Management of Hypertensive Disorders in Pregnancy- An Update

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Abstract

Hypertension is the most common medical disorder in pregnancy. It complicates about 15% of all pregnancies and is an important cause of maternal and foetal morbidity and mortality. According to the onset of hypertension in relation to pregnancy and its duration and the development of proteinuria & convulsion it is categorized into several types. The prognosis depends on duration and severity of hypertension and multi-system involvement. The aim of management is to achieve a gradual and sustained lowering of BP to prevent maternal complications and to allow prolongation of pregnancy for fetal benefit. For management purpose, according to recent NICE clinical guideline gestational hypertension has been classified into mild, moderate and severe types. Till now there is controversy regarding the use of antihypertensives in mild to moderate hypertension. Labetalol, hydralazine & methyldopa are used as first line drugs according to severity of hypertension. Magnesium sulphate is the anticonvulsant of choice and nimodipine is the newer alternative. Obstetric management in all the types of hypertensive disorders is almost same. Expectant management can be considered for women at <34 weeks gestation only in well-equipped centers capable of caring very pre-term babies. Antenatal corticosteroid is recommended for enhancing fetal lung maturity. There is a common consensus that the hypertensive patients should be delivered at 37 weeks as there is no benefit in continuing the pregnancy. For women with any type of hypertensive disorders, vaginal delivery should be considered unless cesarean section is required for the usual obstetric indication.

Keywords: Gestational Hypertension, Pregnancy, Eclampsia, Management.

Introduction

Hypertension (HTN) in pregnancy is diagnosed from an absolute rise in blood pressure (BP) i.e. ≥140/90 mm Hg. Blood pressure is related to gestational age. A diastolic pressure of 90 mm Hg is 3 standard deviation (SD) above the mean for

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mid pregnancy, 2 SD and 1.5 SD above mean at 34 weeks and term respectively. For diagnosis, blood pressure must be elevated at least on two occasions 6 hours apart and measurement should be made with the woman seated.

Hypertension (HTN), the most common medical disorder during pregnancy complicates about 15% of all pregnancies and accounts for one quarter of all antenatal admissions. Despite treatment it remains as an important cause of maternal and foetal mortality and morbidity. Hypertension affects 7-15% of all pregnancy and is associated with 22% of

all perinatal death in USA.² In India and developing countries, eclampsia has been reported to have a maternal mortality of 12 and perinatal mortality rate in severe preeclampsia was found 4.76%.3,4 The main risk to mother are placental abruption, accelerated hypertension leading hospitalization, target organ damage e.g. cerebrovascular catastrophe. The foetal risk includes growth restriction and prematurity due to worsening maternal condition leading to early delivery. Some pregnant women have preexisting risk factors for the development of hypertension which include medical diseases like diabetes, chronic hypertension, chronic kidney disease, autoimmune disease, or the occurrence of hypertensive disorders in previous pregnancy. Other factors have lesser risks e.g. obesity, age, null parity, family history of hypertensive disorders of pregnancy or a blood pressure at the higher end of normal range for age.^{5,6} The aims of management of hypertensive disorders of pregnancy are prevention maternal & fetal of complications and to continue the pregnancy up to term if possible to ensure a safe delivery for both mother & fetus.

Hypertensive disorder of pregnancy include-

- Gestational hypertension
- Pre-eclampsia (PE)
- Eclampsia.
- Chronic hypertension
- Chr. HTN with superimposed PE

Gestational hypertension: Hypertension without proteinuria, developing after 20 weeks of gestation, during labour, or the puerperium in a previously normotensive nonproteinuric woman. It complicates 6-7% of all pregnancies and resolves by six weeks postpartum.^{7,8}

Preeclampsia: Hypertension associated with proteinuria greater than 0.3 g/L in a 24-hour urine collection or 1+ by qualitative urine examination, after 20 weeks of gestation.

Eclampsia: Convulsion occurring in a patient with preeclampsia is known as eclampsia.

Chronic hypertension: It is defined as hypertension present before the 20th week of pregnancy or that present before pregnancy. Hypertension should be documented on at least two occasions measured at least 4 hours apart.⁸ Chronic Hypertension complicates 3-5% of all pregnancies, might be higher in women who become pregnant at 30s or 40s.⁹

Chronic hypertension with superimposed preeclampsia: It is defined as proteinuria developing for first time during pregnancy in a woman with known chronic hypertension.

Management of gestational hypertension

Gestational hypertension is the most frequent hypertensive condition of pregnancy with a prevalence of 6-15% in nulliparae and 2-4% in multiparae. 10,11

On management point of view patients may be categorized into mild (BP 140/90-149/99 mm Hg), moderate (BP 150/100-159/109 mm Hg) and severe hypertension (BP 160/110 mm Hg or more). Women with gestational hypertension require an evaluation whether there is any significant risk factors for poor pregnancy outcome (Box-I).

Box I Criteria to identify high risk women with gestational hypertension

- Blood pressure 150/100 or more
- Gestational age less than 30 weeks
- Evidence of end organ damage (elevated serum creatinine, liver enzymes, LDH, decreased platelet count)

- Oligohydramnios
- Fetal growth restriction
- Abnormal uterine and /or umbilical Doppler velocimetry

Patients with mild hypertension without any risk factors should be managed on outpatient basis with weekly antenatal visit. In mild hypertension antihypertensive is prescribed and BP & urinary proteinuria are measured in each visit and the patients are instructed to count daily fetal movement. No dietery restriction is necessary and normal activities are allowed. If this group of patients present before 32 weeks of gestation, proteinuria and BP should be monitored twice weekly. Development of proteinuria, elevation of BP, decreased fetal movement and IUGR require hospital admission for further evaluation and perhaps delivery. Otherwise these patients may continue the pregnancy upto 37 completed weeks when labour may be induced.2

In case of moderate hypertension patients are treated as outpatient basis with twice weekly visit. BP, proteinuria, renal function, electrolytes, platelet count, transaminase and billirubin are checked in each visit. Women with moderate gestational hypertension with maternal or fetal risk factors (Box-1) require hospitalization for control of BP and prevention or early detection of preeclampsia, end organ damage or fetal compromise. Laboratory investigations e.g. 24 hours urinary protein, platelet count, LDH and other liver enzymes are repeated once or twice a week. For fetal monitoring fetal kick count, ultrasonography (USG) for fetal growth and liquor volume, NST, umbilical and cerebral Doppler velocimetry are done. Pregnancy can be continued upto 37 completed weeks. The use of antihypertensives in moderate hypertension is controversial. Any antihypertensive therapy, decreases the risk of transient, severe hypertension without a clear difference in other maternal or perinatal outcomes e.g. severe preeclampsia, stroke, preterm delivery or perinatal death. Labetalol is used as antihypertensive to keep the BP <150/80-100 mm Hg as there is good evidence to show that it reduces the risk of severe hypertension. 4

Absolute bed rest is not advocated due to risk of developing thromboembolism. The objective of treatment is to avoid the complications of potential severe hypertension like stroke, heart failure pulmonary edema and prevention of preeclampsic-eclampsia & fetal jeopardy. The most commonly used antihypertensive is labetalol, which can be used both in oral and parenteral route according to severity of hypertension. 12,13 Labetalol is safe both for mother and fetus and the only reported neonatal effect is hypoglycaemia, when used in large doses.

Methyldopa is another widely used drug. A quasirandomised trial compared labetolol vs methyldopa found that fewer women who received labetolol developed proteinuria (RR 0.04; 95% CI 0.003 to 0.73).14 An RCT conducted in Sri Lanka compared the effectiveness of nifedipine with methyl dopa. Apgar score was found better in infants of women who received methyldopa. More women needed treatment for acute hypertension in nifedipine group and the difference was statistically significant (RR 1.67; 95% CI 1.16 to 2.40).14,15 BP should be measured at least 6 hourly and urinary proteinuria daily.

Laboratory investigations are done on admission and repeated weekly. For fetal survillence twice weekly- NST and weekly-umbilical & cerebral doppler study are recommended in expectant management of severe gestational hypertension. In cases of prolonged hospitalization, ultrasonographic assessment of fetal growth is done 3 weekly.

Expectant management is terminated when there is uncontrolled hypertension or there is evidence of maternal end organ damage or fetal compromise. Gestational hypertension is not an indication for cesarean section except in cases that are unresponsive to treatment or fetal compromise before 32 weeks.² In other instances, mode of delivery depends upon pelvic assessment and Bishop's score. A prolonged induction delivery interval is avoided in cases of severe gestational hypertension. However in cases of mild hypertension induction of labor and vaginal delivery will be the first choice after 37 weeks.20

Management of preeclampsia

Preeclampsia is a disease that originates and propagates through the placenta and delivery is the ultimate remedy. It is mild or severe depending on the level of BP and on the presence of features of end organ damage. Preeclampsia is mild, if BP is <160 /110 mm of Hg and there is no sign symptoms associated with severe preeclampsia described in Box-II.

Box II Criteria of severe preeclampsia

- Systolic BP is >160 mm of Hg and diastolic BP is >110 mm of Hg
- Proteinuria of >5 g in a 24 hours urinespecimen or 3+ or more on two random urine samples collected at least 4 hours apart
- Oliguria or <500 ml in 24 hours

- Cerebral or visual disturbances
- Pulmonary edema or cyanosis
- Epigastric or right upper quadrant pain
- Impaired liver function
- Thrombocytopenia

The patient is usually hospitalized, actual management of preeclampsia depends on severity of hypertension gestational age at diagnosis. If the gestational age is at 37 weeks patient should be delivered as there is no benefit in continuing the pregnancy. However patient with mild preeclampsia and gestational age <37 weeks who can be relied on to follow the physician's instruction may be treated as outpatients. A typical home regime includes bed rest, daily urine dipstick measurement of proteinuria and BP monitoring. Patients are advised to attend antenatal clinic at least twice weekly for fetal heart rate testing and 24-hour urine protein measurement. Patients are warned of the danger signals such as severe headache, epigastric pain and visual disturbances and on occurrence of these signals with increasing BP and proteinuria hospitalization is advised.

After hospitalization, BP is measured 4 hourly. Urine dipstick measurement of proteinuria and weight is checked daily. Serum creatinine and twenty- four hour urinary protein are measured twice weekly. Liver function test, uric acid, serum electrolytes and serum albumin are measured on admission and weekly.

Ultrasound examination is done on admission and every two weeks to determine gestational age, estimated fetal weight (EFW) and amniotic fluid volume. Abnormal fetal biometry demands evaluation with uterine, umbilical and middle cerebral artery Doppler study and

repeated weekly. Non stress test (NST) is done twice weekly. Expectant management is continued up to 37 weeks if fetal and maternal condition is stable. The antihypertensive of choice is oral labetalol in the dose of 100-400 mg every 8-12 hours.

In case of severe preeclampsia, the obstetric management will depend on the gestational age at the time of diagnosis. Some authorities consider delivery as the definitive treatment regardless of gestational age, although delivery may not be optimal for a fetus that is extremely premature. If a patient presents with severe preeclampsia before 34 weeks' gestation but appears to be stable and the fetal condition is reassuring, expectant management may be considered only in a tertiary center.²⁰

All of these patients must be evaluated in a labor and delivery unit for 24 hours before a decision for expectant management can be made. During this period, maternal and fetal evaluation must show that the fetus does not have severe growth restriction or fetal distress and maternal urine output must be adequate. During expectant management fetal monitoring should include daily NST and ultrasonography performed to monitor the development of oligohydramnios and decreased fetal movement. In addition, fetal growth determination at 2-week intervals must be performed to document adequate fetal growth. A 24-hour urinary protein may be repeated. Daily blood tests should be performed for liver function tests (LFTs), CBC, uric acid and LDH. Patients should be instructed to report any headache, visual changes, epigastric pain, or decreased fetal movement. Contrary to popular belief accelerated lung maturation does not occur

in preeclampsia. A systematic review has shown that a single course of antenatal corticosteroid given before 34 weeks reduces the risk of neonatal death, respiratory distress syndrome, cerebrovascular haemorrhage, necrotizing enterocolitis, respiratory support and intensive care admission.¹⁶

It is recommended that treatment for severe hypertension should be started promptly aiming for a gradual and sustained lowering of BP. Drugs for the treatment of very high BP in pregnancy have been the subject of Cochrane review which concluded that no good evidence exists that any short acting antihypertensive is better than other.¹⁷ Several rapidly acting agents are available to control severe hypertension (Table I).

Table I Rapidly acting anti-hypertensive to control severe hypertension

Drug	Dose	Route	Onset of action
Labetalol	20-50 mg	Intravenous bolus	5 mins, repeat afterv
		over 2 mins	15-30 mins
Nifedipine	5-10 mg capsule	Oral	10-20 mins, repeat
			after 30 mins
Hydralazine	5-10 mg	Intravenous	20 mins ,repeat
			after 30 mins

There is an important concern that a precipitous fall in BP particularly after intravenous hydralazine, may impair placental perfusion resulting in fetal distress. This can be prevented by co-administration of a small bolus of fluid e.g. 250 ml of normal saline at the time of administration of antihypertensive therapy ¹⁸.

Continuous CTG monitoring should be considered in this situation, particularly when there is evidence of existing fetal compromise. The concurrent administration of longer acting oral agents can achieve a sustained BP lowering effect.

- 1. Methyldopa 250-750
- 2. Labetalol 100-mg
- 3. Nifedipine 20 mg
- 4. Prazosin 0.5-5 mg and
- 5. Hydralazine 25-50 mg

The most important consideration in choice of antihypertensive agent is that the institute has experience and familiarity with that agent. It is recommended that protocols for the management of severe hypertension should be readily accessible in all obstetrics units.

Magnesium sulphate is the medication most commonly used for the prevention of in patients with seizure severe preeclampsia. There is good evidence indicating the effectiveness of magnesium sulphate. In the Magpie Trial 26% of the participants had severe preeclampsia, the incidence of eclampsia was 2.7% in the placebo group versus 1.1% in Magnesium sulphate group.¹⁹ Women with severe preeclampsia who are managed expectantly must be delivered under the following circumstances (Box III).20

Box III Criteria for termination of pregnancy in severe preeclampsia

- Non reassuring fetal heart status
- Uncontrollable BP
- Oligohydramnios, with amniotic fluid index (AFI) of less than 5 cm
- Severe intrauterine growth restriction in which the estimated fetal weight is less than 5%
- Oliguria (<500 mL/24 h)
- Serum creatinine level of at least 1.5 mg/dL
- Pulmonary edema
- Shortness of breath or chest pain with pulse oximetry of <94% on room air
- Headache that is persistent and severe
- Right upper quadrant tenderness
- Development of HELLP syndrome

In most cases of severe preeclampsia before weeks. induction of labour unsuccessful and approximately 80% of these women need caesarean delivery.²¹ In case of fetal growth restriction, the incidence of abnormal FHR monitoring pattern during labour is high, so caesarean section is preferable. Regional anaesthesia is preferred to general anaesthesia (GA) for airway cesarean section, especially problems including laryngeal oedema may be increased.^{22,23} However well-conducted GA is also suitable and may be indicated in the presence of severe fetal compromise, edema, haemodynamic pulmonary instability, risk of intraspinal haematoma abruption, placental severe (e.g. thrombocytopenia) or after eclampsia altered consciousness where neurological deficits persist.^{24,25}

Management of preeclampsia

Eclampsia can occur during the antepartum, intrapartum, and postpartum periods. Ninety percent of eclampsia cases occur after 28 weeks' gestation.² The first step in the management of eclampsia is the treatment of convulsion. To decrease the risk of aspiration the patient should be placed in the lateral position. The bedside rails should be elevated to avoid maternal injury. Tongue bite should be prevented by inserting a padded tongue blade between the patient's teeth. Supplemental oxygen by mask should be started at 8-10 L/minute. Magnesium sulphate is the most commonly used anticonvulsant agent worldwide. Cochrane reviews showed that in women with eclampsia magnesium sulphate had statistically significantly better results than previously used drugs like diazepam, phenytoin and lytic cocktail in preventing maternal death and recurrence of convulsion. 26,27,28 Another effective medication in the management of eclamptic patient is nimodipine, a calcium channel blocker which causes selective vasodilatation of the brain vasculature. It is of particular benefit when the mechanism of seizure is cerebral vasoconstriction which is seen in those eclamptic women with normal or mildly elevated systemic blood pressure. Nimodipin is given in doses of 60 mg orally every 4-6 hours. The Cochrane review comparing nimodipine with magnesium sulphate showed that women treated with nimodipine were statistically significantly less likely to develop persistent high blood pressure than those treated with magnesium sulphate.²⁹ Magnesium sulphate should be continued for a minimum period of 24hour following the last convulsion.

Severe hypertension must be addressed after controlling convulsion. The goal is to maintain BP between 140/90 and 160/110 mm Hg. Labetalol or hydralazine can then be administered intravenously for control of BP. Recommended doses of IV bolus of hydralazine (5-10 mg) or labetalol (20-40 mg). Other potent antihypertensive medications e.g. sodium nitroprusside or nitroglycerin, can be used but are rarely required.¹³ Care must be taken not to decrease the BP too drastically; an excessive decrease can cause inadequate uteroplacental perfusion and fetal distress. Diuretics are used only in case of pulmonary edema. Depending on the clinical course, patient's neurologic status for signs of increased intracranial pressure or bleeding (eg, funduscopic examination, cranial nerves) should be checked regularly. Maternal fluid intake and urine output, respiratory rate. oxygenation continuous fetal monitoring are required. Delivery is the treatment for eclampsia after the patient has been stabilized. In current obstetrical practice the large majority of eclamptic women are delivered by cesarean section.² Administration of frusemide and aggressive diuresis should be initiated immediately following delivery and can be maintained for several days. Oral administration of antihypertensive agents like labetalol & calcium channel blockers should be continued in the postpartum period until the blood pressure is normal.

The HELLP syndrome is a recognized complication preeclampsia of eclampsia of pregnancy, occurring in 25% of these pregnancies.³⁰ It is a syndrome having a combination of "H" for hemolysis, "EL" for elevated liver enzymes, and "LP" for low platelet count . It is avariant of severe preeclampsia where hypertension is marked but there is severe involvement of liver and coagulation system and may lead to liver failure and severe bleeding. In a patient with possible HELLP syndrome, some specific blood tests are performed e.g. a full blood count, liver enzymes, renal function and electrolytes and coagulation studies. Often, Fibrin Degradation Products (FDPs) determined, which can be elevated. Ddimer is a more sensitive indicator of subclinical coagulopathy and may be positive before coagulation studies are abnormal. The only effective treatment is prompt delivery of the baby.

Management of chronic hypertension

Chronic hypertension occurs in up to 22% of women of child bearing age, with the prevalence varying according to age, race, and body mass index (BMI). Population-based data indicate that approximately 1% of pregnancies are complicated by chronic

hypertension.³¹ Women mild hypertension (140/ 90-159/109 mm Hg) generally do not require antihypertensive medication. As suggested by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, therapy could be increased or reinstituted for women with pressures exceeding 150/100-160/110 mm Hg.³² In women with BP >180/110mm Hg antihypertensive therapy should initiated or continued. Although there are numerous antihypertensive agents that for the have been used chronic hypertension during pregnancy, methyldopa has been commonly used. It is preferred by most practitioners and appears to be relatively safe and have limited effects on uteroplacental blood flow.³³ Labetalol & Ca-channel blocker can also be used during pregnancy as an alternative to methyldopa. Diuretics also been used to treat chronic hypertension, but there has been concern regarding the potential effect of these medications on normal blood volume expansion associated with pregnancy.

The Working Group concluded, "If diuretics are indicated, they are safe and efficacious agents that can markedly potentiate the response to other antihypertensive agents and are not contraindicated in pregnancy except in settings in which uteroplacental perfusion is already reduced (preeclampsia and IUGR)". 32,33 Angiotensin Converting Enzyme (ACE) inhibitors contraindicated during pregnancy. The teratogenic risk factors of ACE inhibitors associated with severely underdeveloped calvarial bone, renal failure, oligohydramnios, anuria, renal dysgenesis, pulmonary hypoplasia, IUGR, fetal death, neonatal renal failure and

neonatal death. Fetal surveillance should be individualized and based on clinical judgment and on the severity of the disease. Most appropriate fetal surveillance tests commonly used are USG, nonstress test (NST), Biophysical Profile (BPP), modified BPP, CST and doppler velocimetry. The interval and timing of testing in women with chronic hypertension should be individualized. Most of the increased morbidity associated with this condition is secondary to superimposed preeclampsia or IUGR. The general recommendation is that baseline ultrasonography should be obtained at 18-20 weeks of gestation and should be repeated at 28-32 weeks of gestation and monthly thereafter until delivery to monitor fetal growth. If growth restriction is detected or suspected, fetal status should be monitored frequently with NST or BPP. Pregnant patients with uncomplicated chronic hypertension of mild degree generally can be delivered vaginally at term; most have good maternal and neonatal outcomes. Cesarean delivery should be reserved for other obstetric indications. Women with hypertension during pregnancy and a prior adverse pregnancy outcome (stillbirth) may be candidates for earlier delivery after documentation of fetal lung maturity. Women with severe chronic hypertension during pregnancy most often either deliver prematurely or have to be delivered prematurely for fetal or maternal indications. Delivery should be considered in all women with superimposed severe preeclampsia at or beyond 34 weeks of gestation and in women with mild superimposed preeclampsia at or beyond 37 weeks of gestation. Women with chronic hypertension complicated by significant cardiovascular or renal disease

require special attention to fluid load and urine output because they may be susceptible to fluid overload with resultant pulmonary edema. Magnesium sulfate should be used for women with superimposed severe preeclampsia to prevent seizures.

Management of chronic hypertension with superimposed preeclampsia

Preeclampsia superimposed on chronic hypertension is characterized by new-onset proteinuria (or by a sudden increase in the protein level if proteinuria is already present), an acute increase in the level of hypertension (assuming proteinuria already exists), or development of the HELLP syndrome. Currently there is no single reliable, cost-effective screening test for preeclampsia.³⁴ The serum uric acid level was once used as an indicator of preeclampsia but has been found to lack sensitivity and specificity as a diagnostic tool. However, an elevated serum uric acid level may be of some use in identifying pregnant women with hypertension who have an increased likelihood of having superimposed preeclampsia.³⁵ A baseline laboratory evaluation should include hepatic enzyme level, platelet count, serum creatinine level and urinary total protein measurement. Urinary protein to creatinine ratios predict the 24-hour urine total protein level and may provide a faster, simplified method of estimating proteinuria, providing that the protein values are less than 1g in 24 hours.³⁸ In women who have preeclampsia with no suspected progression, laboratory tests should be conducted weekly.^{34,37} If progression of eclampsia is suspected, the tests should be repeated more frequently.

Once the diagnosis of superimposed preeclampsic-eclampsia is made the treatment will be accordingly. Magnesium sulfate should be used for women with superimposed severe preeclampsia to prevent seizures. Delivery should be considered in all women with superimposed severe preeclampsia at or beyond 34 weeks of gestation and in women with mild superimposed preeclampsia at or beyond 37 weeks of gestation. Women with preeclampsia should be counseled about future pregnancies. In nulliparous women with preeclampsia before 30 weeks of gestation, the recurrence rate for the disorder may be as high as 40 percent in future pregnancies. Multiparous women have even higher rates of recurrence.³⁹

Post-partum care in hypertensive women

Patients with severe preeclampsia should be monitored closely for at least 48 hours after delivery because they are at risk for hypertensive encephalopathpy, pulmonary oedema and renal failure. However, women who experienced hypertension during pregnancy may be normotensive immediately after the birth, but then become hypertensive again in the first postnatal week. The need to obtain hypertensive control may delay discharge. Methyldopa should be avoided because of the risk of postnatal depression.

First line antihypertensive agent is atenolol, plus nifedipine or an ACE inhibitor if another agent is required. Women with gestational hypertension, or pre eclampsia, are usually able to stop all antihypertensives within six weeks postpartum. Those with chronic hypertension can resume their prepregnancy drugs. Diuretics, however, are usually avoided if

the woman wishes to breast feed because of increased thirst. Proteinuria in pre-eclamptic women will usually remit by three months post-partum, in the absence of any underlying renal abnormality.³⁸ Persistent proteinuria requires further renal investigation. Women who have become normotensive after suffering from preeclampsia or eclampsia can use standard dose oral contraceptive pill safe.³⁹

Conclusion

Management of the hypertensive pregnant patient is a major challenge. The clinician has two patients the mother and the fetus and two situations the hypertensive woman who becomes pregnant and the who pregnant woman becomes hypertensive. Hypertensive disorders in pregnancy are best managed with a multidisciplinary approach; obstetrician should be the consultant in charge and seek advice from other appropriate specialists (e.g. anaesthetists, neonatologists & physicians) where indicated. This offers a framework for a team approach to the management of hypertension in pregnancy.

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