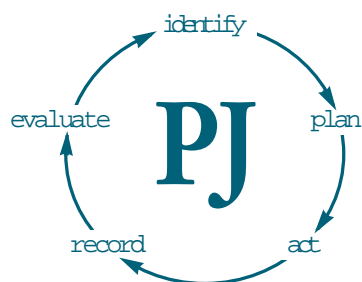


(3) DRUG USE IN PREGNANCY: PART 1

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This article reviews some conditions that require treatment during pregnancy. This part looks at hypertension, diabetes mellitus and depression. Part 2 will cover epilepsy and thyroid disorders



identify gaps in your knowledge

1. What are the drugs of choice for treating hypertension in pregnant women?
2. What are the drugs of choice for treating diabetes in pregnant women?
3. What are the drugs of choice for treating depression in pregnant women?

This article relates to the Royal Pharmaceutical Society's core competency of "appropriate advice, referral or selection of treatment" (see "Medicines, ethics and practice — a guide for pharmacists", number 26, July 2002, pp105–6). You should consider how it will be of value to your practice.

The care of the pregnant woman and her developing baby is one of the paradoxes of modern obstetric medicine. A healthy woman with an uneventful pregnancy will require little intervention. However, women with health problems, either pre-existing or that develop during pregnancy, and that might damage their own health or that of their baby may require appropriate use of diagnostic tests and prescribed medicines. It is important to balance the risks to the fetus associated with treating the maternal illness against the risks to both the mother and fetus of failing to treat the mother.

HYPERTENSION

During pregnancy, a persistent diastolic pressure of 95mmHg and above is the defining level for hypertension. The systolic pressure is usually not taken into consideration, although persistent systolic pressures exceeding 160mmHg are a cause for concern (World Health Organization). Severe hypertension is present when diastolic levels of over 110mmHg are reached.

Hypertension can predate the pregnancy or be pregnancy induced. Women with chronic hypertension who are planning to have a baby should speak to their doctor. Often, important lifestyle changes are required and sometimes, a woman may be prescribed a different antihypertensive. Women who are nulliparous or carrying multiple fetuses are at a higher risk of pregnancy induced hypertension.

Uncontrolled or severe (where there is end organ damage) hypertension presents the usual risks to the mother, such as cardiac hypertrophy, kidney failure and stroke, but it can also present risks to the fetus. Hypertension can reduce blood flow to the placenta, so that the fetus receives less nutrient and oxygen and its growth is therefore retarded.

Adverse events are also seen in women who develop pre-eclampsia (eg, generalised oedema), or placental abruption (eg, haemorrhagic shock, renal failure) in addition to hypertension. The incidence of pre-eclampsia in mild hypertension is 10–25 per cent and up to 50 per cent in chronic hypertension.¹

Prevalence of chronic hypertension in women of childbearing age increases from 0.6–2 per cent in women aged 18–29 years to 4.6–22.3 per cent at age 30–39 years. Although hypertensive disorders are com-

mon in pregnancy and often result in a high incidence of maternal and fetal harm, the choice of treatment remains controversial. Groups of drugs commonly used for hypertension are discussed below.^{1–4}

Diuretics Diuretics reduce placental perfusion and can reduce plasma volume. They are generally contraindicated in pregnancy, and should only be used in rare circumstances such as heart failure or lung oedema. The best studied are the thiazides, in particular hydrochlorothiazide. In a study of 567 women treated in the first three months of pregnancy there was no increase in the overall malformation rate or in any specific malformation.⁵

Methyldopa Methyldopa is one of the drugs preferred for the treatment of hypertension in pregnancy. There is no clear evidence of an increased risk of malformations directly attributable to the drug. Results of a seven-year follow-up study of children born to hypertensive women treated with methyldopa during pregnancy were inconclusive.⁶

Beta-adrenoceptor blocking drugs Beta-blockers are not known teratogens. Labetolol, propranolol, and metoprolol, which have been in long term use, are among the first line drugs of choice for treating hypertension in pregnancy. Timolol eyedrops can be used to treat glaucoma throughout pregnancy.

Atenolol has been shown to retard growth significantly when compared with acebutolol, pindolol and labetalol, but not when compared with a control group.⁷ There is a theoretical risk of neonatal beta-blockade causing neonatal bradycardia, hypotension and hypoglycaemia. Neonatal breathing difficulties and apnoea have been reported following *in utero* exposure to propranolol, but such adverse effects are rare.

Calcium channel blockers Nifedipine and verapamil are the best-studied calcium antagonists in human pregnancy. Although embryogenesis (development and integration of embryonic organs) is a highly calcium-dependent process, there are no substantial data to indicate that calcium channel blockers cause a significant increase in fetal toxicity in human pregnancy.

In the first three months of pregnancy, calcium antagonists are considered to be second line therapy. Nifedipine capsules that act rapidly (within 10–15 minutes) should not be used because they can cause a precipitous fall in blood pressure. The long acting nifedipine preparations given once daily are preferred. Profound hypotension could also be a problem when parenteral magnesium sulphate is used either for prophylaxis or treatment of eclampsia, in addition to

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nifedipine, because of the effects of magnesium ions on calcium channel function. Calcium antagonists have been used successfully in the latter half of pregnancy to treat fetal tachycardia.

Angiotensin-converting enzyme inhibitors Angiotensin-converting enzyme (ACE) inhibitors such as captopril and lisinopril are contraindicated in pregnancy except in cases where the illness is severe and there is no other treatment. When taken during pregnancy ACE inhibitors can cause oligohydramnios (deficiency of amniotic fluid), renal tubular dysgenesis, neonatal anuria, hypocalvaria (retarded ossification of the skull), pulmonary hypoplasia, persistent patent ductus arteriosus (if the ductus arteriosus does not close, the blood will be insufficiently oxygenated, interfering with growth and placing strain on the fetal heart), intrauterine growth retardation, and fetal or neonatal death. A direct action of ACE inhibitors on the fetal renin-angiotensin system, a reduction in amniotic fluid volume and ischaemia due to maternal hypertension and subsequent reduction in fetoplacental blood flow have been implicated. Where clinically appropriate, medication should be changed to one of the other antihypertensive drugs of choice.

Angiotensin-II receptor antagonists Angiotensin-II receptor antagonists (A2s) such as losartan and valsartan are suspected to cause similar fetal lesions and are thought to have an action on fetal kidney metabolism similar to that of the ACE inhibitors. As their role in the management of hypertension has yet to be established the use of A2s in pregnancy is contraindicated unless all other treatment regimens had been ineffective.

Inadvertent exposure to either an ACE inhibitor, or an A2 in the first trimester is not sufficient grounds to recommend termination. However, in cases involving long-term prenatal therapy, the fetus should be monitored for the potential development of oligohydramnios, and fetal growth should be assessed with detailed ultrasound scans.

DIABETES MELLITUS

Diabetes mellitus is due to absolute insulin deficiency (type 1, insulin dependent) or partial insulin deficiency (type 2, non-insulin dependent). Both of these conditions will have predated the pregnancy and should be distinguished from gestational diabetes, which only occurs during pregnancy, usually after week 20.

Gestational diabetes may be due to changes in insulin metabolism, or the production of anti-insulin hormones such as human placental lactogen, progesterone, oestrogens and glucocorticoids which are present in increasing amounts during pregnancy, as the placenta grows. In most pregnant women, the pancreas is able to produce the extra insulin needed to counter insulin resistance, but where the pancreas cannot make enough insulin, gestational diabetes develops. Risk factors include obesity and a family history of diabetes. Some of these women are likely to have had undiagnosed diabetes prior to pregnancy.

Women with any type of diabetes and their babies are at an increased risk of a number of pregnancy complications. In contrast to gestational diabetes, pre-pregnancy type 1 diabetes may be associated with maternal vascular disease resulting in uteroplacental insufficiency, hypertension and pre-eclampsia. Pregnant women with inadequately controlled diabetes mellitus are at a higher risk of having a miscarriage, intrauterine death or a baby with congenital malformations (two to four fold increase), eg, cardiovascular system defects, neural tube defects, bilateral renal agenesis and organomegaly (heart and liver). Increased erythropoiesis, which can lead to fetal hypertension, is also a risk. Significant neonatal morbidity and perinatal mortality (two to three fold increase) has also been reported.

Macrosomia (a large baby) is a common problem where blood glucose control is poor. The fetal pancreas begins to develop during weeks five to eight post conception. From week 12 of gestation onwards, parenchyma, acini and islets of Langerhans are present and insulin and glucagon are formed. The total pancreatic insulin and glucagon increases with fetal age. Maternal hyperglycaemia can induce hyperglycaemia and pancreatic hyperplasia in the fetus. In response to hyperglycaemia, the fetal pancreas produces more insulin, which allows extra glucose to be converted to fat and therefore the fetus is abnormally large. This can make vaginal delivery dif-

ficult and necessitate a caesarian section or delivery before full term.

If maternal blood sugar levels are high, especially in the 24 hours before delivery, the neonate may be hypoglycaemic because of residual hyperfunction of neonatal islet cells. The neonate will therefore have high insulin levels but no longer has a glucose supply from its mother, and in some instances they may need intravenous administration of glucose or dextrose. The neonates of women with diabetes are often also have hyaline membrane disease or respiratory distress syndrome. Maintaining glycaemic control has been shown to reduce adverse outcomes for both the mother and child — pregnant women are often advised to monitor their blood glucose six to eight times a day.

Women with diabetes who are planning a pregnancy should be advised to make sure they achieve tight blood glucose control before conception. Ideally, pregnant women with diabetes should be managed in specialist multidisciplinary antenatal clinics to obtain optimal care. Ultrasound examination to monitor for growth and congenital malformations is recommended.

Insulin Insulin replacement therapy has made it possible for women with diabetes to carry successful pregnancies.^{2,8,9} Human insulin does not cross the placenta and there is no indication that insulin is associated with an increased risk of fetal or neonatal toxicity. It is important that type 1 diabetes should be optimally controlled with insulin before pregnancy and prenatal counselling given. Where gestational diabetes is diagnosed, insulin therapy should be started as early as possible. Human insulin is preferred to that of animal origin because of the possibility of antibody development.

In women with diabetes established before pregnancy, insulin needs during pregnancy often increase in the second trimester. The overall principles in achieving adequate glucose control are achieved by balancing energy supply, energy consumption and replacing insulin. Some glucocorticoids (eg, used antenatally to prevent respiratory distress syndrome) and tocolytics (drugs used to suppress uterine contractions and prevent premature labour) decrease maternal carbohydrate metabolism, so if these drugs are used monitoring of metabolic control is advisable.

Oral antidiabetic drugs Most oral antidiabetic drugs do not cross the placenta. The most commonly used oral antidiabetic drugs, the sulphonylureas (eg, chlorpropamide, tolbutamide) and the newer second generation drugs (glibenclamide, glicazide and glipizide), stimulate the pancreatic beta cells that are still able to function. In contrast, the biguanide derivatives such as metformin decrease glucose synthesis in the liver. There are few data on the effects in pregnancy of the newer antidiabetic drugs such as those that stimulate insulin release (eg, nateglinide, repaglinide) or reduce peripheral insulin resistance (eg, pioglitazone and rosiglitazone). Therefore a reliable risk assessment of their effects on the fetus cannot be made.

Because the oral antidiabetic drugs have not been shown to regulate blood sugar as effectively as insulin, they are generally not considered suitable for treatment of diabetes during pregnancy. Some of these drugs, particularly the sulphonylureas, have been associated with an increased risk of fetal malformations and neonatal hypoglycaemia. However, it is not clear whether this is a direct effect of the drugs or whether it is a secondary effect associated with poor glucose control. Ideally, pregnant women with type 2 diabetes should be treated with insulin in the same way as those with type 1 diabetes. The same guidelines concerning fetal scans are also recommended. The use of antidiabetic drugs in pregnancy is not necessarily an indication for medical termination of pregnancy or the use of invasive diagnostic procedures.

DEPRESSION

Approximately 10 per cent of women will suffer from psychological distress and anxiety during pregnancy. In some women, depression may be severe and treatment with antidepressants may be required. Furthermore, depression often develops after delivery. In some instances this is self limiting, but about 0.2 per cent may develop a psychiatric illness and up to 10 per cent develop a depressive illness.

There is sufficient evidence to show that leaving severe depression untreated can have adverse effects on pregnancy outcome, especially if the mother is suicidal, and can adversely affect the

action : practice points

1. Visit Diabetes UK (www.diabetes.org.uk) and read the recommendations for the management of women with diabetes.
2. Make sure you are aware of the symptoms of depression. Think about how you would respond to a pregnant woman who tells you she is experiencing some of these symptoms.
3. Pregnant women with hypertension are at a higher risk of pre-eclampsia. Make sure that any pregnant woman taking treatment for hypertension is aware of the warning signs (swelling of the face and hands, headaches, blurred vision or spots in front of the eyes and pain in the upper right part of the abdomen).

evaluate

How could your learning have been more effective?
What will you do now and how will this be achieved?

mother-child relationship. Treatment with antidepressants may be required throughout pregnancy and the first couple of months or so after the birth.^{2,10} Therefore, it is important to assess the potential adverse effects of medication on the fetus and on the neonate and child who may continue to be exposed via breast milk.

Tricyclic antidepressants Tricyclic antidepressant (TCA) overdose can cause severe maternal toxicity including convulsion, coma, and arrhythmia, with consequent fetal harm. However, there is no epidemiological evidence of an association between therapy with TCAs and an increased incidence of birth defects or other adverse pregnancy outcome. Occasional suggestions of harm are unsubstantiated. Short term neonatal withdrawal symptoms, such as jitteriness, hyperexcitability, myoclonus (sudden, involuntary muscle contraction), convulsions and suckling problems, have been reported, especially in premature or smaller than average infants. Limited data based on 80 preschool children did not indicate any adverse effects on neurodevelopment, measured using indicators such as global intelligence quotient, language and behaviour.

Selective serotonin reuptake inhibitors Fluoxetine is the only selective serotonin reuptake inhibitor (SSRI) that has been extensively studied in pregnancy, and the data show no increase in either the rate of malformations or the incidence of spontaneous abortions.¹¹ A report of a higher incidence of three or more minor anomalies lacks clinical data and is difficult to assess.¹² Exposure *in utero* to fluoxetine in 55 preschool children did not affect neurodevelopment.¹³ One study of neonatal exposure to fluoxetine in the last three months of pregnancy showed no significant increase in postnatal complications. However, chronic use, or the use of SSRIs near term, has been associated with neonatal withdrawal symptoms in some cases. Neonatal cardiac dysrhythmias, intestinal motility disorders and urinary retention are rare events. There is no clear evidence of an increased risk of fetal toxicity or other pregnancy complications so far with citalopram, fluvoxamine, paroxetine or sertraline.

Monoamine oxidase inhibitors Monoamine oxidase inhibitors (MAOIs) have been associated with a high incidence of toxicity in humans. For example, interaction with tyramine may produce an acute hypertensive crisis. There is no clear evidence of fetotoxicity with phenelzine or tranylcypromine. A recent case report discussed the association between cardiac anomalies, hypertelorism (abnormally wide distance between body parts, eg, eyes) and other defects. No data were found on the use of moclobemide in pregnancy.

MAOIs can exacerbate pregnancy-associated hypertension, which can lead to alterations in placental blood flow, particularly placental hypoperfusion. This can have serious consequences for fetal growth and development. No reports were found describing effects in the neonate specifically related to MAOIs.

Recommendations Amitriptyline and imipramine are the drugs of choice for the treatment of depression during pregnancy, based on the length of time that they have been in use and the cumulative data

on their lack of fetotoxicity, although SSRIs are safer in overdose.

Until more data are available, fluoxetine should be reserved for use in pregnant women where amitriptyline or imipramine is ineffective or poorly tolerated, or for women perceived to be at high risk of suicide. The serotonin/noradrenaline re-uptake inhibitors and the miscellaneous newer antidepressants should be avoided until more data are available. MAOIs should be avoided if at all possible because of their inherent maternal toxicity and lack of published data on safety in pregnancy. If clinically appropriate, the dose of the antidepressant should be tapered three to four weeks before the expected date of delivery to minimise the withdrawal symptoms by the newborn baby.

The second part of this article, to be published next week, will look at epilepsy and thyroid disorders.

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