12

Optimization of hypertension and embryo safe antihypertensives

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Hypertension is the commonest medical complication of pregnancy, affecting 5–10% of all pregnant women. It is a major cause of maternal mortality[1] and contributes significantly to perinatal morbidity and mortality. The specific risks are related to disease severity and the presence of hypertensive target organ involvement. Maternal and fetal outcomes are optimal if pre-existing hypertension is well controlled before pregnancy. This chapter provides an overview of the different hypertensive disorders of pregnancy and highlights the importance of preconception assessment and counseling to optimize pregnancy outcome. The advantages and disadvantages of different antihypertensive drugs in pregnancy are also summarized.

HYPERTENSIVE DISORDERS OF PREGNANCY

Pregnancy may be complicated by four types of hypertensive disorders: chronic (pre-existing) hypertension, gestational hypertension, pre-eclampsia–eclampsia and chronic hypertension with superimposed pre-eclampsia. These disorders differ in maternal and fetal prognosis and the type of pre-pregnancy assessment and counseling required.

Chronic hypertension

Chronic hypertension is present before pregnancy, diagnosed before 20 weeks' gestation, or persistent beyond 12 weeks' postpartum. It may be primary or secondary. Primary hypertension accounts for 90% of chronic hypertension in pregnancy. Simply put, this is essential hypertension with multifactorial predisposing factors, including genetics and ethnicity. Ten per cent of pregnant women with chronic hypertension have underlying secondary causes including endocrine disease (diabetes mellitus, pheochromocytoma), renal disease (glomerulonephritis, renovascular disease) or connective tissue disorders (systemic lupus erythematosus, scleroderma). Chronic hypertension is classified as mild (stage 1), moderate (stage 2) or severe (stage 3), depending on the level of blood pressure and the presence of target organ involvement. Mild hypertension is a systolic blood pressure (BP) of 140–149 mmHg or a diastolic BP of 90–99 mmHg. Moderate hypertension exists when systolic BP is 150–159 mmHg or diastolic BP is 100–109 mmHg, and severe disease is defined as systolic BP ≥160 mmHg or diastolic BP ≥110 mmHg. The disease is considered severe in the presence of target organ (such as kidney and cardiac) involvement regardless of the level of blood pressure. The diagnosis of chronic hypertension may be missed in early pregnancy because of the physiological fall in blood pressure during the first half of pregnancy; however, it should be considered if the first trimester diastolic blood pressure values are in the 80s. It may also be misdiagnosed as gestational hypertension if the patient

first presents in late pregnancy. The diagnosis should also be considered in women who develop recurrent hypertension in pregnancy.

The prevalence of chronic hypertension varies depending on the population studied. Unfortunately, it appears to be rising across all populations, partly due to the increasing body mass index (BMI) of the general population and also due to the current pattern of childbearing in women of advanced age. The health and financial burden of looking after pregnant women with hypertension will increase in the future as more resources are required to meet the cost of additional laboratory tests and more frequent antenatal monitoring.

Maternal complications result from severe hypertension or superimposed pre-eclampsia and include acute left ventricular failure, acute renal failure, intracranial hemorrhage (stroke) and placental abruption. Fetal complications such as preterm delivery, intrauterine growth restriction (IUGR) and increased risk of stillbirth are also related to severe hypertension, superimposed pre-eclampsia and placental abruption. For most women with mild to moderate chronic hypertension, the risks of maternal or perinatal morbidity and mortality are moderate compared to normal pregnancy. However, these are increased significantly in severe hypertension, when maternal age is greater than 40 years, chronic hypertension has been present for more than 5 years, or coexisting medical disorders (such as diabetes, renal disease connective tissue disease, cardiac disease) are also present[2,3].

Gestational hypertension

Gestational hypertension is new onset hypertension after 20 weeks' gestation in the absence of proteinuria. Hypertension is defined as systolic BP ≥140 mmHg and/or diastolic BP of ≥90 mmHg on at least two occasions, at least 4 hours apart and resolving within 12 weeks after delivery. The disease is considered severe if systolic BP is ≥160 mmHg and/or diastolic BP ≥110 mmHg[4]. Gestational hypertension is part of the pre-eclampsia–eclampsia spectrum of disorders and accounts for up to 25% of the syndrome. Up to 25% of cases may progress to pre-eclampsia, and although the rate of progression is unpredictable, it appears to be dependent on the gestational age at onset. For example, Barton *et al.* provided evidence that the risk of pre-eclampsia may increase to up to 50% if gestational hypertension occurs before 30 weeks' gestation[5]. Fortunately, most cases of gestational hypertension are mild to moderate, occur close to term and the risk of poor fetal outcome is only slightly greater than in normal pregnancy. However, severe or early onset disease is associated with significant adverse perinatal outcomes such as IUGR. Women with severe gestational hypertension should therefore be managed in a similar manner to those with severe pre-eclampsia[4].

Pre-eclampsia

Pre-eclampsia is a multisystem disorder of the second half of pregnancy diagnosed by new onset hypertension and proteinuria after 20 weeks' gestation with resolution of both within 12 weeks' postpartum. Hypertension is defined using an absolute cut-off systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg on at least two occasions and at least 4 hours apart. Proteinuria is defined as more than 300 mg urinary protein excretion in 24 hours. Underlying chronic renal disease should be suspected if proteinuria is present before 20 weeks' gestation or persists beyond 12 weeks after delivery. Proteinuria of pre-eclampsia results from glomerular endotheliosis and is part of the underlying generalized endothelial dysfunction. Eclampsia is the occurrence of seizures superimposed on pre-eclampsia. The diagnosis of pre-eclampsia should be strongly considered if gestational hypertension is associated

with persistent symptoms, or the presence of thrombocytopenia or abnormal liver enzymes.

Pre-eclampsia is classified as severe if any of the following are present: (1) proteinuria ≥5 g in a 24 hour period; (2) evidence of multiorgan involvement such as oliguria or pulmonary edema; (3) platelet count <100,000 per mm; (4) abnormal liver enzymes associated with upper abdominal pain (epigastric or right upper quadrant); or (5) persistent signs or symptoms of cerebral irritation (headache, blurred vision, altered mental state)[6]. Unlike chronic hypertension, the hypertension of pre-eclampsia is a secondary manifestation of the disease and contributes to some of its consequences including intracranial hemorrhage or abruption. Severe pre-eclampsia is associated with increased maternal morbidity such as acute renal failure, liver hemorrhage or failure, disseminated intravascular coagulopathy and cerebral hemorrhage. Such complications are common in women with underlying medical conditions and when pre-eclampsia occurs before 32 weeks' gestation. Severe disease is also associated with a 2% increased risk of maternal mortality; the commonest cause of maternal death in pre-eclampsia in the developed world is intracranial hemorrhage[1]. Perinatal complications include increased risk of stillbirth, IUGR and preterm delivery. These risks are significantly greater in women who develop early onset pre-eclampsia but less common if the disease occurs after 36 weeks' gestation.

Pre-eclampsia superimposed on chronic hypertension

About 25% of pregnant women with chronic hypertension develop superimposed pre-eclampsia. This is defined as the onset of new signs or symptoms of pre-eclampsia after 20 weeks' gestation in a woman with chronic hypertension. Making the diagnosis may be difficult, and distinguishing superimposed pre-eclampsia from worsening chronic hypertension requires a high index of suspicion. The diagnosis should be considered if a woman with chronic hypertension develops significant new onset proteinuria after 20 weeks' gestation. Other criteria include: (1) a women with hypertension and proteinuria before 20 weeks' gestation who develops increased proteinuria during the second half of pregnancy; (2) a sudden increase in blood pressure in a woman whose hypertension has previously been well controlled; (3) platelet count <100,000 cells/mm^3); and (4) abnormal liver enzymes (ALT or AST). The risk of superimposed pre-eclampsia is greater if the chronic hypertension has been present for 5 years or longer, associated with impaired renal function or a history of superimposed pre-eclampsia exists from a previous pregnancy. Maternal and fetal prognosis is worse than in *de novo* pre-eclampsia. Once the diagnosis is made, clinical management is similar to severe pre-eclampsia.

PRECONCEPTION COUNSELING OF WOMEN WITH CHRONIC HYPERTENSION

The general aim of preconception counseling is to assess the overall health of the woman, identify any undetected health risks or disease(s), change medication(s) to safer alternatives in pregnancy, and to estimate baseline function(s) for future reference[7]. Ideally any woman planning a pregnancy should have preconception counseling 3–6 months before conception. Unfortunately this goal is poorly achieved, as most pregnancies are unplanned[9]. Counseling is particularly useful in women with pre-existing hypertension, to allow enough time to evaluate the severity of disease and to assess possible reversible secondary causes. In addition to review of antihypertensive medication(s), advice should be offered about lifestyle modifications prior to conception and how the hypertension will

affect future pregnancy. Lifestyle modifications include smoking cessation, reduced alcohol consumption, exercise and reduced salt intake, particularly in black women, as these are well established cardiovascular risk factors. Although data on the effects of salt restriction during pregnancy are inadequate, many agree that the recommended daily intake of 2.4 g still applies during pregnancy. Excessive alcohol intake may aggravate maternal hypertension, whereas smoking increases the risks of abruption and IUGR. Women with a high BMI should be encouraged to lose weight, as obesity is an independent risk factor of adverse pregnancy outcome. A program of exercises and appropriate dietary modifications should be recommended well before pregnancy to allow enough time for weight loss. Although regular exercise is beneficial for non-pregnant women with hypertension and safe during normal pregnancy, data on its safety in pregnant women with chronic hypertension are limited. Weight loss during pregnancy even in obese chronic hypertensives is not recommended, and there is no evidence this reduces the risk of superimposed pre-eclampsia.

The woman's medical records should be reviewed, physical examination performed and relevant tests carried out to evaluate hypertensive target organ complications such as left ventricular hypertrophy, retinopathy and renal disease. Physical examination should include assessment of the carotid, femoral and peripheral pulses, palpation of the kidneys for possible polycystic kidney disease and auscultation for renal artery bruits to exclude renovascular disease. Fundoscopy should be performed to elucidate evidence of arterial disease. Blood urea electrolytes and creatinine are essential to assess renal function. Urine analysis and culture should be performed, and 24 hour urine collection for protein and creatinine clearance requested if indicated. These tests also form a baseline for future reference. Women with underlying renal disease have a higher risk of adverse perinatal outcome independent of superimposed pre-eclampsia and the risk of fetal loss is increased significantly if the blood pressure is poorly controlled[8,9]. A chest X ray, electrocardiogram (ECG), echocardiogram (if long-standing hypertension) and blood test for antinuclear antibody to exclude possible lupus nephropathy should be considered in women with severe hypertension. Thrombophilia screen should be considered if there is a history of venous thromboembolism or recurrent pregnancy loss. Younger women with chronic hypertension usually require more detailed investigation as they are more likely to have a secondary cause. Twenty-four-hour urinary catecholamine metabolites should be assessed to exclude pheochromocytoma if there is a history of sweating or palpitation associated with paroxysmal or severe hypertension. Where indicated, renal imaging and angiography should be performed to exclude possible renovascular disease or adrenal gland pathology.

PRECONCEPTION COUNSELING OF WOMEN WITH PREVIOUS PRE-ECLAMPSIA

Women with a prior history of pre-eclampsia are at increased risk of recurrence during future pregnancies. The magnitude of this risk depends on the severity and gestational age at onset of the previous disease. Optimizing maternal health, including maintaining a normal BMI before pregnancy, is likely to reduce the risk of recurrence. During preconception counseling, a management plan should be formulated, which includes early antenatal booking, frequent monitoring of maternal and fetal well-being and timely delivery. If postnatal review and counseling were not carried out after the previous pre-eclamptic pregnancy, then tests should be performed to confirm reversal of target organ changes and to establish a baseline for future assessment.

PREDICTION OF PRE-ECLAMPSIA

Women attending preconception counseling want to know their risk of developing pre-eclampsia. Unfortunately, our current lack of comprehensive understanding of the pathophysiology of this disease does not allow accurate prediction of future risk. Discussion should take into consideration the presence of chronic hypertension or other maternal risk factors including interpregnancy interval greater than 10 years, maternal age less than 18 years or greater than 35 years, and personal or family history of pre-eclampsia or underlying medical disorders[10,11]. Fetal factors likely to contribute to the risk of disease include multiple pregnancies and triploidy[12]. Currently, Doppler ultrasound of the uterine arteries remains the best tool available test for predicting pre-eclampsia. Persistence of uterine artery notching after 23 weeks appears to reflect failure of trophoblastic invasion. However, the predictive value of this test is only 30%, with a sensitivity and specificity of 75% and 96%, respectively[13].

PREVENTION OF PRE-ECLAMPSIA

Several interventions including low-dose aspirin and dietary supplementation such as calcium, magnesium, antioxidant vitamins and omega-3 unsaturated fatty acids (fish oil) have been investigated for prevention of pre-eclampsia; however, none has shown consistent benefit. Low-dose aspirin has long been considered for prevention of pre-eclampsia. Although several small trials initially suggested substantial benefit, these were not confirmed by larger, well designed, randomized controlled trials[14,15]. It is possible that aspirin studies in high-risk women showed variable outcomes because chronic hypertension was not distinguished from other high-risk conditions. Given that pregnancy outcomes in chronic hypertension are different from other conditions which may be mediated by different factors, the combination of high-risk women into a heterogeneous group may explain the failure of these studies to observe large benefits from aspirin supplementation. A recent Cochrane database meta-analysis established a 10% reduction in the relative risk of pre-eclampsia and preterm birth before 34 weeks and a 9% reduction of stillbirth[16]. In spite of the inconclusive data, low-dose aspirin may be considered on an individualized basis[17]. The optimum time to commence aspirin supplementation is uncertain, however. Most trials on aspirin were started after the first trimester, and although data on its effect on organogenesis are inadequate, its use in women with recurrent early pregnancy loss has not shown any adverse effect. A Cochrane meta-analysis database did not show any evidence of adverse effects when started earlier[18].

Dietary supplementation in pregnancy has not been shown to be effective in preventing pre-eclampsia in low-risk women. Although trials in high-risk nulliparous women have suggested that calcium decreased the risk of pre-eclampsia[19,20], no conclusive evidence shows that an enriched calcium diet beyond the daily requirement provides any benefit in pre-eclampsia prevention. Several studies have also investigated the potential benefit of magnesium supplementation in prevention of pre-eclampsia; however, none has shown any benefit[21,22]. Earlier studies suggested antioxidant vitamin supplementation reduced the risk of pre-eclampsia[23]. However, more recent randomized controlled trials have shown antioxidant therapy (vitamin C and E) does not prevent pre-eclampsia and may even be harmful[24,25]. Women in the preconception period should be encouraged to use the standard daily dietary requirement as part of a balanced diet and to maintain the daily elemental calcium dietary requirement of 1000 mg for general well-being.

ANTIHYPERTENSIVES IN PREGNANCY

Administration of any drug(s) in pregnancy presents a unique set of problems. Not only must the pharmacological mechanisms be considered when prescribing the agent, but the fetus must be kept in mind, as it also is a potential recipient of the drug. With rare exceptions, most substances cross the placenta and, depending upon their lipid solubility and structure, achieve varying concentrations in the fetus. In humans, the mechanisms by which drugs exert teratogenic effects are poorly understood. They may act on maternal receptors with indirect effect(s) on the fetus or may have direct effect(s) on the developing embryo and result in structural anomalies. They may affect the nutrition of the fetus by interfering with the passage of nutrients across the placenta. Many of the antihypertensive agents used in pregnancy appear to affect the fetus by this latter mechanism. The type and frequency of anomalies caused by a teratogenic agent depends critically upon the developmental stage of the fetus at the time of exposure[26]. Teratogenic effects of drugs are also dose and time dependent, with the greatest risk during the first 3 months of pregnancy. However, this may occur at any stage of pregnancy compared to postnatal exposure because of the high rate of cellular proliferation and differentiation in the fetus.

Some antihypertensive drugs are associated with unacceptable fetal and neonatal adverse effects and are therefore contraindicated in pregnancy. Women with chronic hypertension who are planning a pregnancy should be treated with medication that can be continued into pregnancy. Where this is not possible, because of co-existing medical disorders as in diabetic nephropathy, drugs that are not normally recommended in pregnancy such as angiotensin converting enzyme inhibitors could be considered. However, this should be changed to a suitable alternative as soon as pregnancy is confirmed. Antihypertensive therapy for severe hypertension is necessary to prevent maternal cardiovascular complications including intracerebral bleeding and left ventricular failure, about which there is no controversy concerning benefits. In contrast, the evidence base regarding drug treatment of moderate hypertension during pregnancy is too small to prove or disprove benefit. The argument in favor of drug treatment of mild to moderate hypertension is that it prevents severe hypertension and its associated complications.

The adverse effects of antihypertensive drugs may be different in chronic hypertension and in pre-eclampsia because of differences in underlying pathophysiology, such as the placental pathology of pre-eclampsia. The timing, dosage and duration of antihypertensive drug treatment may also contribute to adverse effects. For example, women with moderate chronic hypertension are more likely to require medication for a longer duration compared to those with pre-eclampsia. The true incidence of adverse effects of antihypertensive drugs in pregnancy is difficult to quantify, as data on adverse effects are limited and are usually based on surveillance studies and case reports. Assessing causality from surveillance studies and case reports may not be accurate because of lack of previous exposure data, inability to separate specific effects in multidrug regimens and difficulty in calculating rates of adverse events.

GOALS FOR TREATING HYPERTENSION IN PREGNANCY

No agreement exists regarding the threshold blood pressure beyond which antihypertensive treatment should be started in mild to moderate hypertension in pregnancy. Threshold values between 160/100 mmHg and 140/90 mmHg have been suggested in the absence of target organ damage. Consensus exists, however, that a lower blood pressure

for starting treatment should be considered in the presence of target organ dysfunction. Aggressive control of hypertension is likely to increase the risk of IUGR, because very low maternal blood pressure is associated with low birth weight and increased perinatal mortality[27]. It may be necessary to reduce the dosage or even temporarily discontinue antihypertensives during the first half of pregnancy because of the physiological decline in maternal blood pressure. On the other hand, higher dosage may be required in chronic hypertension during the second half of pregnancy to prevent severe hypertension, although this strategy may not prevent the development of superimposed pre-eclampsia.

ANTIHYPERTENSIVE DRUGS

Antihypertensive drugs are classified, depending on their mechanism of action, into centrally acting drugs, adrenoreceptor antagonists, direct vasodilators, angiotensin converting enzyme inhibitors and receptor blockers, and diuretics. Because of their common mechanisms of action, drugs within each category tend to produce a similar spectrum of adverse effects.

Centrally acting drugs

This group of antihypertensives inhibits sympathetic outflow from vasopressor centers in the brain stem and is associated with unpleasant maternal adverse effects. The commonly used centrally acting drugs in pregnancy are methyldopa and clonidine.

Methyldopa

Worldwide, methyldopa is the most widely used antihypertensive drug in pregnancy, mainly because of its apparent safety, and partly because it is less expensive than some others[28]. It is, however, not useful for acute control of severe hypertension in pregnancy because of its delayed onset of action. It is also the best studied antihypertensive drug in pregnancy in terms of risks to the fetus. In this regard, it does not appear to exert adverse fetal effects[29]. Although data on first trimester use are limited, no evidence of a significant increase in congenital anomalies is present. It also has the longest neonatal and infant follow-up studies (up to 7.5 years). Its unpleasant maternal side-effects including sedation, tiredness, depression and sleep disturbances, make it unsuitable for managing postnatal hypertension. Adverse effects observed in non-pregnant women, such as lichenoid drug erruptions, agranulocytosis, autoimmune thrombocytopenia drug-induced hepatitis, pancreatitis and parkinsonism, are very rare in pregnancy, possibly because of the short duration of use in pregnancy.

Clonidine

Clonidine is not the drug of choice for hypertensive therapy in Europe and North America. In the absence of controlled trials on its use in moderate chronic hypertension, surveillance studies have not shown significant increases in major birth defects. An excess of hyperactivity and sleep disturbance has been reported in 22 children with mean age 6 years, who were exposed to clonidine prenatally[30].

Adrenoreceptor antagonists

The antihypertensive effect of this class of drugs is mediated primarily by reducing cardiac output. Adrenoreceptor blockers are divided into alpha adrenergic blocking agents (alpha blockers) and beta adrenergic blocking agents (beta blockers).

Alpha blockers

Alpha blockers, such as prazosin, act by preventing the release of noradrenaline from postganglionic adrenergic neurons. Prazosin causes a rapid fall in maternal blood pressure, and fetal blood levels are 10–20% of maternal levels. It is, therefore, not suitable for use in pregnancy. Furthermore, fetal transverse limb defects have been reported following its use[31]. This group of adrenoreceptor antagonists is thus not recommended in pregnancy because of fetal adverse effects.

Beta blockers

Beta blockers are the second most commonly used antihypertensives in pregnancy after methyldopa and are widely prescribed in Europe and Australia. Their main mechanism of action is reduction of cardiac output by decreasing heart rate and myocardial contractility. Selective beta blockers, such as atenolol, are widely used in the non-pregnant state, because they have fewer side-effects due to cardioselectivity and also because they are administered once daily. They appear to be equally safe and effective as methyldopa. Whereas cardiac output is increased in the non-pregnant chronic hypertensives, it is reduced in pregnancies complicated by IUGR or pre-eclampsia. However, a large retrospective study of atenolol use in pregnancy suggested it may be associated with IUGR, especially when administered in early pregnancy and continued for a longer duration[32]. Evidence suggests that atenolol impairs fetomaternal circulation and increases uterine artery resistance index (RI) and fetal aortic pulsatility index (PI)[33]. Evidence also suggests that beta blockers may have long-term adverse effects on very low birth weight neonates, resulting in increased neonatal mortality. In this study, seven out of 19 infants (27%) exposed to beta blockers *in utero* died within 15 days after birth compared with those born to mothers on other antihypertensives[34]. Atenolol is thus best avoided in pregnancy, particularly if it is complicated by pre-eclampsia or IUGR because of reduced maternal cardiac output and uteroplacental perfusion.

Non-selective blockers, such as oxprenolol, have intrinsic sympathomimetic activity and lower blood pressure mainly by decreasing vascular resistance and depressing cardiac output to a lesser extent compared to other beta blockers. Their use in pre-eclampsia is therefore less likely to be harmful than that of selective beta blockers. However, non-selective beta blockers may precipitate asthma, and should be avoided in such patients. These agents also impair glucose tolerance and interfere with metabolic and autonomic responses to hypoglycemia and should be avoided in diabetics. Isolated cases of neonatal hypoglycemia[35] and bradycardia[36] have been reported; there were no long-term consequences, however.

Combined alpha and beta blockers

Combined alpha and beta blockers, such as labetalol, lower blood pressure by peripheral vasodilatation without compromising the maternal cardiovascular system. Labetalol is the commonest adrenoceptor antagonist and the second most studied antihypertensive used during pregnancy after methyldopa. It is well tolerated and does not appear to be teratogenic, although data on this point are limited in human pregnancy[37]. It has only 25% of the beta blocking effects and achieves blood pressure control while maintaining renal and uterine blood flow. One study suggested its use in established pre-eclampsia may reduce the amount of proteinuria[38]. There is, however, evidence that it may increase the risk of IUGR in spite of its vasodilatory effects, especially if started in second trimester[39]. Acute administration of labetalol causes a reduction in heart rate, peripheral resistance and blood pressure

without abrupt maternal hypotensive effect and without interfering with uteroplacental circulation. Babies born after acute administration of labetolol for severe hypertension are less likely to have umbilical cord blood pH of less than 7.20 compared to those who have had hydralazine[39].

Vasodilators

Vasodilatory drugs, such as hydralazine, calcium channel blockers, diazoxide and sodium nitroprusside, act directly on blood vessel walls and reduce peripheral vascular resistance by different mechanisms. Diazoxide opens ATP sensitive potassium channels; calcium channel blockers prevent intracellular calcium flux, while sodium nitroprusside acts as a nitric acid donor. Diazoxide and sodium nitroprusside are not recommended for use in pregnancy because they are associated with acute fetal distress, intrauterine death and other undesirable fetal adverse effects[40].

Calcium channel blockers

These are vasodilators which act primarily by inhibiting extracellular calcium influx into smooth muscle cells through slow calcium channels, thus interfering with excitation–contraction coupling. Their vasodilatory effect is proportional to the degree of peripheral vasoconstriction, and therefore the extent of blood pressure reduction appears to be proportional to the pre-treatment blood pressure. Dihydropyridines such as nifedipine act predominantly on the peripheral vasculature, are antagonistic to all forms of vasoconstriction, and also exhibit a mild tocolytic effect. They are therefore useful in acute and long-term control of hypertension. Nifedipine is the commonest calcium channel blocker used in pregnancy. It is safe in therapeutic doses[41]; no teratogenic effects have been reported[42]; and it does not appear to adversely affect fetomaternal circulation when used for short- and long-term control of hypertension. However, severe maternal hypotension has been reported following administration of short-acting nifedipine for acute control of severe hypertension when administered sublingually or coadministered with magnesium sulfate[43,44]. Sublingual administration of nifedipine should be avoided to prevent rapid fall in maternal blood pressure. Nicardipine and nimodipine are also calcium channel blockers used in pregnancy; however, data on their safety and effectiveness are limited.

Hydralazine

Hydralazine decreases blood pressure by reducing peripheral vascular resistance. It causes direct vascular wall dilatation by as yet unexplained mechanism(s); however, it requires an intact endothelium to produce these effects[45]. It is more effective in lowering diastolic than systolic pressure. Its onset of action is 20–30 minutes even with parenteral administration. Hydralazine is the most commonly used drug for acute control of hypertension in pregnancy in North America. It is no more effective than intravenous labetolol; however, it is frequently associated with profound maternal hypotension and fetal distress from decreased fetoplacental perfusion. It is therefore more likely to result in urgent delivery by cesarean section with lower neonatal Apgar scores, compared to parenteral labetalol or oral nifidepine[46]. Abrupt and profound maternal hypotension resulting from hydralazine can be prevented by concomitant administration of a bolus of intravenous fluid. Although it is commonly administered intravenously for acute control of hypertension, it has also been used as second line therapy for long-term management of chronic hypertension. However, chronic administration may result in reduced renal perfusion pressure and fluid retention, thus

blunting its hypotensive effect. Data regarding its use during the first trimester and possible teratogenic effects are inadequate[37]. Hydralazine increases maternal heart rate and cardiac output from reflex sympathetic activation. This causes sustained release of noradrenaline resulting in tachycardia, flushing, nasal congestion, anxiety, restlessness and tremors. Headache is also a common side-effect due to dilatation of the cerebral venous circulation. Reported maternal adverse effects following chronic administration include hydralazine-induced lupus-like syndrome and hepatitis.

Diuretics

Diuretics deplete body water and sodium stores, and lower blood pressure by reducing blood volume and cardiac output. Their use in pregnancy remains controversial because of the potential to reduce or prevent physiological plasma volume expansion and therefore reduce uteroplacental perfusion. There is limited evidence that diuretics prevent plasma volume expansion[47], and women with chronic hypertension on diuretics do not increase their plasma volume to the same extent as occurs in normal pregnancy[47]. Since reduced maternal plasma volume is associated with impaired uteroplacental perfusion and fetal growth, diuretics should be avoided in pregnancies complicated by pre-eclampsia or IUGR. Their use in pregnancy is rare; however, teratogenic effects have not been reported. Maternal adverse effects including pancreatitis, hyperuricemia and hyperglycemia have been reported. Isolated adverse fetal and neonatal effects include fetal bradycardia, neonatal thrombocytopenia and neuroblastoma following *in utero* exposure. It a reasonable option to consider as a preconception antihypertensive in mild to moderate chronic hypertension. It may also be considered for postpartum management of hypertension. Frusemide is particularly useful for managing pulmonary edema complicating pre-eclampsia.

Agents that block production or action of angiotensin

This group consists of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). ACE inhibitors such as captopril, enalapril and lisinopril inhibit ACE. They reduce angiotensin and aldosterone production and thus decrease peripheral vascular resistance. They are widely used to treat hypertension in the non-pregnant state particularly if complicated by renal insufficiency or diabetes. The commonest maternal side-effect is dry coughing, and this is often the commonest reason for patient non-compliance. Angiotensin-II receptor blockers (ARBs) such as candesartan and losartan do not inhibit the breakdown of bradykinin, and thus are less likely to cause persistent dry cough.

ACE inhibitors are contraindicated in pregnancy, because they are associated with increased risk of fetal anomalies. Their use is associated with fetal renal failure, IUGR, oligohydramnios, pulmonary hypoplasia and fetal death[48]. Such fetal adverse effects appear to occur regardless of the gestational age at which these agents are administered. For this reason, care should be exercised when prescribing ACE inhibitors for women of childbearing age as a significant proportion of pregnancies are unplanned. It should be avoided in women with chronic hypertension who are planning a pregnancy, unless there is a compelling long-term indication such a history of diabetic nephropathy. In such cases the patient should be advised to inform her doctor as soon as she misses a period so that the ACE inhibitor can be changed to a suitable alternative. Data on ARBs use in pregnancy are limited. They should be avoided, as their mechanisms of action are similar to ACE inhibitors and they appear to have similar fetal adverse effects[49,50].

POSTNATAL HYPERTENSION AND ANTIHYPERTENSIVE THERAPY

The prevalence of postpartum hypertension is unclear and may represent a continuation of antenatal hypertension (recurrent) or appearance of a new hypertensive disorder (*de novo*). Women who develop postpartum hypertension are likely to stay in hospital longer after delivery, and this often results in anxiety about their recovery. Furthermore, severe hypertension may result in maternal mortality and vascular complications such as stroke. In spite of these risks, few data indicate the best method for managing women who develop hypertension after delivery.

General consensus exists that severe postpartum hypertension (systolic BP ≥160 mmHg or diastolic ≥110 mmHg) should be treated to prevent maternal vascular complications. However, there is no agreement on the benefits of treating mild to moderate disease, particularly when to start drug treatment and which treatment threshold to aim for. In spite of regular use of antihypertensive drugs for postnatal hypertension, little evidence exists for their safety and effectiveness. Data on safety of antihypertensives during breastfeeding are based on surveillance studies and case reports. A review of the available reports showed that the commonly used antihypertensives during pregnancy and breastfeeding such as methyldopa, beta blockers, combined alpha and beta blocker (labetalol) and nifedipine have minimal breast milk to maternal plasma ratios and are therefore safe during breastfeeding[50]. A recent Cochrane review has also shown no evidence that any of these antihypertensives are more effective than the other. The choice of antihypertensive drugs for postnatal hypertension should therefore be based on familiarity[51].

CONCLUSION

Hypertensive disorders of pregnancy are associated with increased adverse outcomes. Preconception counseling offers an opportunity to assess disease severity and ensure control before pregnancy, review antihypertensive agents already prescribed and change to safer alternatives, and formulate a detailed plan of management during pregnancy. It also provides an opportunity to counsel women with a previous history of pre-eclampsia and to discuss their risk of recurrence when this was not provided following the previous pre-eclamptic pregnancy. Although general consensus supports treating severe hypertension in pregnancy, the benefits and risks of antihypertensive drug therapy in a patient with a mild to moderate rise in blood pressure are still uncertain. All antihypertensive agents appear to cross the placenta and reach the fetus to different degrees, but there are inadequate data on the safety of antihypertensive drugs during pregnancy and evidence is limited to surveillance studies. There is no evidence that the commonly used antihypertensive drugs such as methyldopa, beta blockers, the combined alpha and beta blocker (labetolol) and calcium channel blockers (nifedipine) are associated with increased fetal or neonatal adverse effects. There is, however, convincing evidence that ACE inhibitors and ARBs are associated with significantly increased fetal adverse effects and should be avoided in pregnancy. The administration of antihypertensives to pregnant women with either pre-existing hypertension or pregnancy induced hypertension should be carefully discussed with the women by an experienced clinician.

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