

THE MANAGEMENT OF HYPERTENSION IN PREGNANCY

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Hypertension in pregnancy is a common and sometimes serious complication of pregnancy. It is a major cause of preventable perinatal and maternal mortality and morbidity. The principles of management include the recognition of risk factors, early diagnosis, close maternal and fetal monitoring with prompt identification and treatment of complications, the use of anti-hypertensive and anti-convulsant drugs when indicated and the timely delivery of the baby. In order to achieve the optimal pregnancy outcome, a joint approach between the physician, obstetrician and neonatologist is of great importance.

Keywords: Hypertension in pregnancy, Pre-eclampsia, Eclampsia, Anti-hypertensive drugs, Anti-convulsants, Fetal monitoring.

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INTRODUCTION

The incidence of hypertensive disorder in pregnancy is approximately 4.5% (1) of all deliveries. It is the commonest condition complicating pregnancy and is associated with an increase in both fetal and maternal morbidity as well as mortality.

Before proceeding further into the discussion of the management of hypertension in pregnancy, it is important to examine the normal changes in blood pressure during pregnancy and the diagnosis and classification of the disorder.

NORMAL BLOOD PRESSURE CHANGES IN PREGNANCY

Blood pressure normally falls at the beginning of pregnancy and reaches a nadir in the second trimester when the diastolic blood pressure (DBP) is on an average 15mmHg and the systolic blood pressure (SBP) 5 mmHg lower in the lying position compared with the pre-pregnancy level (2). This early pregnancy fall in blood pressure is noted in both the normotensive as well as the hypertensive person. As a result, a woman with chronic hypertension may appear normotensive during the second trimester. Blood pressure returns to the pre-pregnancy level at third trimester.

CLASSIFICATION OF HYPERTENSION IN PREGNANCY

For the purpose of management and prognosis, hypertension in pregnancy can be classified into three main categories:

1. Gestational hypertension and/or proteinuria

This condition is unique to pregnancy, usually occurs after the 20th week of gestation but can occur earlier in the presence of trophoblastic disease. (Hypertension with proteinuria is also known as pre-eclampsia.)

2. Chronic hypertension

Hypertension of whatever cause, antedating pregnancy and persisting beyond the puerperium.

Superimposed pre-eclampsia occurs when proteinuria develops for the first time during pregnancy in a woman with known chronic hypertension.

3. Unclassified Hypertension and proteinuria

Hypertension and/or proteinuria found either:

- i. At first examination at or after the 20th week of pregnancy in a woman without proven chronic hypertension or chronic renal disease, or
- ii. Where insufficient information is available to permit classification.

Eclampsia is regarded as one of the complications of the hypertensive and proteinuric disorders of pregnancy and is not included in the classification (3).

DIAGNOSIS OF HYPERTENSION IN PREGNANCY

The diagnosis of hypertension in pregnancy is at best, arbitrary. Blood pressure increment, mean arterial pressure (MAP) and absolute blood pressure recording have all been used.

As it has been shown that in terms of management and prognosis, the absolute level of blood pressure recording is more important than the rise during pregnancy (4), the blood pressure level rather than the increment from baseline reading is preferred in the diagnosis of hypertension.

Criteria based on combinations of systolic and diastolic blood pressure or on derived values such as the MAP are complicated, and are no better than the DBP as a predictor of fetal outcome (3).

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The criteria using the level of 90mmHg or more diastolic taken at the point of muffling (Korotkoff point IV) throughout pregnancy is simple and precise (5).

In our practice, the diagnosis of hypertension in pregnancy is based on either a DBP of 90mmHg or more on two occasions at least six hours apart, or one reading of DBP 110mmHg or more (6).

Significant proteinuria is present when the 24 hours urinary total protein is more than 500mg (7) or a total urinary protein concentration of 300 or more mg/litre (8).

MANAGEMENT OF HYPERTENSION IN PREGNANCY

All patients with severe hypertension booked at the Singapore General Hospital are assessed jointly in a combined clinic by the obstetrician and the renal physician.

The principles of management of hypertension and specifically that of pre-eclampsia have remained generally unchanged for many years. They are:

1. Early diagnosis of hypertension;
2. Maternal monitoring;
3. Fetal monitoring;
4. Anti-hypertensive drugs whenever necessary;
5. Treatment of complications; and
6. Optimal timing of delivery.

1. Early diagnosis of hypertension

Proper antenatal care aims at identification of patients at risk of developing hypertension and its early detection. Certain risk factors are recognised.

AGE and PARITY have an important influence on the incidence of hypertensive and proteinuric disorders. The primigravidae as well as women over the age of 35 years have increased incidence of the disorder as well as poorer outcome (9, 10). Primigravidae have approximately double the incidence of proteinuric pregnancy-induced hypertension (11). The incidence of pre-eclampsia is higher in those with a FAMILY HISTORY of similar disorder and there are suggestions that severe pre-eclampsia could be inherited as a simple recessive trait (12). RECURRENT pre-eclampsia in a woman with a history in previous pregnancies is not unusual. TWINNING is associated with an increased incidence of both proteinuric and non-proteinuric hypertension (11). Dizygotic twin pregnancies are more likely to have pre-eclampsia than monozygotic (13, 14). Maternal DIABETES is a risk factor (15) as is OBESITY. A wider cuff should be used when measuring blood pressure in the obese; otherwise, a falsely high reading may be obtained. Maternal smoking, surprisingly, is associated with a reduced incidence of pre-eclampsia (16). The relationship of hypertension and polyhydramnios, hydrops fetalis, polyhydramnios and FETAL MALFORMATIONS is debatable. There is higher incidence of hypertension in patients with hydrops fetalis or polyhydramnios where the fetus is normal.

2. Maternal monitoring

Recognition of progression of the disease and its complications improves the obstetric outcome. Complications include loss of blood pressure control, onset of renal and hepatic impairment, cerebral involvement, and coagulation disorders.

Basal investigations are performed to determine possible causes of the hypertension and act as a baseline for follow-up. These include measurement of renal function with uric acid and creatinine, liver function, platelet count, coagulation profile and urinary protein excretion. Urine specimen is examined for the

presence of red blood cells underlying renal disease. Vanillylmandelic acid excretion to screen for phaeochromocytoma is performed in selected cases. A rapid rise in urate is often the first indicator of developing pre-eclampsia.

The mainstay in the treatment of mild hypertension is rest. Rest at home is usually satisfactory in early and mid-pregnancy although admission may be necessary when it is not feasible. All women with severe hypertension must be managed as in-patients.

3. Fetal monitoring

There appears to be little difference in the perinatal mortality between patients with mild and moderate hypertension compared with those who are normotensive.

In women with severe pre-eclampsia, perinatal mortality is doubled. Most of the increased mortality is a result of intra-uterine growth retardation or prematurity and the most important factor affecting the outcome of such babies is the availability of good neonatal back-up.

The significance for the fetus of chronic hypertension in pregnancy is in the increased risk of developing pre-eclampsia. The incidence of pre-eclampsia developing in patients with pre-existing hypertension is two to seven times. The perinatal mortality in these patients is higher than in those where pre-eclampsia develops de novo. In patients who do not develop superimposed pre-eclampsia, perinatal mortality is not increased compared with the normotensive (17) and may even be reduced.

All women booked with the department have a screening ultrasound scan between the 16th and 20th week of gestation. This screening scan correctly dates the period of gestation and identifies fetal abnormalities. It acts as a baseline for fetal growth in pregnancies complicated by hypertension where serial ultrasound scan measurements and liquor volume are assessed at intervals.

Cardiotocographic tracings to assess fetal well-being are done at intervals determined by the severity of the disease.

Doppler studies to assess uteroplacental and umbilical blood flow is an adjunct to the assessment of fetal wellbeing.

Biochemical monitoring of oestriol levels or other placental function tests are not done for the purpose of fetal monitoring in the department. These tests are of little value compared with the biophysical methods.

4. Anti-hypertensive drugs

Hypertension in pregnancy can be categorized as mild to moderate in the range of 140-169/90-109 mmHg and severe as 170/110 or above.

The need for antihypertensive drug therapy is not affected by the cause of the hypertension but by the overall management strategies. This depends on the situation, the gestation and the degree of hypertension.

Treatment is started in all patients regardless of gestation if the blood pressure reaches 170mmHg systolic and/or 110mmHg diastolic. A blood pressure of 170-180/110-120 represents a MAP of 130-140 mmHg which is close to the limits beyond which experimental vascular damage begins (18). Reducing the blood pressure in such cases is mandatory as cerebral haemorrhage is the major cause of maternal death from pregnancy associated hypertension (10). The intention of anti-hypertensive therapy is to keep all blood pressure readings below 170 systolic and 110 diastolic. The decision to treat should be based on the maximum pressure recorded.

While the indication for treatment of severe hypertension is not disputed, that of treating mild to moder-

ate hypertension is not as clear cut. On the evidence available from several studies, there is little to justify treatment of mild to moderate hypertension in pregnancy on maternal grounds (19-22). In patients with hypertension antedating the 20th week however, treatment was associated with a significantly better fetal outcome (19).

Treatment has been advocated to prevent the development of pre-eclampsia in women with essential hypertension (23) and to prevent the progression of mild pre-eclampsia in early pregnancy once it is established (24).

In practice, a blood pressure of say 150/95mmHg at 28 weeks gestation in a woman known to be normotensive before pregnancy and during early pregnancy would be cause for concern as an indicator of developing pre-eclampsia, while a similar level in a woman with documented chronic hypertension, would be expected and need not necessarily be associated with an abnormal pregnancy outcome.

If the woman has been taking anti-hypertensive treatment prior to pregnancy, we tend to stop any diuretic as soon as she presents. An agent of proven safety in pregnancy may be introduced under careful monitoring.

Anti-hypertensive drugs for maintenance of blood pressure control

METHYLDOPA is the anti-hypertensive most used in Britain (25) and in our department. It is the drug of first choice for most obstetricians because of the wide experience of its use in pregnancy. Treatment is initiated at 125 mg to 250 mg three times a day depending on the initial blood pressure. Occasionally, a loading dose of twice maintenance dose may be given. Maximum therapeutic effect is attained in 12 hours and the maximum dosage given per day is 2g. Another drug may be added if the blood pressure is not controlled with the maximum dosage.

Sedation and drowsiness is common with high dosage of the drug especially during the first 48 hours. A history of severe depression is a contraindication to its use although the incidence of depression associated with its use in pregnancy is not noted to be increased. Oliguria may occur and blood urea and creatinine should be checked. Follow-up on children exposed to the drug in-utero showed no gross adverse effect of the drug.

Adrenoceptor blockers are also being used in pregnancy. PROPRANOLOL is the beta blocker that has been most widely used for pregnancy hypertension. Beta blockers carry the theoretical risk of precipitating premature labour which has been reported with high dose propranolol dosage of 240 to 320 mg/day (26). Fetal and neonatal side-effects were thought to be common and included hypoglycaemia, low Apgar scores, fetal bradycardia and neonatal apnoea (27, 28). These complications however, might have been caused by the severe hypertension and placental insufficiency associated with the disease rather than as a result of the drug (29). Propranolol is occasionally used together the Hydralazine

The superiority of LABETALOL over methyldopa has been claimed on limited patients (30). Larger studies showed that the drug is as effective compared with methyldopa but demonstrated little specific advantage (31). The most common side effect is an acute onset of tremulousness or shakiness which must be distinguished from impending eclampsia. Another side effect noted in our patients using the recommended dosage of 100mg three times a day is severe postural hypotension. The incidence is reduced when the initiating dose is reduced to 50mg three times a day.

Claims have been made in one study that the use of OXPRENOLOL resulted in bigger babies (32)

although other studies failed to demonstrate this difference when compared with Methyldopa (33).

ATENOLOL is a cardio-selective beta blocker and is effective in controlling blood pressure in pregnancy (21, 34-36). A slight decrease in fetal heart rate and fetal heart rate variability, neonatal bradycardia and other sequelae of beta blockage occur. In women with severe pre-eclampsia liable to have a compromised growth retarded fetus, its use should be viewed with caution.

Information on other adrenoceptor blockers comes from uncontrolled trials or controlled trials which are too small to be conclusive.

Oral administration of the calcium antagonist NIFEDIPINE has been used for control of severe hypertension (37). Oral dosage of 10mg produces a significant reduction of systolic pressure within 30 minutes but has the disadvantage of a short duration of action. Optimal effect of the drug lasts for only four hours and repeated dosage may be required to maintain blood pressure. It is more suitable for use in combination with other antihypertensives in maintaining blood pressure.

DRUGS BEST AVOIDED IN PREGNANCY

The short and long term administration of THIAZIDE DIURETICS may be associated with a reduction in plasma volume (38) which is likely to aggravate the hypovolemia of severe pre-eclampsia (39). Uteroplacental perfusion is likely to be reduced with plasma volume reduction. The interpretation of serum urate changes, an indicator of the pre-eclamptic process is also invalidated. Besides hypovolemia, diuretics can cause maternal and fetal electrolyte imbalance as well as thrombocytopenia in the neonate. The only indication for the use of diuretics is in cases of congestive cardiac failure.

GUANETHIDINE, BETHANIDINE and DEBRISOQUINE frequently cause postural hypotension. This is most undesirable in a situation where uteroplacental perfusion has to be maintained. A higher perinatal mortality was reported by Michael with the use of these adrenergic blocking agents (40).

CAPTORIL inhibits the enzyme responsible for conversion of angiotensin I to II. The rationale for its use was the postulation that renin-angiotensin abnormality may be the etiological basis of pre-eclampsia. Animal and human studies have shown major adverse effects and the drug should not be used in pregnancy (41, 42).

RESERPINE takes a long time to stabilise blood pressure and has many major side effects including maternal depression as well as respiratory and temperature regulatory dysfunction in the neonate.

SEDATIVES do not have a beneficial effect in the management of mild and moderate hypertension. Their use may dull the patients' symptoms and induce a false sense of security in the medical staff. Fetal heart rate reactivity as well as respiration may be depressed. The use of such drugs as anticonvulsants in the control of imminent eclampsia represents a different issue.

5. Treatment of Complications

Pre-eclampsia is a multi-system disorder and as such, the control of blood pressure is but one of the treatment modalities. Early diagnosis and management of the other complications of pre-eclampsia must be considered. These include the central nervous system, renal system, hepatic system and problems with coagulation.

Eclampsia

Eclamptic convulsion is a major complication with a perinatal mortality of 30-40% and a maternal mortal-

ity of 3-4%. Signs and symptoms of impending eclampsia include headache, blurring of vision, epigastric pain and central nervous system irritability. Eclampsia is characterised by convulsions.

A wide variety of protocols has been used with the aim to control central nervous system irritability and convulsion as well as to lower blood pressure to prevent cerebral vascular and other vascular damage.

Oral sedatives and anticonvulsants are used in the prevention of eclampsia in patients with severe pre-eclampsia or those showing signs of cerebral irritability. The drugs used include PHENYTOIN 100 mg two to three times daily and DIAZEPAM 5 to 10mg two to three times a day.

CHLORDIAZEPOXIDE (Librium) is the most common anti-convulsant used in the department in preventing and controlling convulsions. Its major side effects include maternal and neonatal sedation. The drug is given either intramuscularly or by intravenous infusion. Like all other benzodiazepine group of drugs, it can cause respiratory depression, hypothermia and neonatal hypotonia. Alternatively, bolus or intravenous infusion of DIAZEPAM (Valium) may be used with comparable success and side effects.

Because of the effectiveness of the benzodiazepines, we have little experience with other anticonvulsants. MAGNESIUM SULPHATE is the common drug used in the United States. It acts as a neuromuscular blocking agent with little central depression. The drug may be given intramuscularly or intravenously. The advantages of the drug are its effectiveness and predictability of action. Monitoring of serum Magnesium levels is important as heart block and respiratory paralysis can occur with an overdose.

Infusion of 0.8 percent CHLORMETHIAZOLE is effective in preventing convulsions. It is however a poor choice in most cases as there are several disadvantages. It is difficult to titrate its effect, its formulation requires the administration of a large volume of water. It is cumulative in the patient with hepatic and renal disorders and it results in fetal and neonatal depression.

Antihypertensive drugs in acute blood pressure control

The most common drug used for control of acute blood pressure in our experience is HYDRALAZINE. Intravenous infusion of 100 mg of hydralazine in 500ml of 5% Dextrose is titrated at a rate to reduce the blood pressure to a diastolic level of about 95mmHg. Close monitoring of the blood pressure, urinary output, signs of cerebral irritability and fetal well being must be carried out. Side effects of treatment include headaches, nausea, vomiting, anxiety, restlessness and epigastric pain which are sometimes impossible to differentiate from impending eclampsia. Too rapid reduction of blood pressure may result in failure of uteroplacental perfusion and fetal distress (43-45). Intramuscular Hydralazine has been used (46) but is best avoided because of its unpredictable effect which may result in sudden profound drop in blood pressure.

DIAZOXIDE is a direct acting vasodilator which has a faster and longer action than hydralazine. The recommended dosage of rapid bolus dose of 300mg had resulted in severe hypotension and even maternal death (47-49). Reduction of bolus dose to 150mg or repeated smaller boluses are effective and avoid the hypotension. Uteroplacental blood flow may be reduced and may further compromise a stressed fetus.

Experience in the use of, SODIUM NITRO-PRUSSIDE in pregnancy is limited and there is a theoretical possibility of cyanide toxicity in the human fetus as in the ewe (50). It is best reserved for exceptional circumstances such as refractory hypertension with pulmonary oedema or management of phaeochromocytoma.

NIFEDIPINE (Adalat), a calcium channel blocker has been used effectively. Our experience with sublingual Nifedipine in acute hypertension is accumulating and has been encouraging. Side effects like headache, cutaneous flushing and tachycardia are frequent but no change in the fetal heart rate recording has occurred (51). It is probably a good choice for short term pressure control during the transfer of patients from the general practitioner's clinic to the hospital.

LABETALOL a combined alpha-beta adreno-receptor blocker has been used both intravenously (52) and orally (53) for acute pressure reduction. Side effects are minimal on the mother but there is a possible adverse effect on the newborn particularly in the compromised fetus (54).

Acute Renal Failure

Acute renal failure is one of the most serious complications of pre-eclampsia. Acute renal failure complicating hypertension in pregnancy may be due to a variety of lesions, from simple ischemia and oedema to tubular necrosis and patchy or complete cortical necrosis. The commonest sign of renal failure is oliguria (production of less than 300 ml of urine per day) accompanied by a rising serum creatinine, uric acid and urea. Renal failure is usually severe and frequently fatal.

Coagulopathy

Disseminated intravascular coagulopathy is a complication of severe pre-eclampsia. Platelet count may be reduced indicating an increased consumption and a reduced platelet lifespan. With the knowledge that abnormal coagulation probably mediates at least some of the terminal events of the disorder, various regimens of anticoagulation have been tried. Heparinisation failed to modify the course of severe pre-eclampsia. Dipyridamole (Persantin) and low dose aspirin are being tried but our experience at the moment is too limited for comments.

Hepatic Failure

Jaundice is a characteristic presentation of severe hepatic impairment (55) often associated with coagulation disturbances and haemolysis. The differential diagnosis includes acute fatty liver of pregnancy, haemolytic uraemic syndrome and thrombocytopenic purpura (56). In the presence of liver involvement, urgent delivery is desirable (57).

Placental Abruption

There is an association between placental abruption and pre-eclampsia but whether placental abruption is due to pre-existing pre-eclampsia or whether pre-eclampsia arises as a result of pathological changes in abruption is uncertain (58). Whatever the origin, placental abruption is an obstetric emergency. Coagulation abnormalities should be corrected and delivery be expedited.

6. Timing of delivery

The definitive treatment of pre-eclampsia is delivery. The timing of delivery depends on the risk to the mother, in which case, the fetal interest is secondary, or, when the mother is not in immediate danger, the balance between the risk of prematurity and intrauterine asphyxia. Our neonatologists play an active role in the decision on the timing of delivery.

The general policy is to manage conservatively pre-eclampsia occurring before 36 weeks provided that the mother is asymptomatic, her blood pressure can be controlled, her liver and renal functions are normal and there is no evidence of fetal distress. The development

of signs and symptoms of complications are indications for urgent delivery.

MANAGEMENT OF LABOUR

After a decision is made to deliver the baby, the mode of delivery has to be considered. This depends on the urgency of the situation, the period of gestation and the presence or absence of factors that makes vaginal delivery inadvisable. Patients with severe pre-eclampsia in early gestation are more likely to be delivered by Caesarean section while mild hypertensives near term are more likely to be delivered vaginally.

In the presence of an unfavourable cervix, cervical ripening with prostaglandins may be carried out in patients with mild to moderate hypertension. If the cervix is favourable, labour is induced by artificial rupture of the membranes and oxytocic infusion. The process of cervical ripening and labour is monitored carefully. The blood pressure, urine output and fluid intake must be recorded.

In the absence of coagulopathy, epidural analgesia is an excellent form of pain relief in labour and is the anaesthetic of choice for Caesarean section. General anaesthesia is associated with increased risks. Laryngeal oedema accompanying generalised oedema may complicate intubation. Intubation itself may cause reflex hypertension imposing a transient increase in circulatory afterload. Anaesthesia in patients with severe hypertension is certainly not for the novice.

The third stage of labour is managed actively. A woman with a shrunken intravascular compartment is less tolerant of blood loss than is a normal pregnant woman (59). Postpartum haemorrhage should be prevented with the use of syntocinon. Ergometrine should be avoided because it causes hypertension for which the pre-eclamptic patient is particularly prone (60). Headache, convulsion and death have been reported as major sequelae with ergometrine (61).

With improvement in antenatal care and intrapartum management, the incidence of eclampsia during those periods has decreased considerably in recent years. However the incidence of eclampsia during the immediate postpartum period remained unchanged. One must bear in mind that maternal mortality has occurred as a result of postpartum eclampsia (10) and continued surveillance must be maintained.

Antihypertensive drugs may be discontinued or reduced depending on the degree of hypertension. Sedatives, when required antenatally, are best continued for at least another 24 hours.

POST-PARTUM EXAMINATION

Pre-pregnancy counselling of a patient with a history of severe pre-eclampsia is an essential part of obstetric care. This is even more important if the complicated pregnancy had been unsuccessful. Proper diagnosis and advice will allay fear in the couple regarding their future reproductive prospects.

During the postnatal examination which is usually carried out six weeks after delivery, the blood pressure must be measured. If the blood pressure has returned to normal and there is no proteinuria, the patient can be encouraged to start another pregnancy whenever she desires. In general, severe pre-eclampsia does not recur in subsequent pregnancy and the prognosis is good. There are however a small number of patients in whom severe pre-eclampsia may recur and in these patients, the possibility of unsuspected chronic renal disease may be present. For this reason, patients are advised to report early in the next pregnancy and intensive antenatal care will be instituted to pick up the earliest evidence of pre-eclampsia.

If the patient is still hypertensive and/or proteinuric, our renal physician will continue to manage her. A high prevalence of unsuspected underlying renal disease has been reported (62) in women presenting as pre-eclampsia in pregnancy. In these cases, the timing of subsequent pregnancies depends on the extent of hypertension, the renal function and the nature of the renal lesion as defined by renal biopsy. Contraceptive advice will be given until full assessment can be completed.

THE FUTURE

Recent studies have indicated a place for the use of low dose ASPIRIN in the prevention of pre-eclampsia in high risk patients (63). Together with the possibility of using doppler assessment of utero-placental blood flow in early pregnancy as a screening test for pre-eclampsia (64), there is hope that complications associated with this common problem of pregnancy may be reduced in the near future.

CONCLUSION

The major step, to my mind, in the management of hypertension in pregnancy is the recognition that a multi-disciplinary approach is mandatory to the problem. Close co-operation between the primary health care providers, the obstetricians, the physicians and the neonatologists will contribute to the optimal management of this common and serious complication of pregnancy.

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