The treatment of hypertension in pregnancy

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Abstract

Hypertension in pregnancy is a leading cause of maternal death. It may represent pre-existing essential or secondary hypertension. Alternatively, it may have been induced by the pregnancy. Pregnancy-induced hypertension may develop after 20 weeks' gestation, is not associated with proteinuria and generally resolves 6 weeks postpartum. In genetically-predisposed mothers, pregnancy-induced hypertension may take the form of pre-eclampsia, a condition characterized by hypertension, oedema and proteinuria. Antihypertensive drugs palliate this condition but the definitive treatment is delivery of the fetus. Antihypertensive drugs administered during the first trimester of pregnancy may have teratogenic effects, the period of greatest risk being from the third to the eleventh week of pregnancy. Drugs given later in pregnancy may adversely affect fetal growth and development. Those given close to term may impair labour or may have adverse effects on the neonate. An appendix to the British National Formulary lists the risks associated with the use of antihypertensive drugs during the various trimesters of pregnancy. Antihypertensive drugs commonly used in pregnant women include methyldopa (a drug that gives rise to a false sympathomimetic neurotransmitter), hydralazine (a vasodilator that may interfere with the intracellular release of calcium ions), labetalol (an antagonist at α_1- and β_1-adrenoceptors with partial agonist activity at β_2-adrenoceptors), nifedipine (an inhibitor of calcium ion influx through L-type channels) doxazosin and prazosin (antagonists at α_1-adrenoceptors) and antagonists at β-adrenoceptors. Magnesium sulphate is useful for the prevention and treatment of seizures associated with eclampsia but its co-administration with nifedipine is best avoided.

Keywords hydralazine; hypertension; labetalol; magnesium sulphate; pre-eclampsia; pregnancy

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The cardiovascular changes associated with normal pregnancy

During early pregnancy, factors derived from the vascular endothelium induce peripheral vasodilatation. Blood pressure, therefore, tends to fall. This fall in blood pressure is reflexly limited by an increase in cardiac output, manifest as increased stroke volume and heart rate. Cardiac output reaches its greatest value at the end of the second trimester. After 22–24 weeks of gestation, blood pressure tends to return to the prepregnancy value.

Pregnancy is associated with an expansion of plasma volume. This is partly due to the movement of fluid from the interstitial compartment to the plasma compartment. The size of this increase in plasma volume is determined by the size and number of the fetuses. During pregnancy the output of erythropoietin is also increased. This leads to an increase in the number of circulating erythrocytes. However, the increase in erythrocyte numbers is not in proportion to the increase in plasma volume. Hence the blood haemoglobin concentration tends to fall, producing the 'physiological anaemia' of pregnancy.

Hypertension in pregnancy

In clinical practice, the definition of hypertension in pregnancy tends to vary. Most authorities adopt a definition based on a diastolic blood pressure of greater than 90 mm Hg measured on two separate occasions or a diastolic blood pressure of greater than 110 mm Hg measured on a single occasion. Hypertension is still a leading cause of maternal death, only outranked by thromboembolism. It is currently estimated that hypertension is the direct cause of 7.1 deaths per million maternities. High blood pressure in pregnancy may be due to pre-existing essential or secondary hypertension. However, in the third trimester of pregnancy, hypertension, oedema, and proteinuria may develop even in women who have previously been normotensive. This syndrome is known as pre-eclampsia and occurs in 10–15% of all pregnancies. There is a strong genetic predisposition for this syndrome. A woman with an affected mother has a four-fold increased chance of developing pre-eclampsia compared with the general female population. She will have an eight-fold increased chance of developing the condition if her sister is affected. The fundamental cause of pre-eclampsia is unknown but the syndrome is associated with inadequate development of the spiral arteries of the uteroplacental bed. In consequence, the ability of trophoblastic tissue to produce vasodilator substances is impaired. The effects of the maternal rennin–angiotensin system are therefore less well opposed, and the blood pressure rises. In severe cases convulsions (eclampsia) ensue. Treatment of the hypertensive component of pre-eclampsia only palliates the disease. The definitive treatment is delivery of the fetus. Pregnancy-induced hypertension is a condition that is often difficult to differentiate from pre-eclampsia. It may develop after 20 weeks of gestation, is not associated with proteinuria or other features of pre-eclampsia, and generally resolves 6 weeks postpartum.

Treatment of hypertension in pregnancy

When choosing an antihypertensive drug for use in a woman of childbearing age, it is important to remember that drugs administered during the first trimester of pregnancy may have teratogenic effects. In this respect the period of greatest risk is from

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the third to the eleventh week of pregnancy. In addition, drugs administered during the second and third trimesters of pregnancy may adversely affect the growth and development of the fetus. Drugs given close to term may impair the process of labour or may have adverse effects on the neonate. Table 1 lists some important antihypertensive drugs and provides some indication of the risks associated with their administration during the trimesters of pregnancy.

Clinicians vary in their choice of treatment for hypertension in pregnancy. If the hypertension predates the pregnancy, treatment will reduce the risk of severe hypertension developing but will not protect against superimposed, pre-eclampsia. The aim of treatment is to maintain the maternal mean arterial pressure below 150 mm Hg. Above this value there is a loss of cerebral autoregulation, giving rise to the risk of cerebral haemorrhage. In the management of mild-to-moderate hypertension in the pregnant woman, orally-administered methyldopa is generally considered as first-line treatment. Second-line treatment includes hydralazine tablets (the manufacturer advises restricting use to the third trimester) and modified-release capsules of nifedipine (an unlicensed indication). Third-line treatments include orally-administered agents such as antagonists selective for the α_1-adrenoceptor (e.g. prazosin and doxazosin), antagonists selective for β-adrenoceptors (e.g. atenolol), and labetalol (see below). Ideally, the use of either antagonists at β-adrenoceptors or labetalol should be restricted to the third trimester.

The management of acute, severe hypertension in pregnancy may involve the intravenous administration of hydralazine or labetalol. Alternatively, nifedipine tablets may be used. A protocol should be available on every labour ward for the management of severe pre-eclampsia. This is a state of intravascular depletion in which diuretics can be dangerous. Diuretics should be used in pregnancy only to treat heart failure and pulmonary oedema. Oliguria is a normal feature of pre-eclampsia. Careful fluid balance should be used, with central-line monitoring. It is safer to err on the side of mild renal impairment rather than fluid overload and pulmonary oedema.

Pharmacology of drugs used to lower blood pressure during pregnancy

Methyldopa

Methyldopa is a prodrug, requiring metabolic conversion to yield its active principle: α-methylnorepinephrine (Figure 1). The α-methylnorepinephrine is handled by the norepinephrine neuron in exactly the same way as norepinephrine. In other words,

Agents used to control systemic hypertension and their associated risks during pregnancy

Agent	Trimester of risk	Comments
ACE inhibitors and antagonists at angiotensin-II receptors (e.g. enalapril and losartan, respectively)	1, 2 and 3	Avoid. Risk of interference with fetal/neonatal control of blood pressure and renal function. May cause oligohydramnios (abnormally low volume of amniotic fluid) and fetal skull defects. Toxicity shown in animal experiments
Antagonists selective for α_1-adrenoceptors (e.g. prazosin)		No evidence of tetratogenicity, but manufacturers advise use only when potential benefit outweighs risk
Antagonists at β-adrenoceptors (e.g. atenolol)	1, 2	May inhibit fetal and placental growth. May cause neonatal hypoglycaemia and bradycardia. Greater risk in severe hypertension
Ca^{2+} influx inhibitors (e.g. nifedipine)	1, 3	Diltiazem and some dihydropyridines are teratogenic in animal tests. Verapamil may reduce uterine blood flow and hence cause fetal hypoxia. These agents may inhibit labour. Most manufacturers advise their use only when the potential benefit outweighs the risk
Clonidine		Avoid intravenous injection. May lower fetal heart rate. Risk should be balanced against uncontrolled maternal hypertension
Guanethidine	3	Avoid. Risk of postural hypotension and reduced uteroplacental perfusion
Hydralazine	1, 2	Manufacturer advises avoidance before third trimester. No reports of fetal or neonatal problems following use in third trimester
Labetalol		May cause intra-uterine growth restriction if used long term
Methyldopa		Not known to be harmful
Moxonidine		No information available. Manufacturer advises avoidance
Sodium nitroprusside		Use with caution in pregnancy. Risk of unwanted effects of cyanide metabolite, particularly with prolonged intravenous infusion
Thiazide diuretics (e.g. bendroflumethiazide)	3	Not used to treat hypertension in pregnancy. May prevent the expansion in plasma volume associated with pregnancy and hence reduce placental perfusion. May cause neonatal thrombocytopenia. No evidence of increased incidence of fetal abnormalities
Torasemide	1	Avoid. Toxicity shown in animal experiments

Adapted from Appendix 4, British National Formulary No. 53, 2007. ACE, Angiotensin-converting enzyme.

Table 1

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