INTERNAL MEDICINE GRAND R0UNDS

HYPERTENSIVE DISORDERS IN PREGNANCY

C. VENKATA S. RAM, M.D.

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HYPERTENSION IN PREGNANCY

I. INTRODUCTION

The blood pressure normally falls in pregnancy and reaches its lowest level in the second trimester (Figure 1). This fall occurs in both normotensive women and in women with chronic hypertension (Figure 2). The blood pressure also normally rises in the third trimester and reaches pre-pregnancy levels by term. Any increase in blood pressure represents a pathophysiological expression with serious maternal and fetal consequences (Davey and MacGillivray, 1988; Lindheimer and Katz, 1985). Hypertensive disorders of pregnancy remain a major cause of maternal and fetal morbidity and mortality. Despite the considerable interest devoted to blood pressure regulation and dysregulation in pregnancy, many gulfs remain in our knowledge of hypertension in pregnancy.

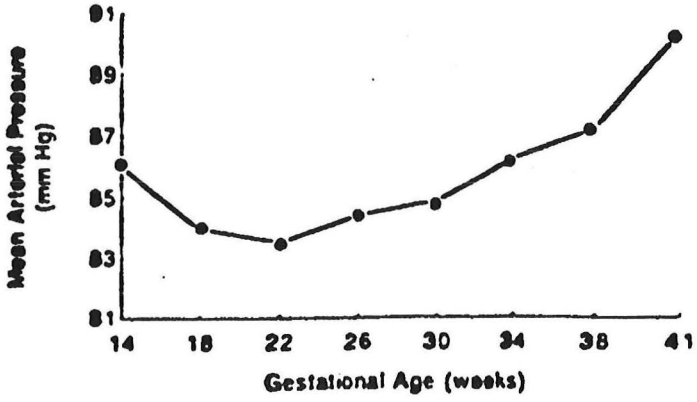


Figure 1: Mean arterial pressure (mm Hg) curve for normal pregnancy from 14-42 weeks' gestation. (From Page and Christianson, 1976).

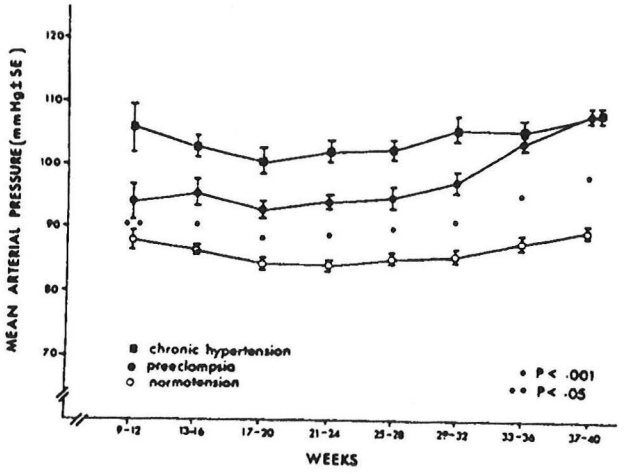


Figure 2: Average mean arterial blood pressures (+ 1 SE) in 710 women who remained normotensive throughout pregnancy, in 46 who developed preeclampsia, and in 37 with chronic hypertension. (From Moutquin JM, Rainville C, Giroux L, Raynauld P, Amyot G, Bilodeau R, Pelland N. A prospective study of blood pressure in pregnancy: prediction of preeclampsia. Am J Obstet Gynecol 1985;151:191-96.)

II. HEMODYNAMICS OF NORMAL PREGNANCY

Cardiovascular System

The single most important physiological change that occurs in the maternal circulation is an increase in the cardiac output. In a pregnant woman, the average resting cardiac output rises by 30%-40% above her pre-pregnant level (Metcalfe and Ueland, 1974). This remarkable increase in cardiac output has several features. First, most of the increments occur early in the pregnancy. Second, the cardiac output varies with the body position; in the supine position, the cardiac output falls from the levels obtained when the subject is in sitting or in the lateral position. Third, the cardiac output starts declining in the last 8 weeks of pregnancy. There is some controversy, however, whether cardiac output really falls toward the end of gestation. In the early stages of pregnancy, the increased cardiac output is accomplished by an increase in the stroke volume. With the advancement of pregnancy, however, stroke volume falls and heart rate increases.

The rise in cardiac output during normal pregnancy is accompanied by a fall in peripheral vascular resistance. It is not clear whether the initial event is a fall in peripheral vascular resistance leading to accentuated cardiac output or vice-versa. A rise in blood volume may contribute to the increased cardiac output (Hytten and Paintin, 1963). It is well known that estrogen exerts an inotropic effect and the physiological rise in estrogen levels during pregnancy may at least partially contribute to the cardiac output. Whatever the mediating mechanism may be, myocardial contractility is enhanced in pregnancy.

Table 1: Cardiovascular Changes in Pregnancy and Pregnancy Induced Hypertension

	Normal Pregnancy	Uncomplicated Essential Hypertension	Pregnancy-Induced Hypertension
CARDIOVASCULAR			
Arterial Pressure	**Reduced**	**Increased**	**Increased**
Cardiac Output	**Increased**	**Normal or Increased**	**Increased**
Systemic Vascular Resistance	**Decreased**	**Increased**	**Increased**
Vascular Reactivity	**Decreased**	**Increased**	**Increased**
Uterine Blood Flow	**Increased**	**Increased**	**Reduced**

The physiological reasons underlying the cardiac output changes are not attributable solely to the metabolic needs of the mother and fetus. When the fetus is small early in pregnancy, the cardiac output is already high. As the pregnancy advances, maternal cardiac output declines while the fetus is steadily growing. Much of the increase is probably due to

the metabolic needs of the fetus. A fraction may be due to the increased work and metabolic needs of the mother's cardiovascular and respiratory systems. A basic hemodynamic change in pregnancy is a fall in peripheral vascular resistance, which can be partially explained by a low-resistance circuit in the gravid uterus. This translates itself into a widened pulse pressure. The mean arterial pressure falls despite the rise in cardiac output.

Peripheral Vascular Resistance

Since the cardiac output increases and since the blood pressure falls or remains the same, the peripheral resistance must fall in pregnancy. Indeed, there is a reciprocal relationship between the cardiac output and the peripheral vascular resistance in normal pregnancy, especially during the early stages. Despite the fall in vascular resistance, blood supply to the gravid uterus is still little more than in the nonpregnant state. The decrease in peripheral vascular resistance is most likely due to relative insensitivity of the pregnant woman to the pressor effects of angiotensin (Gant et al, 1973).

Renal Hemodynamics in Normal Pregnancy

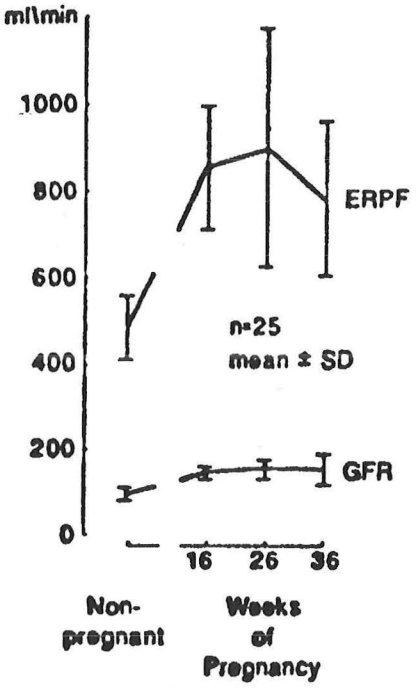
Table 2: Renal Hemodynamics and Plasma Volume Chanbges in Pregnancy and Hypertension

	Normal Pregnancy	Uncomplicated Essential Hypertension	Pregnancy-Induced Hypertension
RENAL			
Renal Blood Flow	**Increased**	**Increased Early Decreased with Severity**	**Decreased**
Glomerular Filtration Rate			
Plasma Volume	**Increased**	**Unchanged**	**Decreased**
Total Body Sodium	**Expanded**	**Contracted**	**Contracted**
Intracellular Sodium	**Increased**	**Normal**	**Increased**
	Decreased in 2nd Trimester	**Increased**	**Normal**

In a pregnant woman, the effective renal plasma flow increases at least by 40% (Davison, 1984; Sims and Krantz, 1958) (Table 2 and Figure 3). The increase in effective renal plasma flow occurs very early in the pregnancy and is generally sustained but for a small drop in the third trimester (Dunlop, 1981). The glomerular filtration rate also increases from 120 ml/min to 200 ml/min, reaching a maximum at 13 weeks, and then remains essentially constant (Davison and Noble, 1981). The amount of increased blood flow received by the kidney in pregnancy is disproportionate to its share in the nonpregnant state. Cardiac output

increases by about 30% but renal plasma flow increases by more than 40%. The early increase in renal plasma flow has been shown to be greater than the change in glomerular filtration rate (GFR), thus reducing the filtration fraction. In one study (Dunlop, 1981), the effective renal plasma flow increased by 80% during early pregnancy but fell significantly in the third trimester. GFR, however, remained at an increased but steady level throughout pregnancy. Both the GFR and effective renal plasma flow (ERPF) are less in the supine than in the lateral position, in concert with changes in the cardiac output.

Figure 3: Absolute changes in GFR and ERPFmeasured serially during pregnancy. (FromDunlop, 1981).



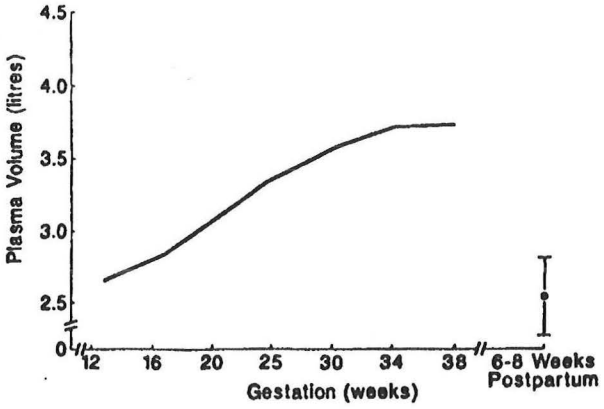


Figure 4: The mean plasma volume ± S.D. in normal pregnancy and postpartum. (From MacGillivray, 1983).

Plasma Volume

Maternal blood volume increases during normal pregnancy, reaching levels exceeding 40% above nonpregnant values (Hytten and Paintin, 1963) (Figure 4). Some of the original observations on plasma volume status in pregnancy were made at this institution by Dr. Pritchard and colleagues (Pritchard et al, 1962). The increase in plasma volume occurs in the first trimester, and after the 30th gestational week there is no further change. Total red cell volume also increases steadily in pregnancy (Pritchard, 1960). The expansion of blood volume, however, is predominantly due to an increase in plasma volume. This phenomenon causes hemodilution, manifested by decreased hemoglobin concentration, sometimes labeled "physiological anemia of pregnancy."

Blood Pressure

Various pregnancy-related physiological adjustments exert important influences on the systemic arterial pressure. The well-known difficulties with conventional sphygmomanometry in measuring the blood pressure are further compounded in pregnancy. Indirect blood pressure measurements may overestimate the readings by 10-12 mm Hg (Ginsburg and Duncan, 1969).

The effect of posture on the blood pressure in pregnancy should be considered. Some investigators have noted a fall when women are supine (Howard et al, 1953). This could be secondary to compression of the vena cava by the gravid uterus causing a decrease in venous return and cardiac output. The level of the cuff relative to the level of heart could account for the change in blood pressure level from supine to the left lateral position.

A change in blood pressure when the patient changes her position from left lateral to supine ("roll-over test") has been utilized to predict preeclampsia. The normal response for reasons described above should be a fall in blood pressure. However, Norman Gant et al from this institution noted that the blood pressure actually rises in the supine position in some patients (Gant et al, 1974b) and this paradoxical response has been used to predict preeclampsia.

III. HUMORAL FACTORS

a) Renin-Angiotensin System in Normotensive Pregnancy

The plasma renin activity (PRA) and plasma renin concentration (PRC) in normal pregnancy are significantly high (Helmer and Judson, 1967; Brown et al, 1966). Throughout the normal pregnancy, there is a progressive rise in the renin substrate (Helmer and Judson, 1967), probably a result of increased levels of estrogen. Although angiotensin II levels are raised in pregnancy, they do not raise the blood pressure in early pregnancy because of the diminished vascular responsiveness which occurs from about 10 weeks of gestation (Gant et al, 1976). These workers were able to demonstrate that volume expansion, which causes a marked increase in pressor response to angiotensin II in the nonpregnant state, fails to elicit such a response in normotensive pregnancy. This implies that the usual finding of decreased vascular sensitivity to angiotensin II being inversely related to angiotensin II is not applicable in pregnancy. The precise relationship between various components of the renin-angiotensin system in normal pregnancy is still not fully elucidated.

b) Renin-Angiotensin System in Hypertensive Pregnancy

There has been considerable interest in the possible role of the renin-angiotensin system in hypertensive pregnancy but there is no firm evidence to assign a major pathogenetic

role to this system in pregnancy. The measurements of various components of the renin-angiotensin system in hypertensive pregnancy have not been performed under standardized conditions. Moreover, the hypertensive state in primigravidas is likely to be different from multiparas or from those with underlying chronic hypertension. Despite various proposals, it is generally believed that PRA and plasma renin concentration are lower in pregnancy-induced hypertension than in normal pregnancy (Symonds and Anderson, 1974; Helmer and Judson, 1967). Women with pregnancy-induced hypertension demonstrate a preferential increase in aldosterone relative to renin concentration implying that certain mechanisms operative in pregnancy may directly stimulate aldosterone (Brown et al, 1992) (Table 3).

Table 3: Endocrine Changes During Pregnancy

	Normal Pregnancy	Uncomplicated Essential Hypertension	Pregnancy-Induced Hypertension
ENDOCRINE			
Plasma Catecholamines	Unchanged	Normal to Increased	Unchanged
Plasma Renin Activity	Increased	High, Low, or Normal	Decreased
Plasma Aldosterone	Increased	Normal	Decreased
Plasma PGE_2 and PGI_2	Increased	Decreased	Decreased
Urinary Kallikrein	Increased		Decreased

The possible contribution of renin or renin like substances elaborated by the uteroplacental unit has not yet been fully explored. How can we relate the role of the renin-angiotensin system in the pathogenesis of hypertension? One possible schema is that in milder forms of pregnancy-induced hypertension, the placental circulation may be compromised by the relatively narrow spiral arteries. The uteroplacental unit responds by augmenting the synthesis and release of renin (Broughton-Pipkin et al, 1981). This may lead to a rise in angiotensin II levels in the systemic circulation. An increase in the systemic blood pressure may stimulate the production of vasodilatory prostanoids by the uteroplacental unit, thus restoring the uteroplacental perfusion. This compensatory chain of events is disrupted in pregnancy-induced hypertension resulting in uteroplacental compromise with resultant serious consequences. The essential role of the renin-angiotensin system in the pathogenesis of pregnancy-induced hypertension is probably secondary in nature and largely based on its interaction with other vasoactive systems, e.g., Prostaglandins.

Prostaglandins

Since Prostaglandins exert vasoactive properties, they have been implicated in the pathogenesis of pregnancy-induced hypertension (Meagher and FitzGerald, 1993). There is no consensus as to whether they have a primary or a secondary role in the pathogenesis of hypertension in pregnancy.

Prostaglandins may participate in the cardiovascular changes of pregnancy. As discussed earlier, one of the hallmarks of normal pregnancy is a fall in peripheral vascular resistance. It has been proposed that prostaglandins may be involved in allowing the peripheral vascular resistance to fall in pregnancy. It is widely believed that most prostaglandins exert local, not systemic, actions. If this were true, increased synthesis of these compounds may not be reflected in plasma or urinary concentration of prostanoids. Nevertheless, in normal human pregnancy, PGE_2 and 6-Keto-PGF_{1a} have been shown to increase progressively (Moutquin and Leblanc, 1983; Coceani and Olley, 1980). Plasma concentrations of PGE_2 and 6-Keto-PGF_{1a} have been found to be increased by many workers (Yamaguchi and Mori, 1985; Lewis et al, 1981). Others, however, could not confirm these observations (Ylikorkala and Makka, 1985). The high urinary levels of PGE_2 in pregnancy undoubtedly reflect renal synthesis of PGE_2 since the circulatory compound is rapidly metabolized (Figure 5).

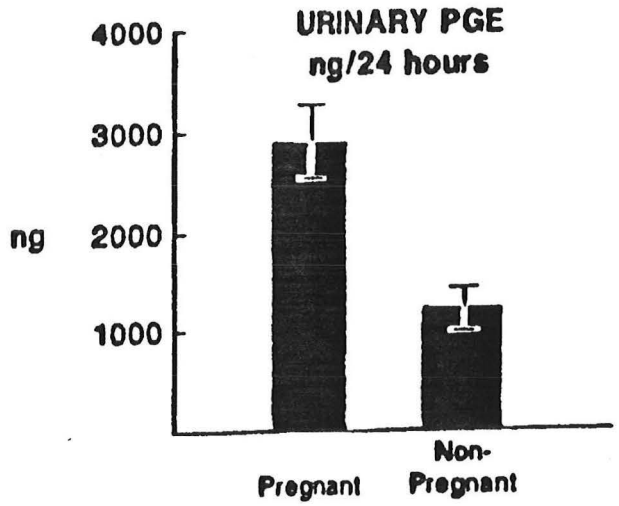


Figure 5: Urinary prostaglandin secretion in pregnant and in nonpregnant women. (From Bay WH and Ferris TF, 1979).

The quantitative contribution of the uteroplacental-fetal unit to maternal prostaglandins is also unclear. Vascular resistance to angiotensin II occurs as early as the 10th week of gestation and so it is not likely that the uteroplacental unit contributes to the maternal Prostaglandins. It is entirely possible that the vascular synthesis of PGF_{1a}, may be responsible for vascular insensitivity in normal pregnancy. Prostaglandin E levels are much higher in pregnant women compared to nonpregnant women (Sperof et al, 1976).

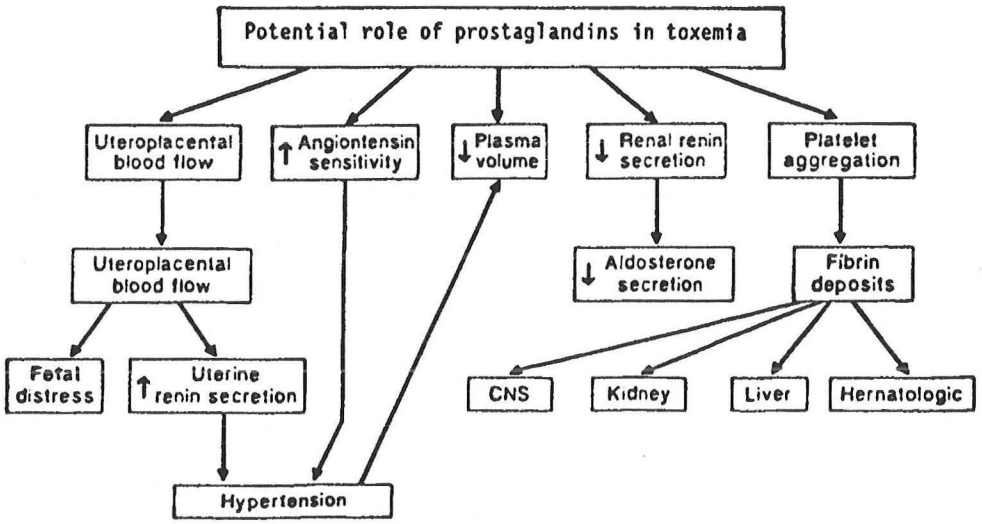
The placentas from preeclamptic women synthesize PGE to a lesser extent than placentas from normal pregnancies (Robinson et al, 1979; Demers and Gabbe, 1976). Demers and Gabbe also noted elevated levels of vasoconstrictor PGF in women with pregnancy-induced hypertension. Minuz et al studied the prostaglandin metabolism in patients with pregnancy-induced hypertension and in women with normotensive pregnancies (Minuz et al,

1988). All the vasodilatory PGs are lower in women with hypertensive pregnancies. In one study, the ratio of vasoconstrictor to vasodilator PGs (TXB9: 6-Keto-$PGF_{1\alpha}$) was significantly higher in pregnancy complicated by hypertension compared to normal pregnancy (Ogino et al, 1986). The differing patterns of prostaglandin metabolism in normotensive and hypertensive pregnancies have been described (Fitzgerald et al, 1987). It was noted that throughout the pregnancy the urinary concentration of 6-Keto-PGF_{1a} was lower in women with preeclampsia compared to normotensive women. In this study, decreased prostacyclin formation antedated the development of preeclampsia.

Uterine blood flow may be mediated by the local actions of PGs. Ferris has suggested that the blood flow to the uterus depends on dual mechanisms: local prostaglandin synthesis and the activity of angiotensin converting enzyme (Ferris, 1988). Uterine blood flow was markedly impaired in pregnant rabbits following -the administration of cyclo-oxygenase inhibitors or angiotensin converting enzyme (ACE) inhibitors. The observations related to ACE inhibitors may have clinical implications. Angiotensin II exerts a trophic effect on uteroplacental blood vessel growth (Fernandez et al, 1985) and conceivably this neovascularization may be attenuated by ACE inhibition resulting in a fall of uterine blood flow. Captopril administration to pregnant rabbits was associated with 86% fetal wastage compared to only 10% in controls (Ferris and Weir, 1984).

FIGURE 6:

A POSSIBLE ROLE FOR PROSTAGLANDINS IN THE PATHOPHYSIOLOGY OF PRE-ECLAMPSIA



Prostaglandins stimulate uterine contractility (Kirton et al, 1971; Kimball et al, 1975). In fact, PGs have been utilized to induce abortions (Thiery et al, 1975). Whether

these actions are direct or indirect is not known. Various lines of PGs have been demonstrated in the utero-fetal unit. The fetus is also a source of prostaglandins (Turnbull et al, 1980). The physiological and pathological contribution of fetal prostaglandins to maternal hypertension is far from clear. Quite conceivably, the vascular tone in pregnancy may be dictated by balancing actions of the renin angiotensin system and prostaglandins. The possible roles of prostaglandins in the pathogenesis of pregnancy-induced hypertension are shown in Figure 6).

IV. VASCULAR REACTIVITY IN NORMAL PREGNANCY AND IN PREGNANCY INDUCED HYPERTENSION

While the pathogenesis of pregnancy-induced hypertension remains to be conclusively defined, there is no doubt that women with pregnancy induced hypertension demonstrate enhanced sensitivity to the pressor effects of angiotensin II (Abdul-Karim and Assali, 1961; Chesley, 1971; Dieckmann and Michael, 1937; Gant et al, 1977) (Figures 7). Vascular reactivity is defined as the amount of a pressor response required to increase the blood pressure to a given level. In most studies, the amount of pressor substance (e.g. angiotensin) required to increase the diastolic blood pressure by 20 mm Hg is utilized as an index of vascular sensitivity.

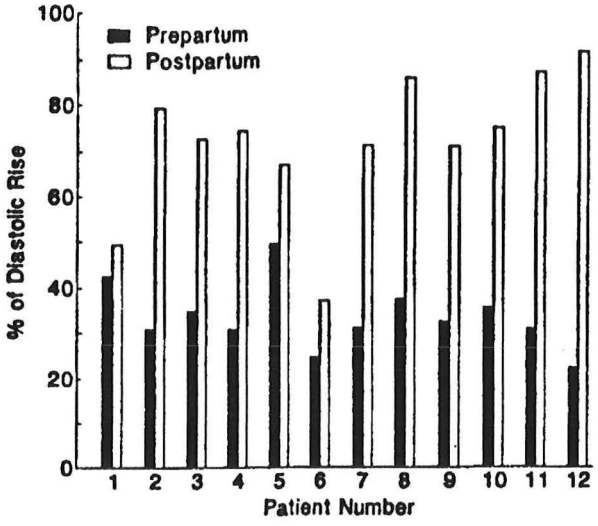


Figure 7: Diastolic blood pressure response to angiotensin of 12 subjects at term and postpartum. The response was taken as a percent of the control blood pressure. Note the striking difference between the prepartum and the postpartum response. (From Abdul-Karim and Assali, 1961).

Gant and co-workers conducted prospective studies of vascular reactivity to angiotensin II throughout pregnancy in 192 primigravida women who were 16 years or younger. The vascular reactivity was assessed by the amount of angiotensin II required to increase the blood pressure by 20 mm Hg. The women destined to develop pregnancy induced hypertension showed an augmented sensitivity to the pressor effects of angiotensin II after the 18th week of

gestation (Figure 8). The data further suggested that between the 28th and 32nd week of gestation, 90% of the women destined to develop pregnancy induced hypertension required less than 8 ng/kg/min of angiotensin to elicit a pressor response, whereas in women who remained normotensive vascular refractoriness was observed. Similarly, women with essential hypertension and superimposed pregnancy-induced hypertension, in contrast to those with essential hypertension alone, showed a remarkable sensitivity to the infusion of angiotensin II (Gant et al, 1977). The vascular sensitivity in pregnancy-induced hypertension is not affected by endogenous angiotensin II levels or by plasma volume expansion (Gant et al, 1980; Cunningham et al, 1975). These observations suggest that impeded vascular response and exaggerated vascular reactivity are found in normal and hypertensive pregnancies respectively.

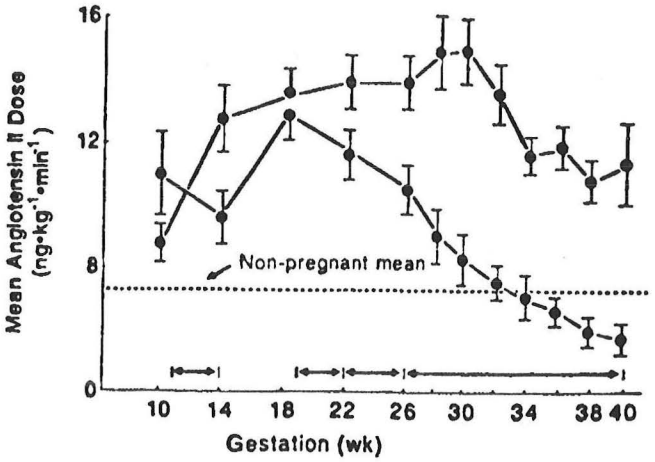


Figure 8: Comparison of mean angiotensin dose required to raise diastolic blood pressure 20 mm Hg in 120 primigravidae who remained normotensive (top curve) and 72 primigravidae in whom pre-eclampsia occurred (bottom curve). (From Gant et al, 1973).

What causes enhanced vascular susceptibility in pregnancy induced hypertension and relative refractoriness in normal pregnancy? The vascular response to angiotensin is not dependent on the endogenous renin-angiotensin system or volume status or receptor affinity. It is possible that it may be a post-receptor event. Vascular sensitivity is altered by Prostaglandins. The pressor response to angiotensin can be blunted during pregnancy by infusion of prostaglandin E_2 and PGI_2 (Broughton-Pipkin et al, 1982a; O'Brien et al, 1977; Broughton-Pipkin et al, 1984). In normotensive pregnant woman, prostaglandin synthetase inhibitors increase the vascular sensitivity to angiotensin II (Everett et al, 1978). Thus it appears that the vascular refractoriness to angiotensin II observed during pregnancy may be mediated by prostaglandins. Normal pregnant women lose the pregnancy-acquired vascular resistance within 15-30 minutes after the delivery of the placenta (Gant et al, 1980). A decrease in the rate of prostaglandin synthesis or an increase in prostaglandin catabolism could result in augmented vascular responsiveness to angiotensin II. Kawasaki and co-workers have shown that oral supplementations of 600 mg calcium from 20th week of gestation to delivery markedly reduced the vascular sensitivity to angiotensin II (Kawasaki et al, 1985).

V. ENDOTHELIAL CELL DYSFUNCTION

Endothelial cell dysfunction may play a role in the pathophysiology of pre-eclampsia (Roberts et al, 1991). Endothelial damage may increase the vascular sensitivity and permeability which characterize the vascular disturbances in preeclampsia. Activation of endothelial cell function can cause similar sequelae. Circulating endothelin levels have been found to be elevated in women with preeclampsia (Florijn et al, 1991; Clark et al, 1992; Schiff et al, 1992) (Table 4).

Table 4: Peptide and hormone levels in preeclampsia, normal pregnancy and non-pregnancy

	Preeclampsia	Normal pregnancy	Non-pregnancy
Endothelin (pmol/L)	22.6 ± 2.0*	12.0 ± 1.0	10.4 ± 0.4
ANP (pmol/L)	93 ± 36	55 ± 8	53 ± 3
Plasma renin activity [ng/(L·sec)]	3.4 ± 1.1†	2.8 ± 0.6†	0.7 ± 0.1
Aldosterone (pmol/L)	1395 ± 261‡	2665 ± 350‡	652 ± 78

*p < 0.005, versus normal pregnancy and non-pregnancy.
†p < 0.05, versus non-pregnancy.
‡p < 0.05, versus normal pregnancy.
(From Clark et al, 1992).

VI. THE ROLE OF NITRIC OXIDE

Nitric oxide, a potent vasodilator released by endothelial cells may play a role in the genesis of pregnancy induced hypertension. Nitric oxide could contribute to the blunted pressor response characteristic of normal pregnancy as well as for exaggerated vascular reactivity in pregnancy-induced hypertension. It has been suggested that diminished nitric oxide synthesis may contribute to vascular changes seen in pre-eclampsia (Seligman et al, 1994) (Figure 9).

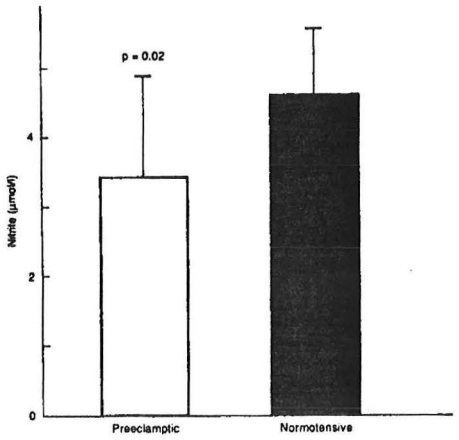


Figure 9: Mean serum nitrite levels determined by Greiss reaction in absence of E. coli reductase. Mean serum nitrite level was significantly lower in preeclamptic patients. Data represent mean ±SEM; n = 26 for both groups. (From Seligman et al, 1994).

VII. DEFICIENT TROPHOBLAST MIGRATION

The normal invasion of spiral arteries by the trophoblast converts them into deep deltas and so improves the blood flow. This adaptive invasion may be defective in pre-eclampsia (Chamberlain G: Raised blood pressure in pregnancy. Br Med J 1991;302:1454-1458) (Figure 10). A histological study of placental bed spiral arteries has confirmed the lack of trophoblastic invasion in hypertensives that is seen in normal pregnancies (Pijnenborg et al, 1991; Khong et al, 1992). Abnormal expression of adhesion molecules resulting in a defective trophoblast cell differentiation has been noted in pre-eclampsia (Zhou et al, 1993). These findings have shed a new light on the fundamental basis of utero-placental perfusion in pregnancy.

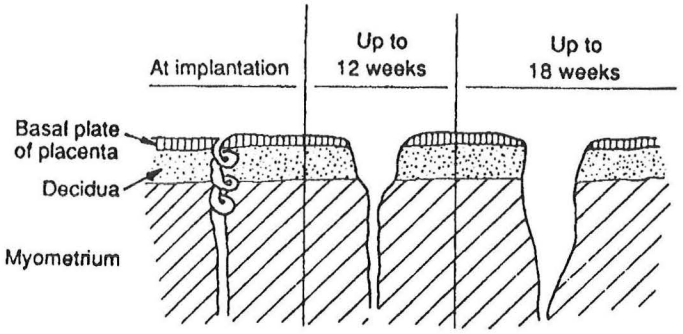


Figure 10: The normal invasion of spiral arteries by the trophoblast converts them into deltas and so improves blood flow. This invasion is defective in preeclampsia. (From Chamberlain G. Raised blood pressure in pregnancy. Br Med J 1991;302:1454-58).

VIII. THE CLASSIFICATION, DEFINITION, AND SIGNIFICANCE OF HYPERTENSION IN PREGNANCY

Hypertension complicates nearly 10% of all pregnancies and is an important cause of maternal and fetal morbidity (Maikranz and Lindheimer, 1987; Kaunitz et al, 1985) (Tables 5 and 6) (Figures 11 and 12). Preeclampsia and eclampsia represent serious manifestations of hypertension.

Table 5: Maternal Complications

1. **Deterioration of isolated high blood pressure to preeclamptic toxaemia which may lead to:**
   a) **Eclampsia**
   b) **Disseminated intravascular coagulation. In its worst form the defibrination syndrome with uncontrolled bleeding develops**
   c) **A Capillary leak syndrome with heavy proteinuria, serious effusions and acute pulmonary edema**
   d) **Epigastric pain due to intrahepatic haemorrhage, infarction and occasionally rupture of the liver**
   e) **Acute renal failure**
2. **Intracerebral bleeding (petechial, major haemorrhage, rupture of aneurysm)**
3. **Cerebral venous thrombosis**
4. **Left ventricular failure**
5. **Myocardial infarction**
6. **Dissection of the aorta**
7. **Complications related to antihypertensive therapy**

Table 6: Fetal Complications

1. **Intrauterine growth retardation**
2. **Intrauterine death**
3. **Abruptio placentae with rapid onset of fetal hypoxia**
4. **Obligatory pre-term delivery and the dangers associated with prematurity:**
   a. **Respiratory distress syndrome**
   b. **Hypoglycaemia**
   c. **Hyperbilirubinaemia**

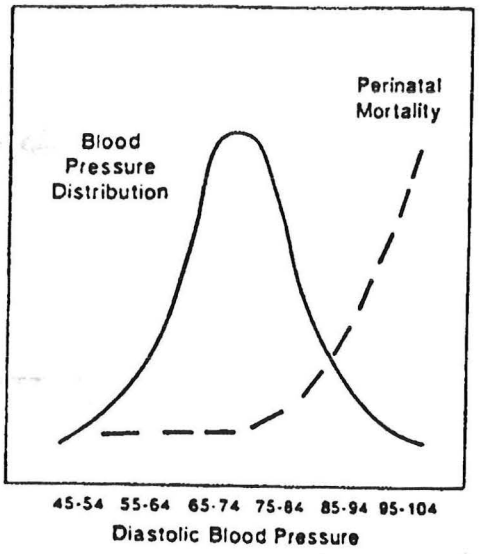


Figure 11: Relationship between diastolic blood pressure and perinatal mortality. (From Davey DA and MacGillivray I. Clin Exper Hypertens 1986;B5:97-133).

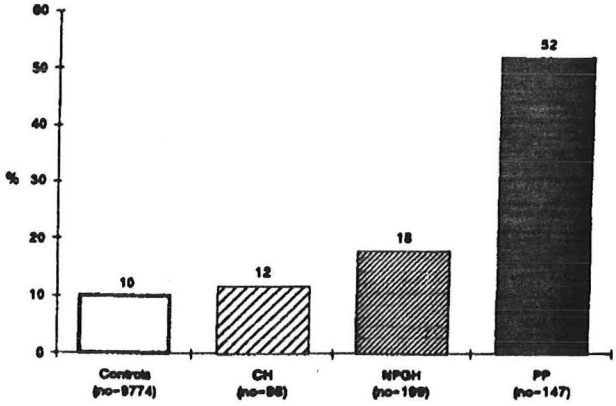


Figure 12: Percentage of small for gestational age infants in different groups studied: comparison with general population. CH, chronic hypertension; NPGH, nonproteinuric gestational hypertension; PP, proteinuric pre-preeclampsia. (From Ferrazzani et al, 1990).

The definition of hypertension in pregnancy has given rise to considerable controversy in the past because the blood pressure normally decreases by second trimester and then gradually increases to pre-pregnant levels at or near term. In order to set the stage for further elaboration, let us quickly look at the recommended definitions of hypertension. The American College of Obstetrics and Gynecology has established the following criteria for diagnosing hypertension in pregnancy:

1) Systolic blood pressure $\geq$ 140 mm Hg
2) Diastolic blood pressure $\geq$ 90 mm Hg
3) Increase of $\geq$ 30 mm Hg in systolic blood pressure
4) Increase of $\geq$ 15 mm Hg in diastolic blood pressure

Any of the above criteria should be present on at least two occasions separated by a minimum of 6 hours. Epidemiological data clearly suggest that diastolic blood pressures of 75 mm Hg and 85 mm Hg should be considered the upper limits of normal in the second and third trimesters of pregnancy (Friedman and Neff, 1977; Page and Christianson, 1976). Thus any tendency towards the blood pressure to increase far and above these limits should alert the physician to the possibility of gestational hypertension which mandates special attention to be devoted to the patient.

The blood pressure should be measured with a sphygmomanometer utilizing phase V Korotkoff sound as the diastolic blood pressure. The time of the day when the blood pressure is measured has to be taken into account. In uncomplicated pregnancy, the blood pressures decreases during the nighttime (Redman et al, 1976; Lubbe, 1984) (Figure 13). However, this normal circadian rhythm is disrupted in pregnancy induced hypertension resulting in persistent blood pressure elevation during the night (Seligman, 1971). Ambulatory blood pressure (ABP) measurements in pregnancy have yielded inconsistent results (Olofsson, 1995; Bellomo et al, 1995; Olofsson and Persson, 1995; Ferguson et al, 1994; Contard et al, 1993). The circadian variation in blood pressure is altered only in pregnancy induced hypertension but not in chronic hypertension associated with pregnancy.

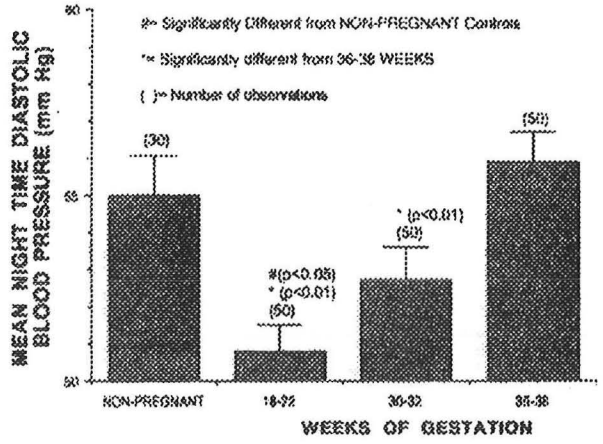


Figure 13: Mean (±SEM) nighttime diastolic blood pressures recorded as mm Hg during three gestational periods and in non-pregnant women. (From Ferguson et al, 1994).

Classification of Hypertension in Pregnancy

According to the guidelines of the American College of Obstetrics and Gynecology, hypertension noted in a pregnancy is classified into four categories:

1) Preeclampsia/eclampsia
2) Chronic hypertension
3) Chronic hypertension with superimposed preeclampsia/eclampsia
4) Late or transient hypertension

Preeclampsia is also referred to as pregnancy-induced hypertension. It is characterized by de novo development of hypertension in late pregnancy, often associated with edema and proteinuria. This syndrome accounts for more than 50 percent of all hypertensive disorders in pregnancy. Although preeclampsia typically presents after the 20th gestational week, it may occur earlier in pregnancy. When associated with placental dysfunction, preeclampsia occurs primarily in nulliparous women. Because preeclampsia is a harbinger of eclampsia, prompt treatment should be instituted. Preeclampsia can result in two dangerous complications; one, a syndrome characterized by hemolysis, liver dysfunction, and coagulation abnormalities - commonly known as HELLP (hemolysis, elevated liver enzymes, low platelets) - which constitutes a medical emergency. Second is progression to eclampsia, a convulsive phase of preeclampsia. Both these complications require immediate termination of pregnancy.

Chronic Hypertension

Pregnant women may have chronic underlying essential or secondary hypertension. The clinician should distinguish chronic hypertension from pregnancy-induced hypertension because of the obvious differences in clinical significance and therapeutic approaches. Chronic hypertension in pregnancy is diagnosed by:

1) Presence of hypertension prior to 20th gestational week
2) History of hypertension antedating pregnancy
3) Persistence of hypertension following delivery
4) Stigmata of hypertensive vascular disease

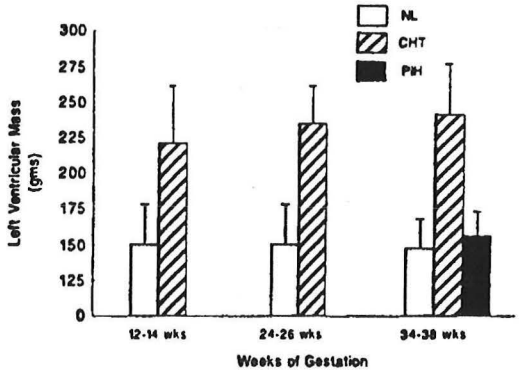


Figure 14: Left ventricular mass in grams according to weeks of gestation is depicted. NL = Normal pregnancy; CHT = pregnancy with chronic hypertension; PIH = pregnancy-induced hypertension. *Denotes $p < 0.01$ in the CHT group in comparison with either the NL or the PIH group. (From Thompson et al, 1986).

Patients presenting with chronic hypertension in pregnancy are at increased risk for maternal and fetal morbidity. Patients with chronic hypertension and who are at high risk are likely to benefit from medical therapy (Chari et al, 1995). It has been shown that in pregnancy-induced hypertension, the left ventricular mass is normal whereas it is significantly increased in women with chronic hypertension (Thompson et al, 1986) (Figure 14). Even in gravidas with chronic hypertension the blood pressure decreases early in gestation. Blood pressure may subsequently rise as the pregnancy advances. Gravidas with history of chronic hypertension are at an increased risk of developing preeclampsia and related complications (Chesley, 1978; Gant and Pritchard, 1984).

Chronic Hypertension With Superimposed Preeclampsia

Patients with preexisting hypertension, are at a high risk of developing superimposed preeclampsia (Gant et al, 1984; Redman 1980). In fact the major risk appears to be related to preeclampsia rather than preexisting hypertensive disorder. Patients with chronic hypertension are often multiparas who may present late in gestation with rapid escalation of blood pressure and onset of heavy proteinuria.

Late/Transient Hypertension

Some women develop hypertension in the late third trimester or puerperium which resolves within 10 days of delivery. Patients who exhibit this form of hypertension should be followed closely since they may ultimately develop chronic hypertension.

High blood pressure in pregnancy should be viewed as a distinct pathophysiological abnormality different from hypertension in the nonpregnant state because of immediate risks to two individuals - mother and fetus. Hypertension in pregnancy can be hazardous to the mother (Gallery, 1985; Department of Health and Social Security Report, 1979; Maikranz and Lindheimer, 1987) and the fetus (Chesley and Annitto, 1947; Chesley, 1978). The situation is a true "double jeopardy".

Patients at an Increased Risk for Hypertensive Disorders in Pregnancy

There are a number of risk factors for preeclampsia (Eskenazi et al, 1991). The following factors have been identified as predisposing the patient to develop hypertension in pregnancy.

1) Nulliparity
2) Pre-eclampsia in a previous pregnancy
3) Genetic Factors
4) Plural Pregnancy
5) Chronic Hypertension
6) Hydatidiform Mole
7) Fetal Hydrops
8) Diabetes Mellitus

Certain immunological factors have been incriminated in the predisposition to preeclampsia (Chen et al, 1994). Prior use of contraceptive methods (condoms, diaphragm, etc., that prevent sperm exposure) has been noted to enhance the risk of pre-eclampsia (Klonoff-Cohen et al, 1989). Previous blood transfusion is associated with decreased incidence of pre-eclampsia (Feeney et al, 1977). A definite role of these immunological hypotheses has not been tested.

IX. CLINICAL MANIFESTATIONS OF HYPERTENSION IN PREGNANCY

Chronic hypertension is a common cardiovascular disorder. Consequently a physician making the diagnosis of hypertension in a pregnant woman should try to make a distinction between chronic hypertension and pregnancy-induced hypertension. The clinical outcome and management of these separate conditions is quite distinct for obvious reasons. By obtaining a careful history and by performing a thorough physical examination aided by simple laboratory tests, it is not difficult to make the accurate diagnosis of pregnancy induced hypertension.

1. SYSTEMIC BLOOD PRESSURE

As discussed earlier, the systemic blood pressure generally falls in pregnancy. Thus, even a small increase in blood pressure of a pregnant woman should be taken seriously, confirmed, and followed closely. Hypertension in pregnancy is defined as (a) BP > 140/90 and/or (b) a rise in systolic BP > 30 mm Hg or a rise in diastolic blood pressure > 15 mm Hg. The levels should be documented at least twice 6 hours apart and should be based if possible on the knowledge of previously known blood pressure levels. In patients with no recorded previous blood pressure measurements, the diagnosis could be difficult. Although the British use the 4th Korotkoff sound for the diastolic blood pressure, we in this country continue to use the 5th Korotkoff sound (National High Blood Pressure Education Program Working Group, 1990). The blood pressure should be measured with the woman in the sitting, lateral, and semi-recumbent position.

Recently, continuous ambulatory blood pressure recordings have been increasingly used in the diagnosis and management of hypertension. The normal diurnal variation of blood pressure is disrupted in pregnancy-induced hypertension. Normally, the blood pressure falls during sleep. In women with pregnancy induced hypertension, the normal fall of blood pressure during the night did not occur and it has been proposed that a disrupted circadian rhythm may be present in these individuals.

2. PREDICTIVE VALUE OF 'ROLL-OVER' TEST

The report by Gant and colleagues that an exaggerated diastolic blood pressure response to supine posture was predictive of subsequent development of pregnancy-induced hypertension generated considerable interest (Gant et al, 1974b). When Gant and co-workers were performing the angiotensin infusion tests, they noted that in some patients there was a diastolic rise in blood pressure when they turned from the side to supine position. They were able to show a positive correlation between the angiotensin sensitivity and the postural rise in blood pressure in women destined to develop pregnancy-induced hypertension. It was suggested that a rise in DBP > 20 mm Hg induced by turning from the side to supine position

could be used as a screening test for pregnancy induced hypertension. These findings were not confirmed by others (MacGillivray, 1983; Campbell, 1978). In these later studies, the sensitivity of 'roll-over' test varied between 16 to 46%. A number of factors including the gestational week, right or left lateral position of the woman, sample size, and definition of preeclampsia may have contributed to the discordant results. Nevertheless, 'roll-over' test is not generally used as a screening test for pregnancy-induced hypertension.

3. PROTEINURIA

Proteinuria is a salient feature of preeclampsia. If proteinuria is detected on routine urinalysis, it should be followed by a 24-hour collection. Obviously, other causes of proteinuria such as urinary tract infection and kidney disease should be excluded. Total protein excretion of 300 mg/24 hours or more is abnormal.

4. EDEMA

Peripheral edema of arms and legs is quite common in normal pregnancy. The presence of edema by itself is not a reliable diagnostic sign of preeclampsia. Periorbital edema, however, is strongly indicative of preeclampsia.

5. DOPPLER ULTRASOUND

Doppler wave forms from utero-placental circulation have been shown to be abnormal in pre-eclampsia (Steel 1990; Trudinger and Cook 1990). Thus, uteroplacental Doppler may have a possible diagnostic role in the early detection of hypertensive disorders of pregnancy. However, its predictive value is not known and further evaluation of this technique is warranted.

6. OTHER FEATURES

Elevated uric acid level, decreased platelet count, visual changes, oliguria, liver dysfunction, and abdominal pain are associated features of preeclampsia.

X. MANAGEMENT OF HYPERTENSION IN PREGNANCY

The specific treatment of hypertension in pregnancy is still a matter of considerable discussion and debate. The only effective treatment of hypertension in pregnancy is to deliver the fetus. The occurrence of hypertension in a previously normotensive woman may cause substantial vascular damage. Moreover, untreated preeclampsia may deteriorate into eclampsia, which is a dreaded but preventable medical complication of pregnancy. Hypertension may also exert an unfavorable outcome on the fetus. Thus, it is prudent to treat hypertension in pregnancy (Table 7). The goals in the management of hypertension in pregnancy are:

1) Prevention of maternal complications
2) Prevention of fetal complications
3) Delivery of a viable fetus
4) Avoidance of adverse drug effects on the mother and fetus

Table 7

(1) Bed Rest
(2) Fluid Status
(3) Antihypertensive Drugs
(4) Termination of Pregnancy

Bedrest

Once hypertension is detected in pregnancy, bedrest is often recommended as the initial therapy. However, it is difficult to determine what is meant by rest. Bedrest is advocated to decrease the blood pressure, edema, and to prolong pregnancy until the fetus has reached viability (Tables 8 and 9). At Parkland Memorial Hospital, patients with pregnancy-

Table 8: Blood Pressure Response in 545 Nulliparous Women With Pregnancy-Induced Hypertension Hospitalized in the Parkland Hospital High-Risk Pregnancy Unit. (From Cunningham and Leveno, 1988)

Response			Number	%
Good initially (diastolic decreased to < 90 mm Hg)			441	(81)
Hypertension recurred before labor	183	(41%)		
Hypertension recurred in labor	199	(45%)		
Remained normotensive	59	(13%)		
Moderate (hypertensive intermittently)			70	(13)
Poor (hypertensive persisted)			34	(6)

Table 9: Gestational Ages at Admission and at Delivery in 545 Nulliparous Women Hospitalized for Pregnancy-Induced Hypertension in the Parkland Hospital High-Risk Pregnancy Unit (From Cunningham and Leveno, 1988)

Gestational age	When admitted		At delivery
Less than 30 weeks	5%		0.2%
30-32 weeks	16%	69%	2%
33-36 weeks	48%		11%
37 weeks or greater	31%		87%

induced hypertension are put to maximum rest and supervised closely. Whether the bedrest in the hospital is superior to rest at home is a matter of opinion. Of course, implementation of rest at home can be extremely unreliable. In one study, bedrest in the hospital setting was no more effective than rest at home (Matthews, 1977). In another study, the duration of gestation and outcome were no different between the hospital rest and home rest regimens (Matthews et al, 1980). The perinatal mortality rate for the infants of 545 nulliparous women who were hospitalized for bedrest was 9/1000. In contrast, for 31 women initially hospitalized but who later left the hospital against medical advice, the perinatal mortality was 129/1000. More than 75% of infants born to hospitalized patients weighed more than 2500 grams at birth. The incidence of fetal growth retardation was not different from that of non-hypertensive obstetrical population. Despite the lack of a clear physiological basis, bedrest is a harmless measure which not only serves as a therapeutic effort but also provides an opportunity to observe the mother and fetal growth. Bedrest (left lateral position) is accompanied by:

1) Lower blood pressure levels
2) Mobilization of extracellular fluid
3) ↑ Renal perfusion with diuretics
4) ?? ↑ Uterine blood flow
5) ↓ Sympathetic nervous system activity

Salt Restriction

It was widely believed in the past that 'excessive' weight gain during pregnancy predisposes the patient to develop preeclampsia. And attempts were made to vigorously restrict the salt intake by pregnant women. Although salt restriction may prevent excessive weight gain in some cases (because of reduced food intake) there is no evidence that salt restriction prevents pregnancy induced hypertensive disorders. Earlier recommendations to restrict the salt intake met with an extraordinary rebuttal and it was even suggested that a liberal salt intake lowered the incidence of pregnancy-induced hypertension (Robinson, 1958). This study was not well controlled and a direct link between salt and blood pressure in pregnancy was not established. The current thinking is that neither a low or a high salt intake in pregnancy is likely to have an effect on the development of hypertension.

Diuretics

Because of the presence of edema and hypertension (cardinal features of preeclampsia) diuretics have been used in this condition. They also have been used (in uncontrolled fashion) as a prophylactic measure. The use of diuretics has remained controversial over many years. Several studies were conducted to evaluate the possible effects of diuretic therapy in pregnancy with conflicting results (Collins et al, 1985). Initially,

Finnerty and co-workers reported dramatic results using diuretics in lowering the blood pressure in women who had hypertension in pregnancy. It was also reported that diuretics decreased the incidence of toxemia (Finnerty and Vetko, 1966; Cuadros and Tatum, 1964). Others, however, found no decrease in the incidence of preeclampsia with the use of diuretics (Flowers et al, 1962; Wesley and Douglas, 1962; Kraus et al, 1966). It has been proposed that if diuretics are used early in pregnancy, hypertensive complications can be avoided. This claim was proven to be erroneous by other workers (Tervila and Vartiainen, 1971). Surprisingly, Tervila and Vartiainen reported an increase in the incidence of proteinuria with diuretic therapy. The mechanism for this finding is unclear but the study group was not properly defined. A review of the world literature on the use of diuretics in nearly 7000 women concluded that diuretics exerted no beneficial effects on perinatal outcome (Collins et al, 1985).

Since hypertension in pregnancy is characterized by diminished intravascular volume (Gallery et al, 1979a; Rubin, 1986), it does not make much sense to use diuretics in pregnancy. On the average, the plasma volume deficit is around 500 ml in pre-eclamptic pregnancies compared to normal pregnancies. In one study, diuretics reduced the incidence of edema but not pregnancy induced hypertension (Campbell and MacGillivray, 1975). The birth weights of babies born to mothers treated with diuretics, however, were markedly reduced probably as a result of dehydration caused by diuretic therapy. The thiazide diuretics may also exert an unfavorable action on placental function (Shoemaker et al, 1973; Gant et al, 1971). Thus, for many valid reasons, diuretics should not be used routinely either to treat or prevent pregnancy induced hypertension. There is a clear-cut danger in giving diuretics because of their side-effects on the mother and fetus (MacGillivary, 1983; Lindheimer and Katz, 1973). In some cases of preeclampsia, actually fluid therapy may be required to improve the central hemodynamics.

Methyldopa

Methyldopa is a popular drug for the treatment of pregnancy-induced hypertension of mild to moderate degree. It has a CNS mechanism of action resulting in a fall of peripheral vascular resistance. Methyldopa has been used for many years with no reports of adverse effects on the fetus. The largest prospective study to date using methyldopa in pregnancy-induced hypertension attested to its efficacy and lack of adverse effects (Redman et al, 1977). Methyldopa is also useful in controlling chronic hypertension in a pregnant patient. It does not reduce the occurrence of superimposed preeclampsia (Lees and Rubin, 1987). Although it may cause some side effects (like sedation, dry mouth, etc.), methyldopa has a long record of safety in pregnancy.

Hydralazine

Hydralazine, a direct vasodilator, has been extensively used in the treatment of hypertension in pregnancy. Often, it has been used as a second line drug in moderate to severe hypertension. In the treatment of hypertensive crisis, it is given by parenteral route. Hydralazine has been shown to reduce the blood pressure without decreasing the placental blood flow (Lundell et al, 1983). Hydralazine continues to hold a prominent therapeutic role in hypertension in pregnancy, especially complicated hypertension (Paterson-Brown et al, 1994).

Clonidine

Clonidine is a centrally acting alpha-agonist with similar mechanism of action as methyldopa. In a double-blind study, both methyldopa and clonidine were equally effective in the treatment of pregnancy induced hypertension (Hovarth et al, 1985). Clonidine crosses the placenta rather easily (Hartikainen-Sorri et al, 1987). Children born to mothers treated with clonidine exhibited unusual behavioral changes (Huisjes et al, 1986). In view of this report and the pharmacological actions of clonidine, its use in pregnancy should be viewed with caution.

Beta-Blockers

Beta-blockers have been used in the management of hypertension in pregnancy generally with a favorable response (Rubin, 1986). Of all the beta-blockers, propranolol has been used widely in pregnancy. It does not seem to matter whether a beta-blocker has nonspecific pharmacological properties or is cardioselective, with or without intrinsic sympathomimetic activity. It has been proposed that a cardioselective beta-blocker such as atenolol has certain advantages over other beta-blockers (Rubin, 1983). But there may not be major differences among the beta-blockers. The efficacy of beta-blockers has not been questioned but the fear is that these drugs may cause potential adverse effects on the fetus. Reported adverse effects include precipitation of premature labor, fetal growth retardation, and in the neonatal-hypoglycemia, bradycardia, respiration depression and death (Lees and Robin, 1987; Habib and McCarthy, 1977). Significant hypotension was noted in some neonates born to mothers receiving beta-blockers (Woods et al, 1982; Dumez et al, 1981). Despite these anecdotal observations, the track record of beta-blockers in pregnancy is good generally (Lees and Rubin, 1987). Both beta-blockers and methyldopa are equally effective in the treatment of pregnancy induced hypertension (Williams and Morrisey, 1983; Fidler et al, 1983; Livingstone et al, 1983). A beta-blocker is probably better tolerated by the mother than methyldopa, but the latter has the advantage of having been the most widely used antihypertensive drug in pregnancy. In 120 women with pregnancy induced hypertension, atenolol has been found to be effective and safe (Rubin et al, 1983a). Despite the cumulative experience with the use of beta-blockers in pregnancy (obtained in England), the potential benefits and risks should be carefully considered since these drugs cross the placental barrier.

Labetalol

Labetalol, a combined alpha and beta-blocking drug, differs from a pure beta-blocker from a hemodynamic perspective. Acute administration of labetalol causes a rapid fall in pregnancy induced hypertension without altering the cardiac output. Symonds et al reported that labetalol is an effective drug in the management of hypertension in pregnancy (Symonds et al, 1982). In a comparative study, the perinatal morbidity (from respiratory distress syndrome) was less in the labetalol treated group compared to methyldopa (Michael and Potter, 1982). Also, labetalol appeared to be as effective as methyldopa in the treatment of pregnancy induced hypertension (Sibai et al, 1990). Although no large-scale data are available, labetalol appears to be an effective drug in treating not only mild but also more severe forms of hypertension.

Prazosin

This alpha-receptor blocker has been used to treat severe pregnancy induced hypertension (Lubbe and Hodge, 1981; Rubin et al, 1983b). This drug may cause postural hypotension. No specific beneficial or adverse effects have been noted in the brief experience with Prazosin in pregnancy induced hypertension.

Calcium Antagonists

This group of drugs is being increasingly used in the treatment of hypertension including in the pregnant woman (Walters and Redman, 1984; Allen et al, 1987; Lawrence and Broughton-Pipkin, 1987). Although nifedipine is rapidly effective in controlling severe pregnancy induced hypertension, there is insufficient experience to warrant routine use of these agents in pregnancy induced hypertension. One consideration is their potential (unproven) effects on calcium, bone metabolism, and hormonal regulation in the fetus.

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitors should be avoided in the treatment of hypertension in pregnancy. Reports linking the ACE inhibitors to fetal wastage in several animal species have appeared in the literature (Ferris, 1981; Ferris and Weir, 1984; Broughton-Pipkin et al, 1982b). ACE inhibitors have been shown to provoke renal failure in the newborn (Schubiger et al, 1988; Rosa et al, 1989). Since ACE inhibitors may alter functions of renin-angiotensin system and prostaglandin metabolism, these drugs may exert harmful effects on the fetus.

Drugs Used in the Treatment of Hypertensive Crises

A list of drugs which can be used to lower the blood pressure acutely in the emergency management of severe hypertension in pregnancy including eclampsia are listed in Table 10.

Table 10: Hypertensive Crisis

- **NITROPRUSSIDE**
- **?? LABETALOL**
- **TRIMETHAPHAN - CAUTION**
- **HYDRALAZINE**
- **?? DIAZOXIDE**

Of all the listed drugs, hydralazine enjoys the reputation of relative safety. It has been shown to have a beneficial effect on uteroplacental blood flow (Brinkman and Assali, 1975).

Diazoxide

Although diazoxide has been previously advocated for the acute treatment of severe hypertension in pregnancy, its use has declined (Ram and Kaplan, 1984). Diazoxide relaxes the uterus and therefore delays the labor. Some centers still use small doses of diazoxide to treat severe hypertension in pregnancy.

Sodium Nitroprusside

Experience with this rapidly acting, effective vasodilator in the management of hypertension in pregnancy is limited (Stempel et al, 1982). Whether it is safe for the fetus is not known. However, when maternal health is compromised as a result of uncontrolled severe hypertension, nitroprusside infusion should be considered (Rubin, 1986).

Labetalol (Parenteral)

For acute reduction in blood pressure, labetalol can be given as an infusion or as bolus injections (Ram and Hyman, 1987). There are no reported adverse effects on the fetus but its use, if at all, in pregnancy should be left to the experts.

Both labetalol and hydralazine are equally effective in controlling severe hypertension in pregnancy (Garden et al, 1982). The former drug, however, does not cause tachycardia.

XI. MANAGEMENT OF ECLAMPSIA

Eclampsia is a complication of preeclampsia, and convulsions with severe hypertension dominate the clinical picture. Eclampsia is an obstetric emergency and does not fall in the domain of an internist. Therapy of hypertension is only one component in the overall management of eclampsia. With regard to the treatment of hypertension, hydralazine is the usual drug of choice. Other drugs like diazoxide, nitroprusside, and labetalol are used with variable frequency.

Hydralazine (IM or IV) is a staple agent for use in eclampsia. The experience and the protocols developed at Parkland Memorial Hospital for the treatment of eclampsia have earned widespread recognition (Pritchard et al, 1984; Pritchard and Pritchard, 1975; Cunningham and Pritchard, 1984). Recent studies have shown that magnesium sulfate is superior to phenytoin for the prevention of eclampsia in hypertensive pregnant women (Lucas et al, 1995; Naidu et al, 1996). The following principles are responsible for the therapeutic success in managing eclampsia:

1) Control of convulsions with magnesium sulfate
2) Control of hypertension with hydralazine
3) Avoidance of diuretics
4) Initiation of delivery

XII. GOALS OF ANTIHYPERTENSIVE THERAPY IN PREGNANCY

1) To Prevent hypertension related maternal complications
2) To prevent the fetal complications
3) To permit prolongation of gestation till optimal fetal maturity is reached
4) To avoid adverse effects of therapy on the mother and fetus as well

XIII. THERAPEUTIC TRIALS IN PREGNANCY

Leather et al, conducted the first randomized clinical trial ever undertaken of antihypertensive therapy in pregnancy (Leather et al, 1968). Patients were assigned to methyldopa plus a diuretic or to no treatment. The active treatment group experienced a lesser magnitude of proteinuria and there was improved perinatal mortality. Several years later, Redman and colleagues conducted a clinical trial with methyldopa in a group of women with pregnancy induced hypertension (Redman et al, 1976). In this study, a significant excess of perinatal mortality occurred in the no-treatment group. This study demonstrated that methyldopa is a safe drug to use in pregnancy.

In another trial, women with pregnancy-associated hypertension were randomized to labetalol or no treatment (Walker et al, 1982) . The trial was too small to delineate any major differences except in the blood pressure levels. Rubin et al conducted a double-blind placebo-controlled trial with atenolol (Rubin et al, 1983a). It was concluded that atenolol is beneficial in the treatment of pregnancy associated hypertension because it not only lowered the blood pressure but also reduced the incidence of proteinuria and infant respiratory distress syndrome. However, there was no benefit obtained in women who already had proteinuria before the treatment was initiated. The atenolol treated group had more babies with bradycardia. Another beta-blocker, metoprolol, was tested against a placebo in some women with pregnancy induced hypertension (Weichman et al, 1984). In this study, although metoprolol lowered the blood pressure it did not prevent the occurrence of preeclampsia.

In all the above cited trials, fetal and perinatal mortality was lowered in the treatment group but a statistical significance was seen only in one study (Redman et al, 1976). The effect on proteinuria was variable with no clear effects of the drug. No major adverse effects on the fetus were noted.

Randomized trials have been conducted comparing different antihypertensive therapies (Fiddler et al, 1983; Gallery et al, 1985; Horvath et al, 1985). In the investigation conducted by Fiddler et al comparing a beta-blocker (oxprenolol) with methyldopa, there were no differences in fetal mortality rate which was quite low in both groups. Gallery et al (1985), utilizing the same drugs noted that babies born to mothers receiving methyldopa were smaller compared to oxprenolol . Good blood pressure control with either of the drugs was associated with good fetal growth. The only double-blind controlled trial of different antihypertensive treatments was conducted by Horvath et al (1985) who concluded that clonidine and methyldopa were equally effective in pregnancy induced hypertension.

In patients with severe hypertension in pregnancy, labetalol was found to be as effective as methyldopa (Redman, 1982). Labetalol, in contrast to diazoxide, provides a smoother control of blood pressure.

In all the trials, maternal and fetal complications were negligible with only minor differences. But these trials were conducted in the developed countries. It is possible that in non-westernized countries, small differences in mortality may be of great importance.

XIV. HOW LONG SHOULD ANTIHYPERTENSIVE DRUGS BE ADMINISTERED FOR HYPERTENSION IN PREGNANCY?

In the true pregnancy induced hypertension, the blood pressure falls following the delivery. In a majority of patients, the need for antihypertensive therapy ceases immediately. There may be some exceptions to this observation. Even if the blood pressure does not fall promptly after the delivery, in nearly all patients, antihypertensive drugs can be stopped within 6 weeks. The blood pressure level may not recede promptly in patients with chronic hypertension and superimposed preeclampsia. Patients with preexistent chronic hypertension may require long-term therapy.

XV. ANTIHYPERTENSIVE DRUGS IN LACTATION

Perhaps one of the most common questions posed to an internist by nursing mothers is whether antihypertensive drugs can be safely used. Most antihypertensive drugs indeed appear in the breast milk. Any drug passes from plasma to milk through a semipermeable lipid membrane such that an equilibrium is established between plasma and the aqueous component of the milk (milk ultrafiltrate). A drug that is avidly bound to proteins is unlikely to pass readily into milk (Anderson, 1979; Rasmussen, 1971). Lipid soluble drugs pass more readily into milk than do water

soluble drugs (Lien and Gudauskas, 1974). Thiazide diuretics (Werthmann and Krees, 1972), propranolol (Bauer and Pape, 1979; Levitan and Maniton, 1973), methyldopa (Hauser et al, 1985; Jones and Cummings, 1978), and reserpine (Knowles, 1972) have been shown to be clearly excreted in milk. One cannot be absolutely certain about the consequences in breast-fed infants. If antihypertensive drugs are prescribed to a lactating woman, the pharmacological effects on the fetus (like sedation, nasal congestion) should be monitored.

XVII. CHILDREN BORN TO WOMEN WITH PREGNANCY INDUCED HYPERTENSION

The goal of careful management of pregnancy induced hypertension does not end with the delivery of a viable fetus but also to ensure that the child growth and development are normal. Most studies on this subject have been only carried out for a brief period following the delivery. Although any negative effects may be obvious at an earlier age, it is important to know of the child development for an extended period of time. Limited data on this vital aspect are available (Ounsted, 1988) and they do not give any indication that child development is impaired. Long-term studies have not yet been done except with methyldopa. Children born to mothers who received methyldopa were carefully followed for 7 1/2 years (Redman, 1980; Redman, 1982). Physical and intellectual developments were noted during the 7 1/2 year period. There were no major differences in these children. In another study 22 children prenatally exposed to clonidine were compared with a control group at 6.3 years (Huisjes et al, 1986). The authors noted an excess of sleep disturbances in children whose mothers received clonidine in pregnancy. While this and other reports on the subject are of considerable importance, conclusions should not be drawn as to the superiority of one drug over another since controlled studies have not been performed in pregnancy. Once a normal baby is born to a mother exposed to antihypertensive drugs in pregnancy, the chances for normal growth and development are excellent (Ounsted, 1988).

XVIII. CHRONIC ESSENTIAL HYPERTENSION IN PREGNANCY

Pregnancy can punctuate the course of chronic essential or secondary forms of hypertension. Thus, special attention should be given to all women with hypertension in pregnancy irrespective of the nature of hypertensive disorder. In normal pregnancy, there is a lowering of systemic blood pressure but this phenomenon is not observed in women with preexistent hypertension. There are two major studies which looked at the natural history of chronic hypertension in pregnancy (Browne and Dodds, 1942; Chesley and Annitto, 1947) in 540 women. No patients received antihypertensive therapy. There was a significant relationship of blood pressure to fetal survival and occurrence of preeclampsia. Many observations have subsequently confirmed the risk of untreated chronic hypertension in pregnancy (Page and Christianson, 1976; Silverstone et al, 1980; Redman et al, 1977). It is therefore necessary to treat chronic hypertension in pregnancy.

It is not possible to give concrete recommendations about the choice of drugs in the management of chronic hypertension in pregnancy. Suffice it to say that volume contraction (diuretics) should be avoided unless there is a compelling reason. Methyldopa, hydralazine, and beta-blockers (with certain qualifications) have been used. Although the newer drugs are certainly effective, they are not matched by the safety record of conventional drugs like methyldopa. If the maternal or fetal health is compromised by uncontrolled, severe hypertension, then the choice of therapy is less important than urgent blood pressure control. It is best to use a single agent rather than combination therapy since the drug interactions in the fetus are not established.

XIX. PROGNOSIS OF HYPERTENSION IN PREGNANCY

For patients with chronic essential hypertension, the prognosis after successful gestation is probably no different from that of hypertension in the non-pregnant state. Dr. Chesley has followed women surviving eclampsia closely for a long period (Chesley, 1975). In Caucasian women with eclampsia as primiparas, neither the mortality nor prevalence of hypertension is different from that in unselected women matched for age and other factors. However, in black women and in white nulliparous women experiencing eclampsia, the long-term morbidity and the incidence of hypertension are increased compared to unselected match control s. In some individuals, pregnancy may unmask the underlying predisposition to develop hypertension. Women who remain normotensive throughout gestation have a significantly lower prevalence of hypertension than matched controls (Fisher et al, 1981). Continued normotension throughout pregnancy can be considered as an excellent indicator against the propensity to develop future hypertension.

XX. PREVENTION OF PRE-ECLAMPSIA

A number of approaches to prevent pre-eclampsia have been used such as administration of diuretics, low-dose aspirin, and calcium supplementation (Cunningham and Lindheimer, 1992). There is no evidence that dietary sodium restriction or diuretic therapy modifies the incidence or clinical course of hypertension in pregnancy. A meta-analysis of several trials that included 7,000 women showed no benefit from prophylactic diuretic therapy (Collins et al, 1985). Similarly, chronic dietary sodium restriction during pregnancy has not been shown to be a useful modality (Steegers et al, 1991).

Since diminished dietary calcium intake has been implicated in pregnancy induced hypertension, calcium supplementation has been tried for the prevention of pre-eclampsia (Villar et al, 1987; Lopez-Jaramillo et al, 1989; Belizan et al, 1991) (Figures 15 and 16). In these trials, calcium 1-2 g/day was administered after 22-24 weeks of gestation. The rationale is that pregnancy imposes greater maternal calcium requirements and that a negative calcium balance may trigger vascular smooth muscle contraction and vasoconstriction. Meta-analysis of randomized controlled trials strongly suggests that calcium supplementation during pregnancy leads to prevention of pre-eclampsia and a reduction in blood pressure (Bucher et al, 1996; Carolli et al, 1994) (Figures 17 and 18).

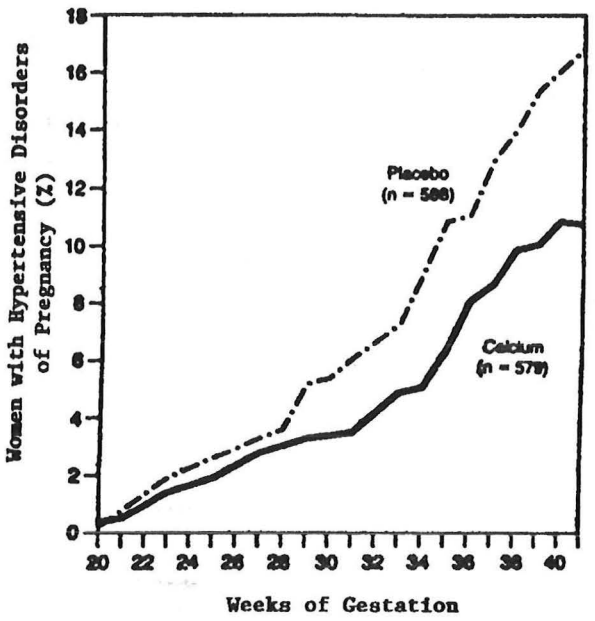


Figure 15: Percentage of Women in the Calcium and Placebo Groups in Whom Hypertensive Disorders of Pregnancy (Gestational Hypertension and Preeclampsia) Developed, According to the Week of Gestation. The values were calculated by life-table analysis. The risk of hypertensive disorders of pregnancy, particularly after the 28th week of gestation, was significantly lower in the calcium group than in the placebo group (P = 0.01) by the log-rank test). (From Belizan et al, 1991).

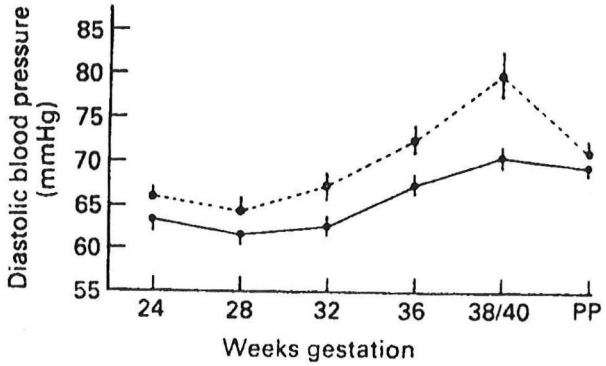


Figure 16: Variations of diastolic blood pressure in the calcium-treated and placebo-treated groups during pregnancy and in the postpartum period (mean ± SEM). ●—●, Calcium (n=49); ○---○, placebo (n=43). PP, Postpartum. (From López-Jaramillo et al, 1989).

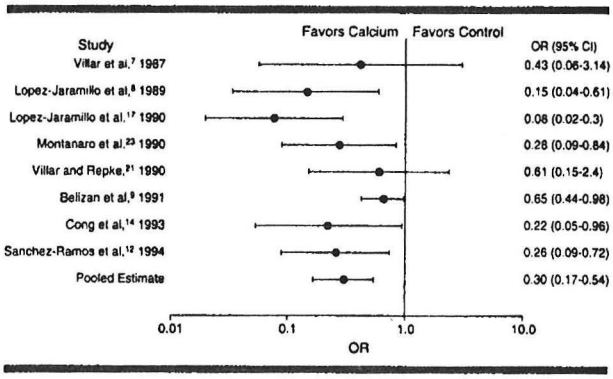


Figure 17: Calcium supplementation in pregnancy: effect on incidence of hypertension. The scale is logarithmic. OR indicates odds ratio; CI, confidence interval. (From Bucher et al, 1996).

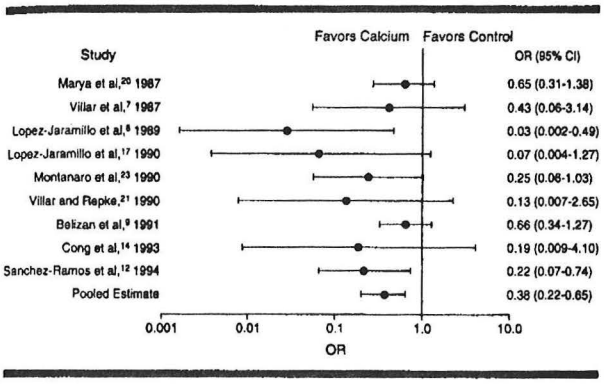


Figure 18: Calcium supplementation in pregnancy: effect on preeclampsia. The scale is logarithmic. OR indicates odds ratio; CI, confidence interval. (From Bucher et al, 1996).

An interesting strategy to prevent pre-eclampsia involves the use of low-dose aspirin therapy. Small amounts of aspirin (30-60 mg/day) may produce a greater inhibition of thromboxane production (Figure 19) compared to that of prostacyclin, thus reversing the possible prostaglandin mediated pathophysiology of preeclampsia. The preliminary reports about the usefulness of this approach showed promising results (Wallenburg et al, 1986; Crandon et al, 1979). Although a recent study (Italian Study of Aspirin in Pregnancy, 1993) questioned the benefits of aspirin, a meta-analysis of six trials which included 394 subjects concluded that low dose aspirin reduces the risk of pregnancy induced hypertension and low birth weight (Imperiale and Petrulis, 1991). Although a large trial failed to demonstrate any benefit of prophylactic low-dose aspirin therapy (CLASP Collaborative Group, 1994), in selected high risk patients, aspirin therapy has been clearly shown to reduce the occurrence of preeclampsia (Hauth et al, 1993; Sibai et al, 1993) (Tables 11 and 12; Figure 20).

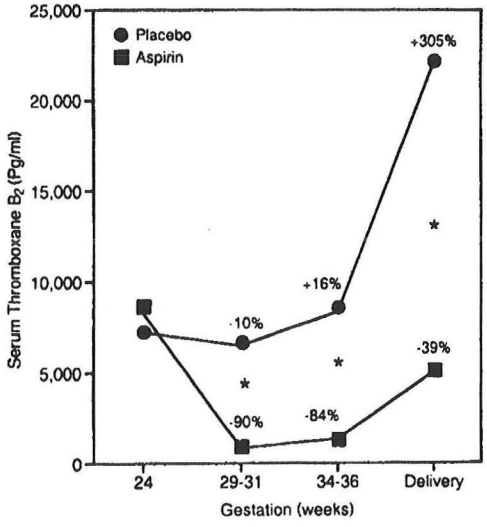


Figure 19: Median serum TxB_2 levels at randomization, at 29 to 31 and 34 to 36 weeks' gestation, and at delivery in women who received aspirin or placebo. *asterisks*, Significant decrease from randomization in aspirin group ($p < 0.001$) at all sampling times; *plus* and *minus percent*, changes relative to baseline values for both groups. (From Hauth et al, 1993).

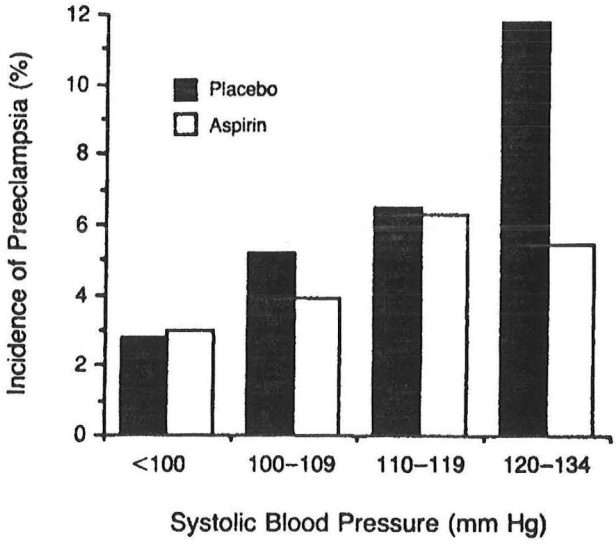


Figure 20: Incidence of Preeclampsia among Nulliparous Pregnant Women, According to the Systolic Blood Pressure at the Initiation of Treatment.
Low-dose aspirin treatment reduced the incidence of preeclampsia significantly (P=0.01) in the subgroup of 519 women whose initial systolic blood pressure was 120 to 134 mm Hg, but not in the other groups. (From Sibai et al, 1993.)

Table 11: Prevalence of Hypertensive Disorders in Pregnancy According to Treatment Group (From North et al, 1995)				
	No treatment (n=76)	Aspirin (n=27)	Heparin and antiplatelet drugs (n=44)	Significance
Gestational hypertension	8 (10.5%)	6 (22.2%)	5 (11.3%)	not significant
Preeclampsia	21 (27.6%)	7 (25.9%)	1 (2.3%)	p = 0.001

Table 12: Fetal Outcome in Treatment Groups (From North et al, 1995)					
	No treatment (n=77)	Aspirin (n=27)	Heparin and anti-platelet drugs (cn=44)	Heparin versus no treatment O.R. (95% CI)	Heparin + aspirin groups versus no treatment O.R. (95% CI)
Perinatal deaths	9 (11.7%)	0	1 (2.3%)	0.17 (0.02-1.4)	0.10 (0.02-0.62)
Gestation (weeks)	37(22-42.4)	37 (28-41)	36 (26-38)		
Preterm delivery					
≤28 weeks	10 (13%)	1 (3.7%)	1 (2.3%)	0.15(0.02-0.98)	0.19 (0.05-0.79)
≤32 weeks	15 (19.5%)	2 (7.4%)	4 (9.1%)	0.41 (0.13-1.3)	0.38 (0.14-1.0)
Birth-weight (g)	2,880(350-4260)	2,820(1140-3870)	2,630(850-4390)		
<1,500 g	16 (20.8%)	2 (7.4%)	4 (9.1%)	0.38 (0.12-1.2)	0.35 (0.13-0.96)
<1,000 g	10 (13%)	0 (0%)	2 (4.6%)	0.31 (0.07-1.4)	0.19 (0.05-0.79)
Small for gestational age	16 (20.8%)	6 (22.2%)	7 (15.9%)	0.72 (0.24-2.1)	0.85 (0.38-1.93)

XXI. CONCLUSIONS

Hypertension, especially preeclampsia is a major complication of pregnancy causing significant morbidity and mortality in both fetus and mother. Clinicians face a dilemma in treating hypertension in pregnancy. The physician has to decide whether it is really worth lowering the blood pressure. We are also faced with the situation of dealing with two individuals - mother and the fetus. Thus, from every perspective, the clinician has to focus on both. In severe hypertension and hypertensive crises, there is little room for deliberation. The blood pressure ought to be brought down and the pregnancy should be promptly terminated. The circumstances are more complex when less severe degree of hypertension is detected in pregnancy. In gestational hypertension manifesting itself late in the third trimester, any therapeutic approach is likely to yield an acceptable outcome; if hypertension appears early, pregnancy should be prolonged while closely monitoring the maternal health and fetal growth. Any sign of fetal distress or maternal complication warrants institution of measures aimed at shortening the gestation. The goals of therapy are straight forward, but not always simple - prevention of hypertensive complications, allowing fetal maturity and avoidance of therapeutic misadventures. Established antihypertensive drugs with proven safety should be chosen over newer drugs with an unknown side-effect profile. Over the years we have learned many lessons concerning the significance and outcome of hypertensive disorders peculiar to pregnancy. In the absence of a single explanation for blood pressure elevation in pregnancy, inevitably there will be conflicting views on how to treat the condition. However, the experience gained from this institution (which is widely accepted) strongly dictates adherence to an established protocol. Until a superior alternative is offered, the principles discussed here should be applied in managing hypertensive disorders in pregnancy.

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