sufficient.

### Diuretics

Diuretics are widely used in non-obstetric practice for controlling hypertension and treating cardiac failure. The use of loop diuretics in pregnancy for treatment of cardiac failure appears to be safe, and a recent review of the use of thiazides for the control of hypertension in pregnancy concluded that there was no evidence of a deleterious effect.<sup>4</sup> Nevertheless, pre-eclampsia is a condition in which intravascular volume depletion occurs, and further depletion by diuretics may have a critical effect on the compromised uteroplacental blood flow. For this theoretical reason diuretics are not generally used for controlling hypertension during pregnancy.

### DRUGS FOR HYPERTENSIVE EMERGENCIES

#### Diazoxide

There are no reports on the use of diazoxide in the first trimester. It crosses the placenta and has been implicated in abnormal hair growth and development.<sup>29</sup> Prolonged exposure late in pregnancy is commonly associated with neonatal hyperglycaemia. Diazoxide is not well cleared by the neonate.<sup>29</sup>

Early experience with diazoxide was based on the misguided belief that rapid infusion of large boluses was required. Subsequent experience shows that the risk of severe maternal hypotension is diminished or abolished when lower doses (30-100 mg) are given more slowly. The hypotensive effect is obtained without altering uterine blood flow.<sup>30</sup> Diazoxide should be reserved for use in intrapartum emergencies.

#### Sodium nitroprusside

There is little published information on the use of this drug in pregnancy. Short term use has been satisfactory in small numbers of patients. When facilities exist for accurate and continuous blood pressure monitoring sodium nitroprusside is the drug of choice for treating hypertensive emergencies and eclampsia.

### What are the causes of leucoderma and what treatment is advised?

There are several conditions in which there is an acquired depigmentation of the skin, the most common of which is idiopathic vitiligo.<sup>1</sup> In this disorder there is often a positive family history and it is not infrequently associated with several conditions that are considered to be "autoimmune." There is an increased frequency of hyperthyroidism, hypothyroidism, Addison's disease, and pernicious anaemia as well as an increased incidence of organ specific and autoantibodies. Antimelanocyte antibodies have been identified in the serum of patients with vitiligo; however, this is uncommon and these patients have multiple endocrinopathies. Immune factors are concerned in the pathogenesis of the disorder. Occupational leucoderma can develop after exposure to several chemicals that are usually substituted phenols. Outbreaks of vitiligo have occurred among workers engaged in manufacturing these phenolic compounds, particularly *p*-tertiary butylphenol. Other causes of leucoderma are post-inflammatory, such as occur in eczema and psoriasis, or infections such as pityriasis versicolor, leprosy, and syphilis.

The treatment of vitiligo is unsatisfactory, though in some patients a satisfactory repigmentation of the affected areas of skin may be achieved with prolonged oral psoralen photochemotherapy. The amount of exposure to long wave ultraviolet light has to be gradually increased. The dose of 8-methox and of 4,5'8-trimethylpsoralen is 0.6 mg per kg body weight and either of these is given two hours before subsequent phototherapy. Natural sunlight appears to be more effective than artificial sources of long wave

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ultraviolet light. Treatment is usually given three times a week and a course of photochemotherapy is prolonged, lasting many months and sometimes years. Other treatments are the use of cosmetic camouflage and sunscreens.—S BLEEHEN, professor of dermatology, Sheffield.

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*A patient is taking dispersible mefenamic acid (Ponstan) for painful sequelae of infantile poliomyelitis. When he smokes his pipe he becomes dizzy. What is the pharmacological interaction between mefenamic acid and nicotine?*

I am not aware of any interaction between mefenamic acid and nicotine. Both nicotine and mefenamic acid may produce dizziness but this does not necessarily mean that they would be more likely to do so in combination. Non-steroidal anti-inflammatory drugs increase intestinal permeability<sup>1</sup> and if they have a similar effect on the permeability of the bronchial mucosa mefenamic acid might increase nicotine absorption. Nicotine, however, is already well absorbed after inhalation so that this seems an unlikely explanation.—LINDA BEELEY, consultant clinical pharmacologist, Birmingham.

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