

# THE DIAGNOSIS AND MANAGEMENT OF HYPERTENSIVE DISEASE IN PREGNANCY

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## Abstract

Hypertensive disorders of pregnancy are responsible for a significant proportion of maternal and perinatal deaths. This group of disorders include the specific hypertensive disease of pregnancy; preeclampsia/eclampsia, as well as chronic hypertensive disease antedating pregnancy with or without superimposition of preeclampsia/eclampsia. The natural course and management of these 2 distinct entities are different, and therefore every attempt should be made to make the correct diagnosis. The differential diagnosis depends on accurate history and physical examination, as well as biochemical tests, specifically serum uric acid. The treatment of chronic hypertensive disease is outlined, with emphasis on the indications for antihypertensive medications, close monitoring of the fetoplacental unit, and timing of delivery. The management of the severe cases (hypertensive crisis and/or severe superimposed preeclampsia) is also discussed.

## Key Words

Pregnancy, hypertensive disorders, chronic hypertensive disease, preeclampsia/eclampsia, superimposed preeclampsia/eclampsia, differential diagnosis, management, hyperuricemia, antihypertensives.

## Introduction

Hypertensive disorders complicate 5-10% of all pregnancies. These include the specific hypertensive disease of pregnancy, i.e., preeclampsia/eclampsia as well as cases of chronic hypertensive disease of various etiologies antedating the pregnancy. It is clear that these disease entities differ in pathogenesis and pathology but still they share a similar clinical picture characterized by hypertension, edema, and/or proteinuria. Hypertension is defined as an increase in the systolic pressure  $\geq 30$  torr and/or the diastolic pressure by  $\geq 15$  torr over nonpregnant or early pregnant levels measured twice at least 6 hours apart. Proteinuria is defined as urinary excretion of protein in excess of 0.3 g/L in a 24 hour sample or in excess of 1 g/L in a random sample. Edema is defined as a rapid increase in weight, that is,  $> 1$  lb/week.

The commonly accepted classification of these hypertensive disorders is that of the American College of Obstetricians and Gynecologists' Committee on Terminology (1972):

1. Preeclampsia/eclampsia: This is a specific hypertensive disease peculiar to human pregnancy and in which hypertension is usually associated with edema and/or

proteinuria. It characteristically affects primigravidas during the second half of their pregnancy. Preeclampsia can occur before the twentieth week only in association with trophoblastic disease. Eclampsia is the occurrence of convulsions — not caused by a coincidental neurologic disease, for example, epilepsy — in a preeclamptic patient.

2. Chronic hypertension concurrent with pregnancy: This includes hypertension (of whatever cause) that either antedates pregnancy or is recognized in the first half of pregnancy (in the absence of trophoblastic disease). Hypertension can be primary (essential) or secondary to renal disease or, rarely, to other conditions, for example, pheochromocytoma. Usually, hypertension persists beyond 6 weeks postpartum.
3. Superimposed preeclampsia/eclampsia: These are patients with known hypertensive or renal disease who later develop the additional features of preeclampsia/eclampsia.
4. Transient (gestational) hypertension: The term describes patients in whom hypertension develops for the first time in the last weeks of pregnancy or during labor or the first day postpartum and usually clears within 10 days postpartum. There is usually no evidence of either chronic hypertension or preeclampsia; that is, there is no associated edema or proteinuria.

## Differential Diagnosis

### of Hypertensive Disorders of Pregnancy

Hypertensive disease is chronic, is not causally related to the pregnant state, and will not be cured by delivery. On the other hand, preeclampsia has an acute onset and, usually, a rapid progressive course. It is caused by pregnancy and is not cured until the patient is delivered. The differences in the pathogenesis and natural history of these two conditions dictate that the approach to their management should be different and, therefore, every attempt should be made to differentiate these two conditions. This is usually possible if an accurate medical history is available and if the patient is seen in early pregnancy and a careful examination is done at that time.

A patient with history of hypertension and/or renal

disease prior to pregnancy or one in whom either condition is diagnosed in the first half of pregnancy would not pose diagnostic difficulties. However, in a patient who is seen for the first time in the second half of pregnancy, the true nature of her hypertensive disorder may not be evident. There is a transient midtrimester drop of the blood pressure in normal pregnancy as well as in pregnancies complicated by chronic hypertension. If a patient is normotensive at this time (20-26 weeks) and later develops hypertension, preeclampsia should always be suspected. However, chronic hypertension or occult renal disease cannot be excluded even if there is no documented history of either. The diagnosis of preeclampsia is substantiated if the patient is a primigravida, if there is associated edema and/or proteinuria, hyperreflexia, and by the finding of retinal arteriolar spasm and/or retinal sheen on ophthalmoscopic examination.

A strong family history of hypertension, evidence of left ventricular hypertrophy [clinical or by electrocardiogram (ECG)], retinal changes [thickening of arteriolar walls, arteriovenous (A-V) nicking] strongly point to chronic hypertensive disease. History of repeated urinary tract infections, the presence of abnormal findings (for example, casts) on microscopic examination of a urinary sediment, or the presence of retinal exudates or hemorrhages point to underlying chronic renal disease. In the absence of these findings in a primigravida, the diagnosis of preeclampsia should be made. On the other hand, in a multigravida the diagnosis of preeclampsia should always be considered doubtful, except in the presence of known predisposing causes, for example, twins, molar pregnancy, or diabetes. Most of the multiparas with hypertensive disorders will have underlying occult kidney or hypertensive disease, as was shown in renal biopsy studies including ours.<sup>1</sup>

A specific biochemical test that in the author's experience was found to be very helpful in the differential diagnosis is serum uric acid (SUA). In chronic hypertensive or renal disease SUA is usually normal or slightly elevated. In the more severe cases SUA will be increased, but proportionately to the increase of other nitrogenous end products, i.e., creatinine and blood urea nitrogen (BUN). On the other hand in preeclampsia, there is hyperuricemia in the absence of elevation of the other nitrogenous end products. Otherwise, SUA will be increased relatively more than the increase in BUN and creatinine.<sup>2</sup> One must remember that in interpreting these tests, that SUA, BUN and creatinine levels are normally decreased during pregnancy. This decrease results from the increased clearances of these substances and the hemodilution of pregnancy. Other biochemical tests are not that helpful; for example, creatinine clearance is impaired in both preeclampsia, and chronic hypertensive disease.<sup>2 3</sup>

A definite diagnosis can only be reached by pathological examination of renal biopsies; patients

with preeclampsia will have a characteristic glomerular lesion described as glomerular capillary endotheliosis,<sup>4</sup> while other renal lesions will be seen in other entities.<sup>1</sup> Renal biopsy, however, is reserved for those cases in which renal disease is strongly suspected and in which the determination of its nature will influence the specific management. Finally, 6 weeks postpartum, all preeclamptic patients should be normotensive, whereas the majority of patients with chronic hypertension will still be hypertensive; the others will be normotensive, only to become hypertensive again in a following pregnancy.

#### Management

Patients with mild hypertension that was untreated prior to pregnancy usually perform very well. In only a small proportion of these patients, hypertension will be exacerbated during pregnancy and they will require the institution of antihypertensive therapy. The fetal mortality (1.7%) is only slightly higher than in the general population. However, there may be an increase in the incidence of fetal growth retardation (secondary to placental insufficiency). In all patients requiring antihypertensive therapy, management should also include evaluation of fetal growth by ultrasonography and evaluation of fetal well-being beginning at 32-34 weeks, utilizing any or all of the available tests, that is, nonstress tests (NST), contraction stress tests (CST), and estriol (E<sub>3</sub>). Spontaneous onset of labor is usually awaited unless there is evidence of fetal jeopardy which will indicate induction of labor.<sup>5</sup>

On the other hand, patients with severe hypertension are definitely at an increased risk. The fetal death rate has been reported to be 23%, and the maternal mortality rate to be approximately 1%, due to cerebrovascular accidents and/or heart failure. Those patients with moderate to severe hypertension who were treated prior to pregnancy should be continued on antihypertensive therapy. We would discontinue diuretic therapy if that has been used. Patients with chronic hypertensive disease do not increase their plasma volume as do normal pregnant women and diuretic therapy may exaggerate this abnormality. Their use may further reduce a compromised placental circulation especially if sodium intake has been restricted.<sup>6</sup> Ordinarily we use methyl dopa and/or hydralazine even if the patient has been using other drugs. The usual daily dose is 1-2 g of methyl dopa (maximum of 3 g), and 50-200 mg of apresoline, orally. On the other hand, other authors have allowed their patients to continue diuretic therapy<sup>7 8</sup> and may also allow their patients to use other antihypertensive drugs, for example, propranolol or other B-blockers, such as metoprolol<sup>9</sup> and oxprenolol.<sup>10</sup> The mechanisms of action, benefits, problems, indications, and description of the different regimens of antihypertensive therapy during pregnancy are beyond the scope of this article and have been reviewed recently.<sup>7 8 11</sup>

In addition, these patients should be encouraged to

reduce their activity and to have adequate bedrest. They will require frequent hospitalization to stabilize their blood pressure and to evaluate their kidney function. Fetal growth should be evaluated with ultrasonography, and fetal well-being should be monitored closely with NST, CST, and E and, if available, HPL, beginning at 30-32 weeks. Usually these patients are admitted at about 36 weeks to allow closer monitoring. Delivery is indicated once fetal lung maturity is ascertained by amniotic fluid studies, i.e., lecithin/sphingomyelin (L/S) ratio, or occasionally earlier if there is evidence of fetal jeopardy.<sup>5</sup>

Superimposition of preeclampsia has been reported to occur in 15-30% of hypertensive patients (compared with an incidence of 5% in normotensive patients). The incidence of superimposition is markedly increased if there is associated renal functional impairment. It has been reported that the risk is almost 100% if urea nitrogen is > 20% mg/dL, and serum creatinine is > 1.5 mg/dL.<sup>11</sup> Superimposed preeclampsia is a serious complication for both the mother and her fetus. Abruptio of the placenta occurs in about 6% of these patients. Unfortunately, superimposed preeclampsia occurs earlier in pregnancy than primary preeclampsia, increasing the risk to the fetus considerably because of prematurity. Fetal death rate is reported to be 16% and 41% in preeclampsia superimposed on "mild" and severe hypertension, respectively.

Superimposition can occur insidiously but more often it occurs suddenly, creating an obstetric "emergency." However, it can be predicted by absence of a midtrimester drop in blood pressure and/or enhanced sensitivity to angiotensin infusion.<sup>11</sup> The criteria for the diagnosis of superimposed preeclampsia are (a) increase of blood pressure (30 torr systolic and/or 15 torr diastolic) over previous readings, (b) increasing proteinuria in a chronic hypertensive patient, and (c) appearance of retinal arteriolar spasm on funduscopy. The diagnosis is substantiated if uric acid shows a further increase in relation to the other nitrogenous end products and the creatinine clearance is further impaired.

Once the diagnosis of superimposed preeclampsia is made (or suspected), the patient should be admitted and treated aggressively. If gestation has reached 35-37 weeks delivery should be effected. If it is 35 weeks, and there are no signs of "severe" superimposed preeclampsia, both the mother and fetus shall be closely monitored. If the blood pressure is stable, and the results of the fetal well being tests are normal, expectant treatment is continued until 35 weeks, or until fetal lung maturity is established. If maternal condition worsens at any time or in the presence of fetal jeopardy, delivery must be effected regardless of fetal lung maturity. If the cervix is favorable when delivery is indicated, induction may be attempted. However, in the more severe cases when the need to deliver is urgent and specially in preterm pregnancies when the

cervix is mostly unfavorable, cesarean section is the method of choice.<sup>5</sup>

In instances where hypertensive disease is worsening, i.e., unstable/increasing blood pressure despite full therapeutic doses of antihypertensives, increasing proteinuria, further impairment of renal function or if signs of "severe" superimposed preeclampsia develop, i.e., increase of systolic pressure of >30 torr, proteinuria > 5 g/24 hr, oliguria < 500 ml/24 hr, onset of cerebral or visual symptoms, onset of pulmonary edema or in the presence of hyperreflexia (4+ or sustained clonus), the following additional measures need to be taken:

#### A. Antihypertensives

If the diastolic pressure continues to be > 110 mm Hg or the systolic pressure > 180 torr, intravenous hydralazine is administered. Hydralazine is a potent vasodilator, hence its beneficial effect in superimposed preeclampsia, a disease in which generalized vasospasm is an important pathophysiologic feature. A bolus of 5 mg is given intravenously and the blood pressure is checked every 5 minutes. If no adequate response is obtained in 20 minutes another 5 mg bolus is given intravenously and is repeated until a satisfactory response is obtained. This is followed by a controlled intravenous infusion of 5% dextrose in one-half normal saline, with the rate of infusion titrated to keep the diastolic pressure slightly > 100 mm Hg. Alternatively, repeated intravenous boluses (5-10 mg) are given whenever the diastolic pressure rises to  $\geq$  110 mm Hg.

Palpitation and headaches are relatively common, whereas nausea and vomiting are less common side effects of hydralazine. It is important to distinguish these from symptoms of impending eclampsia, which have to be looked for diligently in these patients.

Rarely, when the hypertension is very severe, as in hypertensive crisis, other antihypertensives may be utilized:

1. Diazoxide: Diazoxide is a benzothiadiazine derivative with marked vasodilator and no diuretic effects. It has an immediate onset of action, which lasts for 1-18 hours with a mean of 7.5 hours. Diazoxide is given in 30 mg boluses and the dose repeated every minute until the diastolic pressure is 110 mm Hg.<sup>12</sup> The main disadvantage of diazoxide is that it sometimes causes profound hypotension that may result in fetal death. To safeguard against severe hypotensive effects, the patients should be well hydrated before the injection. It has been also noted that the incidence of severe hypotension is much higher if the drug is given concomitantly with hydralazine or methyldopa. Hence, if a patient presents with severe hypertension, diazoxide should be used as the initial drug and hydralazine not given for at least 4 hours.<sup>8</sup> If severe hypotension occurs in spite of these precautions, the treatment is the rapid infusion of 1-2 L of Ringer's lactate. Rare-

ly, ephedrine has to be used if there is no response to the intravenous loading. Because of this risk, and with the availability of other antihypertensives diazoxide is now rarely used in obstetrics.

2. Sodium nitroprusside: This is another very potent vasodilator with almost instant action. It causes a predictable and consistent fall in blood pressure. Nitroprusside is uniquely specific for vascular receptors and dilates both resistance and capacitance blood vessels. It has no effect on the heart or autonomic nerve centers. No change in uterine blood flow has been observed in either normotensive or hypertensive sleep.<sup>9</sup> Its action is readily reversible once the administration is discontinued. A solution containing 100  $\mu\text{g}/\text{mL}$  of sodium nitroprusside is infused intravenously at a dose of approximately 1  $\mu\text{g}/\text{kg}/\text{minute}$ . The rate of infusion has to be titrated according to the blood pressure response. The container and the intravenous tubing should be covered, because the drug is light sensitive. This drug is metabolized by the liver to thiocyanate. It crosses the placenta and corresponding, or higher, blood levels are achieved in the fetus. This is a major concern, because the fetal liver may not be as capable of metabolizing nitroprusside as the adult liver and the danger of fetal cyanide toxicity exists even in an asymptomatic mother. Moreover, in severely preeclamptic patients with marked impairment of hepatic function, maternal cyanide toxicity is a potential danger, which has limited nitroprusside use in these patients. It should only be used to control blood pressure in case of an acute hypertensive crisis that is unresponsive to diazoxide or hydralazine, and the patient should be delivered as quickly as possible thereafter.<sup>8</sup>

#### B. Diuretics

The use of diuretics in the management of these patients is generally considered inadvisable, because these patients are already hypovolemic. In patients with oliguria, correction of the fluid balance (volume deficits) usually results in increase in urinary output. If not, urgent delivery is probably safer than repeated administration of mannitol or furosemide (Lasix). However, diuretics are indicated when there is impending left heart failure or for the treatment of acute pulmonary edema. In these situations, Lasix, given as 20-40 mg intravenous boluses, is the drug of choice. Its administration and the rate of infusion of colloid or crystalloid solutions should be monitored closely, preferably with a balloon flotation (Swan-Ganz) catheter (See below).

#### C. Maintenance of Fluid, Acid-Base, and Electrolyte Balance

In patients with hypertensive disease, the plasma volume is not as much expanded over non-pregnant values as in normal pregnant women. Hypovolemia is more pronounced in patients who develop superimposed

preeclampsia. This hypovolemia contributes to the oliguria and further reduces the placental flow caused by vasoconstriction of decidual arterioles. Controlled fluid replacement is an important component of therapy; replacement could be by either 5% dextrose in one-half normal saline, balanced salt solution, plasminate, salt free albumin, or blood, in case of blood loss. However, care should be exercised not to overload the circulation because the infusion is carried in the face of a contracted vascular bed (generalized arteriolar vasospasm). Hence, it is imperative to monitor the central circulation in these patients. In most instances, a central venous pressure catheter is probably adequate, but in the more severe cases, a balloon flotation (Swan-Ganz) catheter passed into the pulmonary artery is advisable. This provides for continuous measurement of pulmonary capillary wedge pressure, pulmonary artery pressure, left ventricular end diastolic pressure, pulmonary and total peripheral vascular resistances, and cardiac output.<sup>12</sup> A concomitantly inserted arterial line will provide for accurate monitoring of arterial blood pressure, arterial blood gases, and pH.

In a previous study, we found a tendency to metabolic acidosis in severe preeclampsia.<sup>14</sup> Sodium bicarbonate therapy may be necessary to correct their acidosis.

#### D. Anticonvulsants

In the United States, magnesium sulfate ( $\text{MgSO}_4$ ) is the drug of choice for the management of severe (including superimposed) preeclampsia/eclampsia. The drug has a curarelike action on the neuromuscular junction, decreasing the amount of acetylcholine liberated by the nerve impulses. In addition, it reduces the excitability of the cerebral cortex, raising the threshold for convulsions.  $\text{MgSO}_4$  is a very effective anticonvulsant, and it is very rare (2-4%) that eclamptic convulsions will or recur when it is given in proper dosage.  $\text{MgSO}_4$  when given as an intravenous bolus will cause a moderate but transient drop in blood pressure, probably due to peripheral vasodilation. It also has a slight diuretic effect, probably due to vasodilation of the glomerular afferent arterioles. Studies in the monkey have shown a significant increase in uterine blood flow, but it is not known if a similar effect is produced in humans.<sup>11</sup> Initially, 10-20 mL of 20% solution, that is, a 2-4 g of  $\text{MgSO}_4$  is administered intravenously over a 5-15 minute period. In our institution and at most centers, this bolus is followed by a continuous intravenous infusion of  $\text{MgSO}_4$  at the rate of 1-2 g/hour. On the other hand, Pritchard (1975)<sup>15</sup> advocates the use of the intramuscular route after the initial bolus. In the rare cases (2-4%) when convulsions persist despite therapeutic levels of  $\text{MgSO}_4$ , 250 mg of either amobarbital (Amytal) or phenobarbital, or 5-10 mg of diazepam are injected slowly intravenously. Magnesium sulfate infusion is usually continued for at least 24 hours postpartum.

Certain precautions have to be taken to avoid magnesium toxicity: (a) The deep tendon reflexes should be checked hourly with intravenous infusion or before the subsequent intramuscular dose. (b) The respiratory rate should not be less than 12/minute. (c) Urine output should not be less than 25-30 mL/hour. In hospitals where blood magnesium levels can be easily obtained, these should be monitored periodically. The antidote for magnesium, that is, calcium, should be readily available at all times. Ten milliliters of 10% calcium chloride or gluconate would quickly reverse magnesium toxicity.

Several other drug regimens have been advocated from time to time, and some are still used in other parts of the world. At present, diazepam (Valium) is probably the most commonly used drug outside the United States.<sup>10</sup> However, MgSO<sub>4</sub> has been used over the years in this country with such good results (maternal mortality of 0% in large reported series)<sup>15</sup> that obstetricians, in general, do not foresee any benefits to be derived from switching to other regimens. The management of eclampsia is beyond the scope of this article and is discussed elsewhere.

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