MEDICAL GRAND ROUNDS

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HYPERTENSION IN PREGNANCY

An Internist's Perspective

C. Venkata S. Ram, M.D.

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Preeclampsia, the disease of theories.
- Zweifel, 1916

Everyone from allergist to zoologist has proposed hypotheses and suggested rational therapies based upon them, such as mastectomy, oophorectomy, renal decapsulation, trephination, alignment of the patient with the earth's magnetic field with her head pointing to the North Pole, and all sorts of medical regimens.
- Chesley, 1971

CONTENTS

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I. INTRODUCTION

Normal pregnancy is associated with a fall rather than an increase in blood pressure. Therefore, any increase in blood pressure represents a pathophysiological expression with serious maternal and fetal consequences (Lindheimer and Katz, 1985). Hypertensive disorders of pregnancy remain a major cause of maternal and fetal morbidity and mortality. Despite the considerable interest and attention devoted to blood pressure regulation and dysregulation in pregnancy, many gaps remain in our knowledge of hypertension in pregnancy. Literature is replete with controversial and divergent views on this subject. I will discuss the problem of hypertension in pregnancy from an internist's perspective.

Due to improved understanding of the multiple physiological factors governing the pregnancy and how these may be deranged in hypertensive disorders, our current clinical approaches are rational, if not complete. Various refined techniques have sharpened the precision with which hypertension can be accurately diagnosed in a pregnant patient and pharmacological developments have widened the therapeutic options. In order to understand the pathophysiological significance of elevated blood pressure in pregnancy we must first consider the hemodynamics of normal pregnancy.

II. HEMODYNAMICS OF NORMAL PREGNANCY

Cardiovascular System

From a hemodynamic standpoint, the single most important change that occurs in the maternal circulation is an increase in the cardiac output. In an average pregnant woman, the resting cardiac output rises 30%-40% above her prepregnant level (Metcalfe and Ueland, 1974; Ueland et al, 1969). This remarkable increase in cardiac output has several unique features. First, most of the increment occurs 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 towards the end of gestation. It has been suggested that the noted decline in cardiac output was spurious due to measurements being made in the supine position (Lees et al, 1967). In the early stage 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. In the resting state, the overall increase in cardiac output is associated with an increase in heart rate (15 beats/min) (Hytten and Leitch, 1971) and stroke volume (about 10 ml). This increase in cardiac output is responsible for the heart murmurs heard in the majority of patients (Cutforth and MacDonald, 1966) although recent echocardiographic studies surprisingly reveal a high incidence of tricuspid regurgitation in pregnant patients (Limacher et al, 1985).

Mechanisms of Increased Cardiac Output

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, there is increased myocardial contractility and increased velocity of circumferential fiber shortening in pregnancy (Rubler et al, 1977; Rubler et al, 1973).

The physiological reasons underlying the cardiac output changes are not entirely attributable 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. The maternal rate of oxygen consumption increases progressively during pregnancy. 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. The discrepancy between the increments in cardiac output and oxygen consumption was noted by Burwell more than 50 years ago (Burwell, 1938) who likened the maternal circulatory state to an arteriovenous fistula. 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 (Table 1).

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

Peripheral Vascular Resistance

Systemic blood pressure is a product of cardiac output and 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). I will discuss this phenomenon in detail later with reference to pathophysiology of pregnancy induced hypertension.

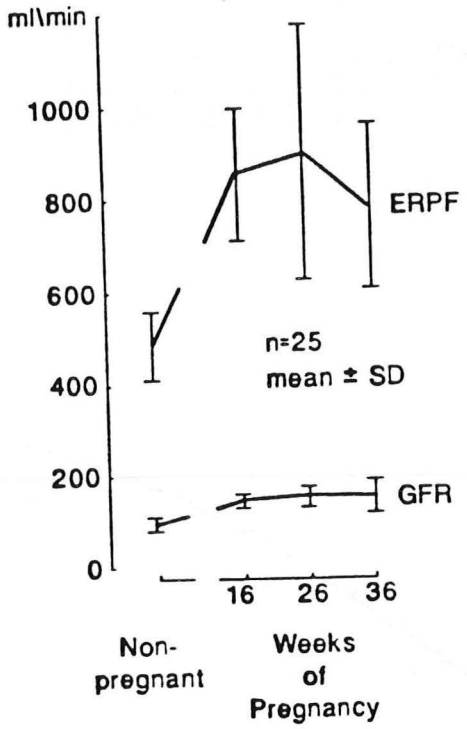
Renal Hemodynamics in Normal Pregnancy

In a pregnant women the effective renal plasma flow increases at least by 40% (Dunlop, 1981; Davison, 1984; Atherton, 1983; Sims and Krantz, 1985) (Table 2). The increase in effective renal plasma flow

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

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

Figure 1: Absolute changes in GFR and ERPF measured serially during pregnancy. (From Dunlop, 1981).



occurs very early in the pregnancy and is generally sustained but for a small drop in the third trimester (Dunlop, 1981; Dunlop, 1979) (Figure 1). 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; Davison and Hytten, 1974). The amount of the 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%. It should be noted that if glomerular filtration rate is measured late in pregnancy with the subject in the supine position, it may be reduced (Lindheimer and Katz, 1977; Chesley, 1978). 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. The increase in GFR results in an increased filtration of sodium from 20,000 mmol/day to 30,000 mmol/day (Davison, 1984). This obviously leads to a considerable increase in tubular reabsorption of sodium despite the opposing effects of increased progesterone levels.

Plasma Volume

Maternal blood volume increases during pregnancy, reaching levels exceeding 40% above nonpregnant values (Hytten and Paintin, 1963). 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 in normal pregnancy (Pritchard, 1965); 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 (Figure 2). This phenomenon causes hemodilution, manifested by decreased hemoglobin concentration, sometimes labelled "the physiological anemia of pregnancy."

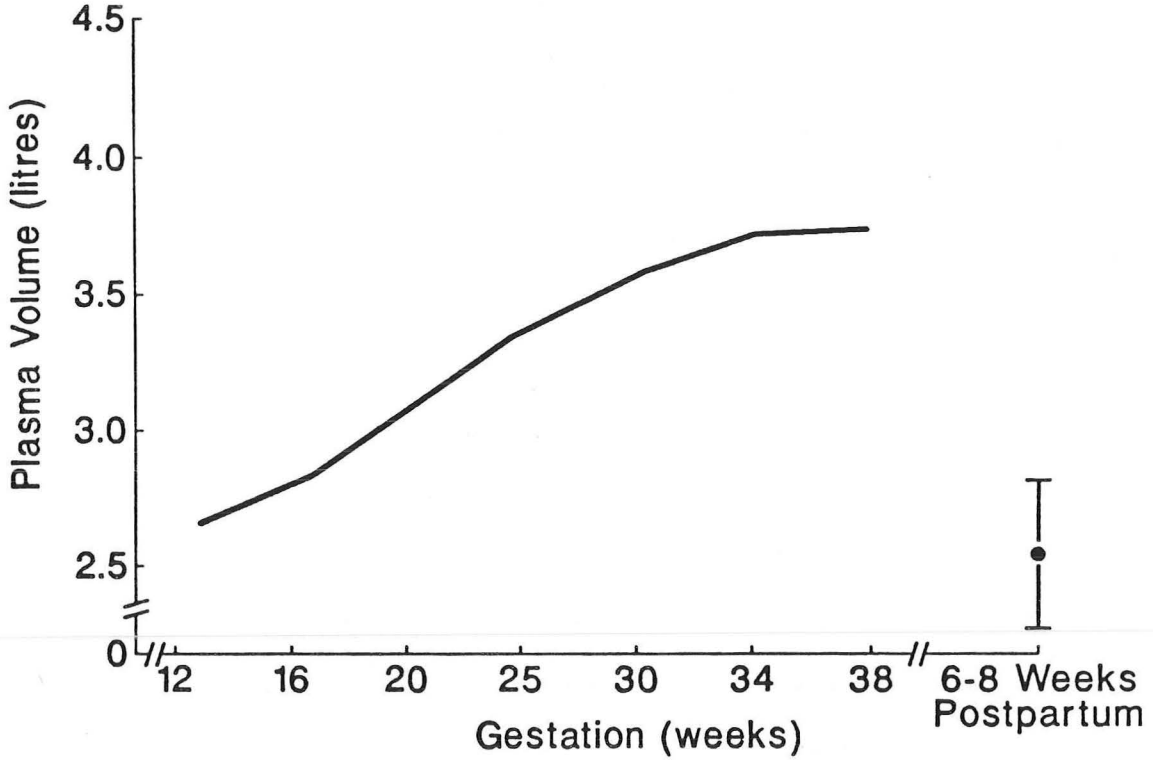


Figure 2: The mean plasma volume ± S.D. in normal pregnancy and postpartum. (From MacGillivary, 1983).

The mechanisms responsible for plasma volume expansion are not conclusively defined but several pertinent observations have been made on this subject. Both the plasma renin activity and plasma aldosterone levels increase during normal pregnancy. The increased plasma renin activity has been attributed to estrogenic stimulation of renin substrate production (Tapia et al, 1973). It is noteworthy that plasma volume increases despite appropriate increases in atrial natriuretic peptide (ANP) (Cusson et al, 1985).

Blood Pressure

Various pregnancy-related physiological processes exert an important influence 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)

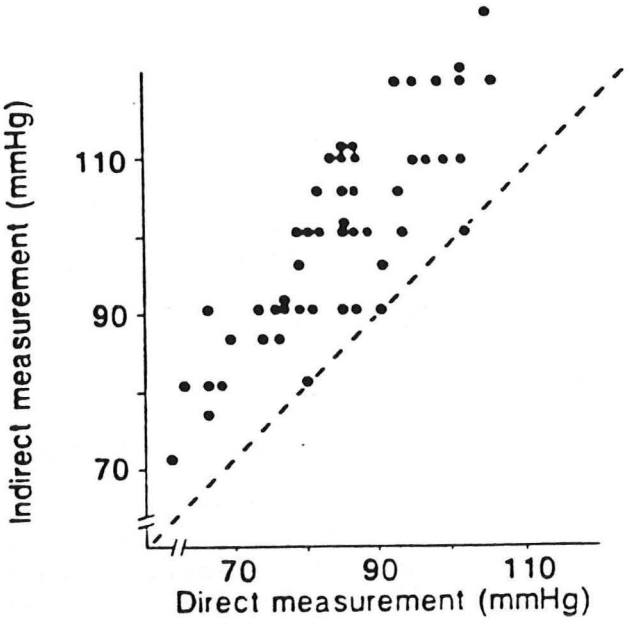


Figure 3: Correlation between values obtained simultaneously by indirect sphygmomanometric (Korotkoff Phase IV) and direct intra-arterial measurement of diastolic blood pressure in normotensive and hypertensive pregnant women (n = 50, one random pair of values per individual). Mean (± s.e.m.) difference between indirect and direct measurements is 15.7 ± 1.0 mm Hg). (From Wallenburg HS. Hemodynamics in hypertensive pregnancy. In: Rubin PC, ed. Hypertension in Pregnancy. New York: Elsevier, 1988:69).

(Figure 3). Because of the hyperkinetic circulation in pregnancy, the Korotkoff sounds are often audible even when no pressure is applied to the cuff. It is because of this observation that the British use the 4th Korotkoff sound rather than the 5th for diastolic blood pressure. However, we in this country continue to utilize the 5th Korotkoff sound as the diastolic blood pressure level. It should also be noted that in normal pregnancy, there is a fall in systemic blood pressure in the second trimester (Wilson et al, 1980). Blood pressure may then rise to nonpregnant levels by term (DeSwiet, 1980; MacGillivray et al, 1969) (Figure 4).

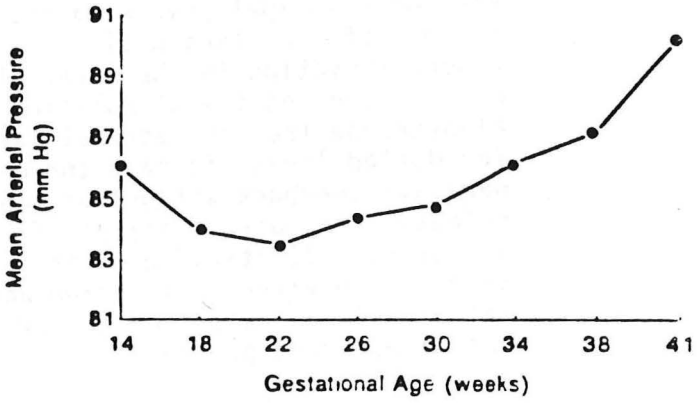


Figure 4: Mean arterial pressure (mm Hg) curve for normal pregnancy from 14-42 weeks' gestation. (From Page and Christianson, 1976)

The effect of posture on the blood pressure in pregnancy should be considered. Some investigators have noted a fall when women were supine (Quilligan and Tyler, 1959; 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 heart could account for the change in blood pressure level from supine to the left lateral position. Although the effect of posture on blood pressure is not resolved, it is appropriate to record the blood pressure in a standard fashion and the same position should be used each time in a given patient.

A change in blood pressure when the patient changes her position from left lateral to supine ("roll-over test") has been utilized to predict the risk of 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 rose in the supine position in a group of subjects (Gant et al, 1974) and this paradoxical response was used to predict preeclampsia. I will discuss more about this phenomenon later.

III. HUMORAL FACTORS

Renin-Angiotensin System

The renin-angiotensin system is an important mechanism of blood pressure regulation in normal pregnancy as well as possibly in pregnancy-induced hypertension. Renin is an enzyme secreted by the juxtaglomerular cells of the kidney in response to a variety of physiological and pathological stimuli. It acts on the renin substrate (angiotensinogen), an alpha-2 globulin synthesized in the liver, to form a decapeptide, angiotensin I. Angiotensin converting enzyme (ACE) converts inactive angiotensin I to angiotensin II, an octopeptide with potent vasoconstrictor effects. Angiotensin II also stimulates the production of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone in turn exerts a number of actions on electrolytes and extracellular fluid status. Angiotensin II is rapidly destroyed by angiotensinase (Figure 5).

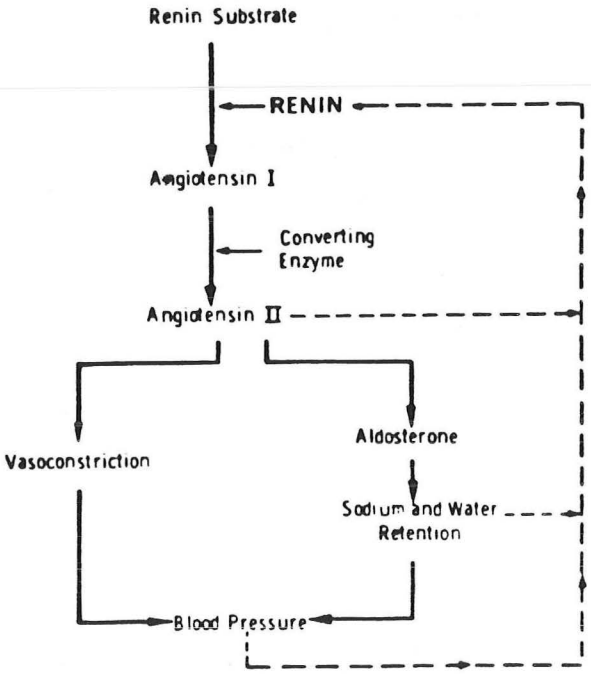


Figure 5: A scheme of the renin-angiotensin system indicating the formation of angiotensin II and the two principal physiological actions of angiotensin II: direct vasoconstriction in the arterial circulation and the stimulation of aldosterone from the adrenal cortex. The dotted lines indicate three negative feedback actions on renin release: the direct effect of angiotensin II itself and the suppressive effects of sodium and water (volume) retention and of increased blood pressure.

Renin is not measured directly because it tends to be unstable at high levels of purity. The rate of production of angiotensin I, therefore, is generally measured and referred to as plasma renin activity (PRA). Depending on the method used, the PRA may be measured as total, i.e. acid-activated renin concentration or active, i.e. non-acid activated renin concentration. Plasma renin substrate is quantified by adding excess renal renin to plasma and allowing the reaction to occur in an

environment devoid of angiotensinase. Angiotensin II is extremely difficult to measure because of its short half-life and other methodological difficulties.

In addition to the renal site, other sources of renin have been described - placenta, uterine muscle, chorion, and amniotic fluid (Skinner et al, 1968; Brown et al, 1964; Stakeman, 1960; Brown et al, 1963).

a) The Renin-Angiotensin System in Normotensive Pregnancy

The PRA and plasma renin concentration (PRC) in normal pregnancy are significantly raised above those in the nonpregnant state (Helmer and Judson, 1967; Brown et al, 1966) (Table 3). 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 cause a rise in 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 the components of the renin-angiotensin system in normal pregnancy still remains to be elucidated. There is no good correlation between PRA and aldosterone levels in pregnancy in contrast to the nonpregnant state. Although the activity of the renin-angiotensin system is enhanced in pregnancy, factors influencing the concentrations of various components in the nonpregnant state continue to operate in pregnancy. Thus, sodium depletion and upright posture stimulate PRA in pregnancy (Lindheimer et al, 1973; Ylikorkala et al, 1974; Becker et al, 1978; Bay and Ferris, 1979). In essence, the governing stimuli operate in pregnancy but have to act on the system that is already activated by some other factor.

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	Normal	Decreased
Urinary Kallikrein	Increased	Decreased	Decreased

b) The 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 the 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; Weir et al, 1973; Helmer and Judson, 1967). Symonds and Anderson noted that with bed rest PRA rose in patients with pregnancy induced hypertension.

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 (Figure 6). The uteroplacental unit responds by augmenting the synthesis and release of renin (Kokot et al, 1972; 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 severe forms of pregnancy-induced hypertension resulting in uteroplacental compromise with serious consequences (Figure 7). 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. Serum ACE levels have been measured in pregnancy-induced hypertension with variable, non-discriminatory findings (Oats et al, 1984; Fuentes and Goldkrand, 1987; Oats et al, 1987).

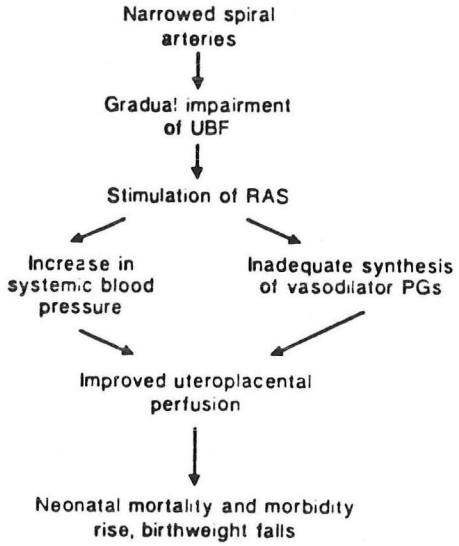


Figure 6: Schematic representation of proposed events in mild and moderate pregnancy-induced hypertension.

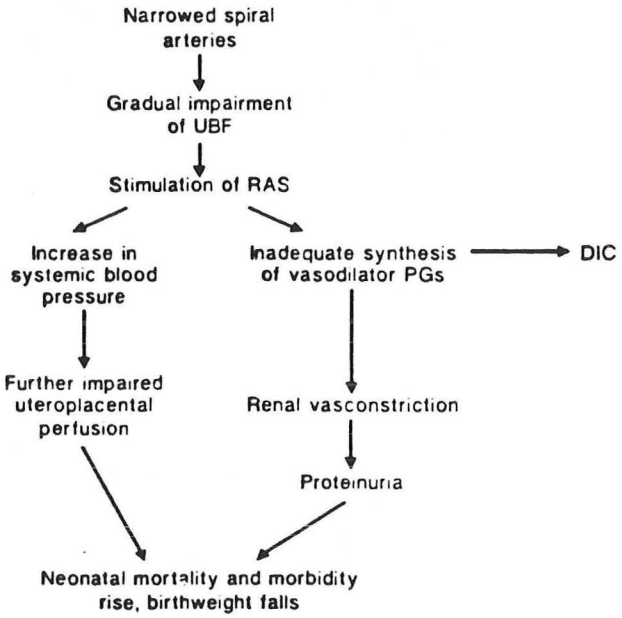


Figure 7: Schematic representation of proposed events in severe pregnancy-induced hypertension (PIH).

UBF = uterine blood flow; RAS = renin-angiotensin system; PGs = prostaglandins; DIC = disseminated intravascular coagulation. (From Broughton Pipkin and Symonds).

Prostaglandins

Since prostaglandins have potent vasoactive properties, they have been implicated in the pathogenesis of pregnancy-induced hypertension. Despite considerable research in this area, there is no consensus as to whether they have a primary or a secondary role in the pathogenesis of hypertension in pregnancy.

Prostaglandins are 20-carbon fatty acids which exert a number of local actions on the vascular tissue and renal function. The precursor for fatty acid synthesis is arachidonic acid which is released by cellular phospholipids. Arachidonic acid is metabolized to an intermediate (unstable) compound, PGH_2, which is enzymatically converted to one of many biologically active compounds (Figure 8). In the vascular tissue PGH_2 is transformed into prostacyclin or PGI_2 which is a potent inhibitor of platelet aggregation and is a vasodilator. PGI_2 has a very short half life and so its rate of synthesis is measured indirectly by determination of a metabolite, 6-Keto-$PGF1_\alpha$. In blood cells (including platelets) arachidonic acid is converted to thromboxane A_2 which is subsequently transformed into thromboxane B_2. Thromboxane A_2 has vasoconstrictor properties and causes platelet aggregation. The uteroplacental unit is known to be a site for synthesis and metabolic actions of prostanoids.

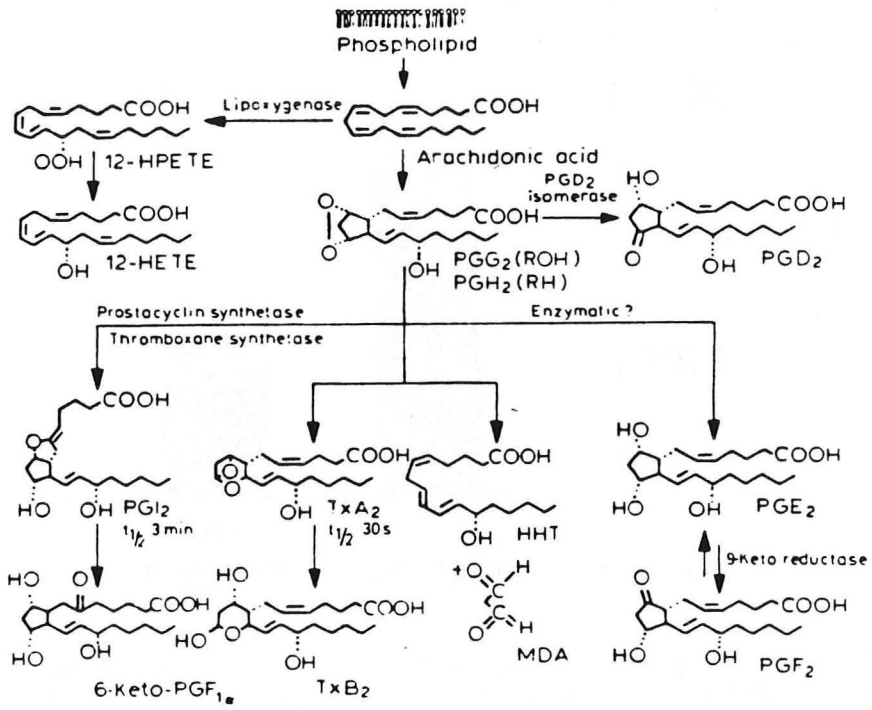


Figure 8: Synthesis of the prostanoids.

Prostaglandins and Blood Pressure Regulation 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-$PGF1_\alpha$ have been shown to increase progressively (Moutquin and Lebfanc, 1983; Coceani and Olley, 1980)(Figure 9). Plasma concentrations of PGE_2 and 6-Keto-$PGF1_\alpha$ have been found to be increased by many workers (Moodley et al, 1984; Yamaguchi and Mori, 1985; Lewis et al, 1980; Lewis et al, 1981). Others, however, could not confirm these observations (Greer et al, 1985; 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. Markedly augmented synthesis of 6-Keto-$PGF1_\alpha$ has been found in human pregnancy as well as in animal models (Mitchell et al, 1975; Venuto et al, 1975; Goodman et al, 1982).

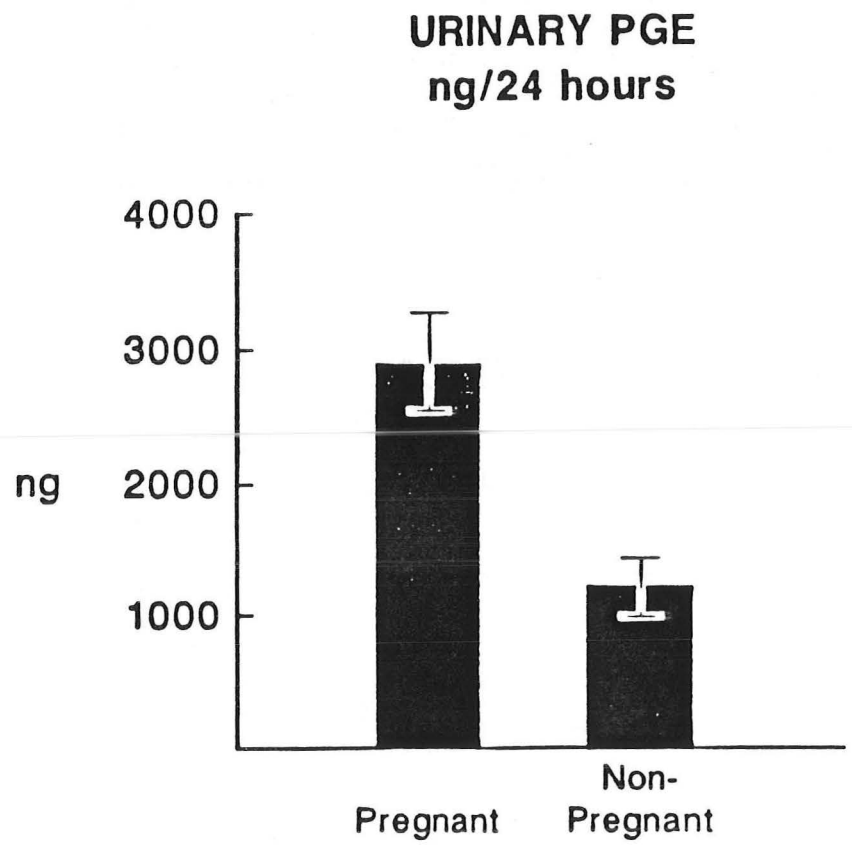


Figure 9: Urinary prostaglandin secretion in pregnant and in nonpregnant women. (From Bay WH, Ferris TF. Hypertension 1979:1:410-415.)

What causes enhanced production of prostaglandins during pregnancy? There is no conclusive response to this question. 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 PGI_2 may be responsible for vascular insensitivity in normal pregnancy.[2] Prostaglandin E levels are much higher in pregnant women compared to nonpregnant women (Ferris et al, 1976; 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; Ryan et al, 1969). 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 were significantly lower in women with hypertensive pregnancies. In one study, the ratio of vasoconstrictor to vasodilator PGs (TXB_2: 6-Keto-$PGF1_\alpha$) was significantly higher in pregnancy complicated by hypertension compared to normal pregnancy (Ogino et al, 1986). More recently, the Vanderbilt group has confirmed the differing patterns of prostaglandin metabolism in normotensive and hypertensive pregnancies (Fitzgerald et al, 1987)(Figure 10). It was noted that throughout the pregnancy the urinary concentration of 6-Keto-$PGF1_\alpha$ was lower in women with preeclampsia compared to normotensive women. In this study, decreased prostacyclin formation antedated the development of preeclampsia.

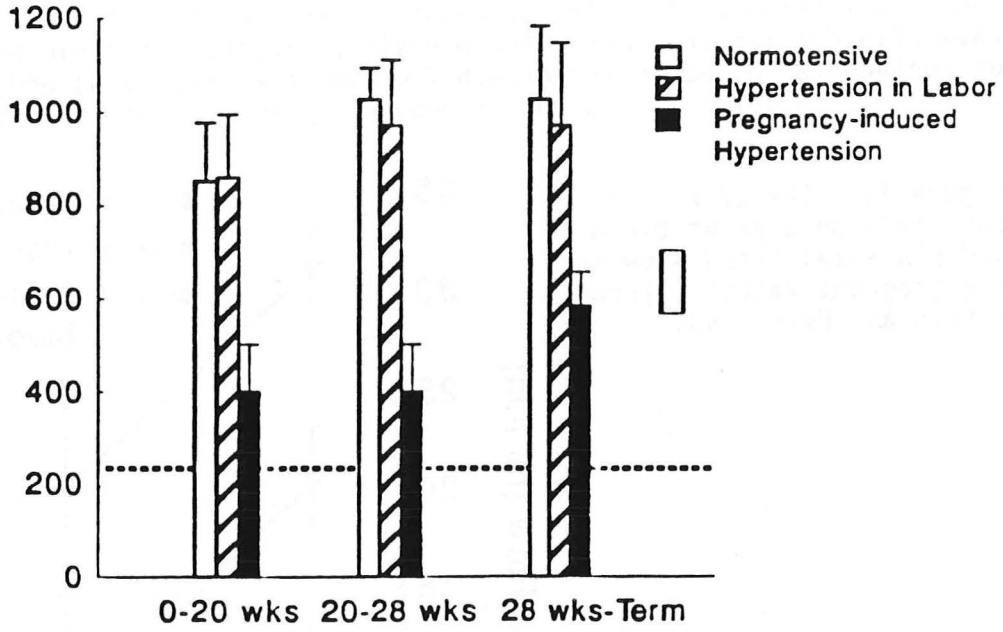


Figure 10: Excretion of 2,3-dinor-6-keto-$PGF_{1\alpha}$ throughout gestation in normotensive women (n = 24), in patients with hypertension during labor (n = 22), and in those with pregnancy-induced hypertension (n = 12). The hatched horizontal line represents the upper 95% confidence limit for normal age-matched, nonpregnant subjects. (From Fitzgerald et al, 1987).

Table 4: MATERNAL MEAN ARTERIAL PRESSURE AND LEFT UTERINE ARTERY BLOOD FLOW (MEAN ± SE)

	Baseline	Hypertension	Posttreatment
Mean arterial pressure (mm Hg)	92.24±2.05	108.33±2.95*	88.33±5.40
Left uterine artery blood flow (ml/min/lamb)	236.95±32.65	260.25±55.85	320.31±54.26*

*p<0.03

(From Keith et al, 1987. Hemodynamic values before and after treatment with a thromboxane synthetase inhibitor in an ovine model of pregnancy-induced hypertension.)

Uterine blood flow may be mediated by the local actions of PGs (Table 4). 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 (Figure 11). 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

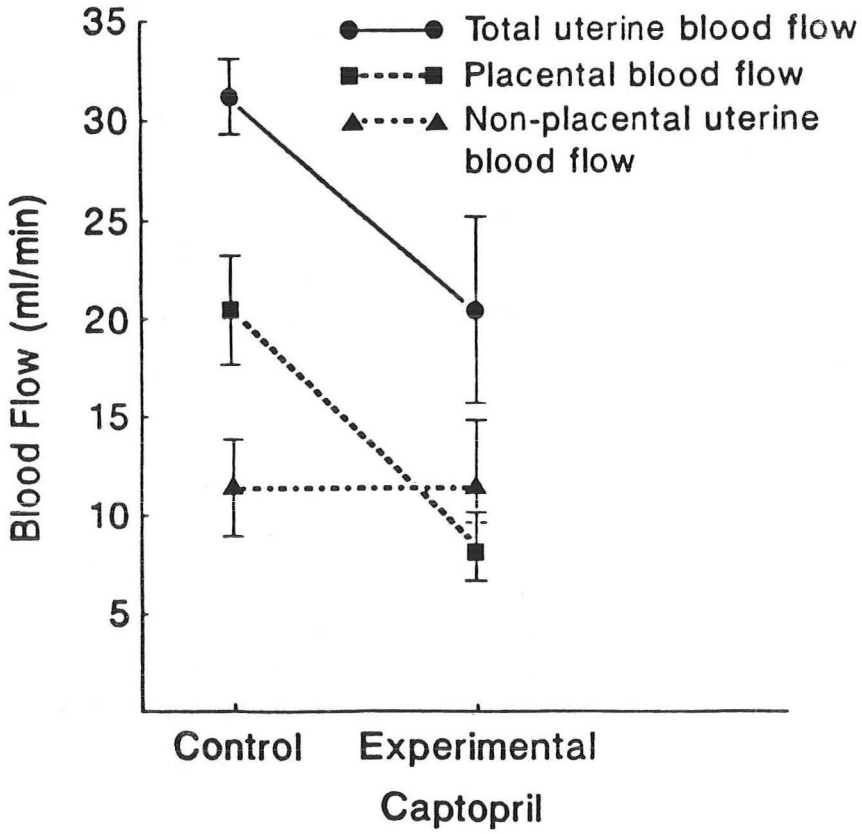


Figure 11: The effect of captopril on uterine blood and placental blood flow in the pregnant rabbit. (From Ferris and Weir, 1984)

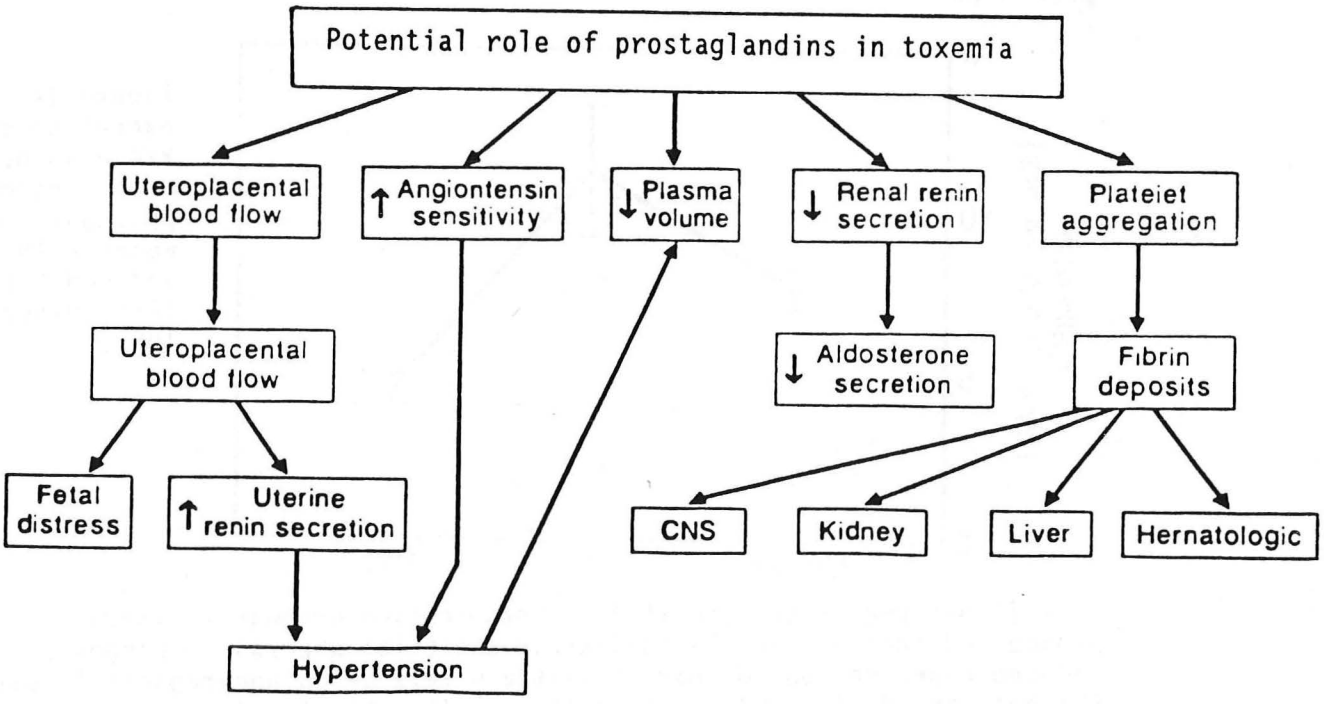
fall of uterine blood flow. Captopril administration to pregnant rabbits was associated with 86% fetal wastage compared to only 10% in controls (Ferris and Weir, 1983) (Table 5).

Table 5: Fetal Survival With Chronic Captopril Administration to Rabbits (From Ferris, 1984)

	No of fetuses alive total	Survival %
Controls (n = 12)	80/81	99
Captopril		
2.5 mg/kg (n = 10)	18/89	20
5.0 mg/kg (n = 11)	6/80	7.5

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. The possible role of prostaglandins in influencing an array of circulatory functions in pregnancy is shown in Figure 12. Quite conceivably, the vascular tone in pregnancy may be dictated by balancing actions of the renin-angiotensin system and prostaglandins as depicted in Figure 13.

Figure 12: **A POSSIBLE ROLE FOR PROSTAGLANDINS IN THE PATHOPHYSIOLOGY OF PRE-ECLAMPSIA**



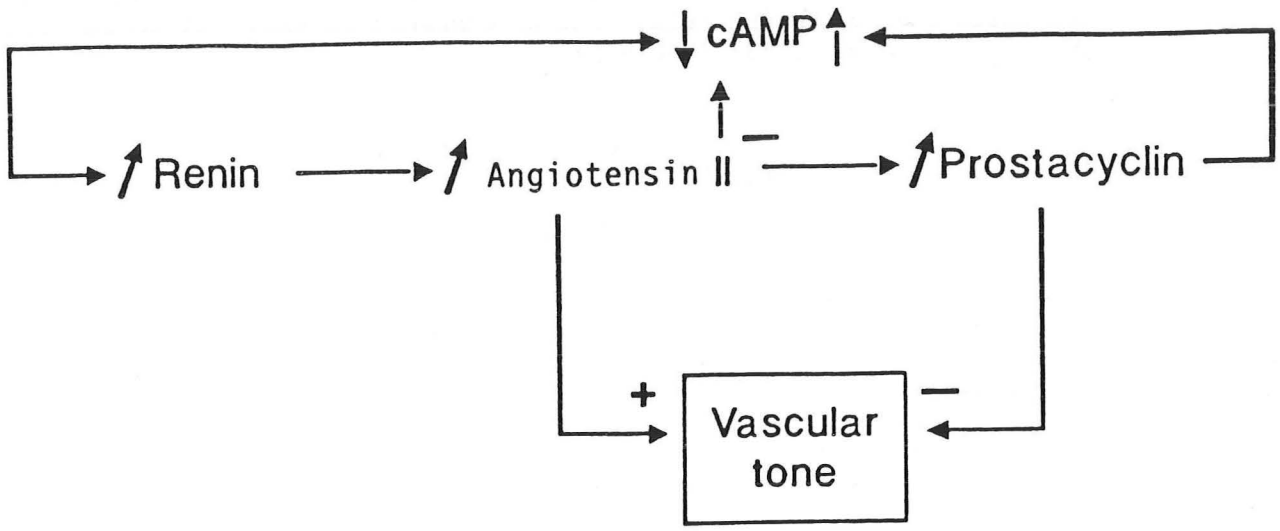


Figure 13: Mechanism to produce a balance between angiotensin II-induced vasoconstriction and prostacyclin-induced vasodilatation. (From Fievet P et al. J Hypertens 1986;4(Suppl 5):S88-S91.)

Kallikrein-Kinin System

Among the putative substances which have been identified to exert a vasodepressor function is the kallikrein-kinin system. This system participates in a physiological cascade of events which bears some resemblance to the renin-angiotensin system. Kallikrein is a proteolytic enzyme, which reacts with an alpha$_2$- globulin (Kininogen) to release bradykinin. Besides a vasodilatory function, the kinin system promotes sodium and water excretion. The study of the kallikrein-kinin system has been plagued with difficulties in measuring the kallikrein activity with precision.

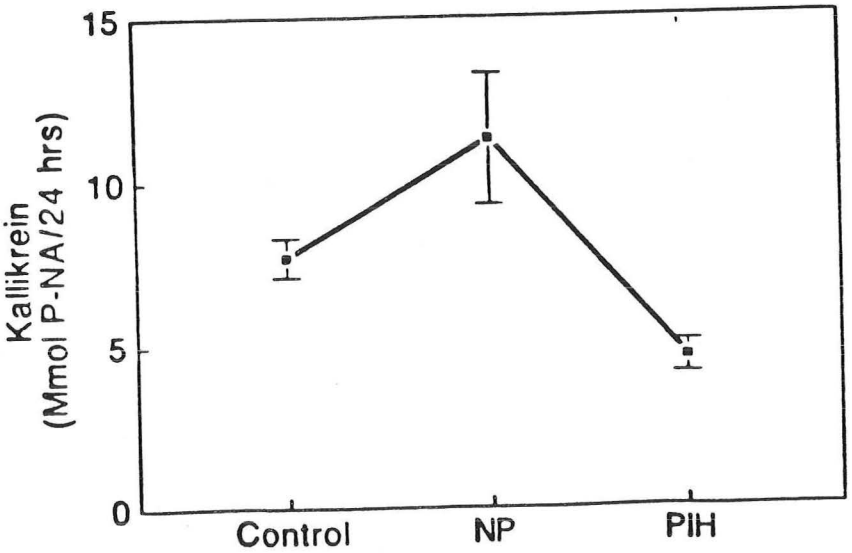


Figure 14: Urinary excretion of kallikrein in normotensive women, normotensive pregnant women, and women with pregnancy-induced hypertension. (From Minuz et al, 1988).

It has been suggested that in normotensive pregnancy, there is a pronounced increase in the kallikrein excretion whereas in pregnancy-induced hypertension, urinary kallikrein fell below nonpregnant levels (Elebute and Mills, 1976)(Figure 14). Interestingly, in women with

preeclampsia, the kallikrein activity in the amniotic fluid is depressed (Bodzenta et al, 1981). The urinary kallikrein excretion reflects the activity of the renal kallikrein-kinin system. This system participates in regulating renal hemodynamics and electrolyte excretion. In pregnancy-induced hypertension, changes also occur in the regulation of prostaglandins and the renin-angiotensin system (Sipila et al, 1986). These interactions are complex and poorly defined. The changes in the kallikrein-kinin system in conjunction with alterations in other regulatory mechanisms may somehow influence the direction of blood pressure in pregnancy.

Serotonergic Mechanisms

Serotonin (5 hydroxytryptamine) is a naturally occurring amine which exerts a number of effects on circulation by promoting vasospasm and affecting platelet function. Whether activation of serotonergic mechanisms is important in hypertension is not known. Serotonin content in the uterine tissue and placenta increases during pregnancy (Clark et al, 1980). Serotonin is a vasoconstrictor of the uterine vasculature.

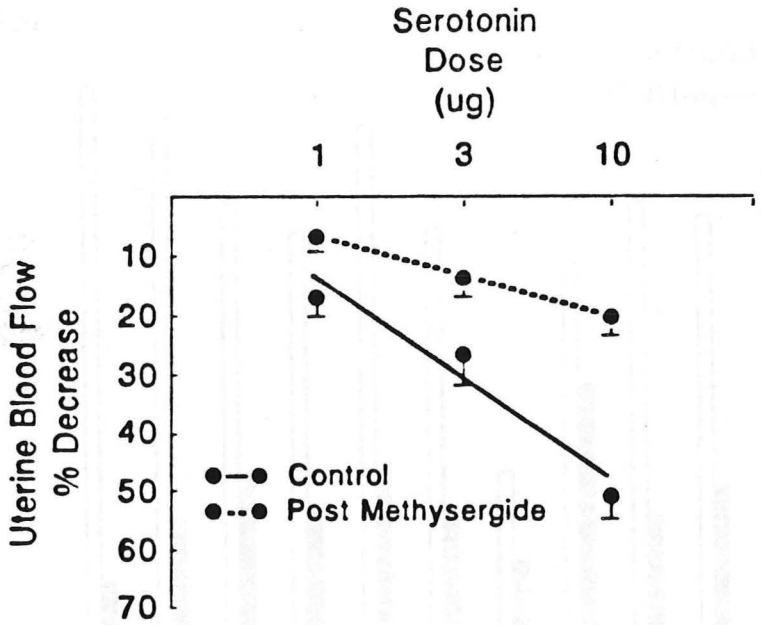


Figure 15: Effect of intra-arterial bolus injections of serotonin (1-10 μg) on uterine blood flow before and after the serotonin receptor antagonist, methylsergide (1 mg/kg), in late term pregnant ewes.

The levels of circulating serotonin levels in pregnant, nonpregnant, and preeclamptic women have been studied, yielding inconsistent results (Weiner, 1987; Gujrati et al, 1985; Jelen et al, 1979). Serotonin is rapidly metabolized and thus, it is not possible to realize the significance of its circulating levels. Thus, an increase or decrease in circulating serotonin would not necessarily preclude a role for it in pregnancy-induced hypertension. Experimental use of methysergide, a serotonin antagonist, resulted in an improvement of uterine blood flow in pregnant sheep (Clark et al, 1980)(Figure 15). Ketanserin, a more specific antagonist of serotonin, has been shown to be effective in the management of hypertension in pregnancy (Weiner et al, 1984). The lack of correlation between the circulating serotonin levels and the blood pressure suggests that serotonin may or may not directly influence the blood pressure. However, serotonin may amplify the biology and actions of other vasoactive mechanisms, e.g. catecholamines, prostaglandins, renin system, etc.

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

While the pathogenesis of pregnancy-induced hypertension remains to be conclusively defined, there is little doubt that women with pregnancy induced hypertension demonstrate enhanced sensitivity to the pressor effects of angiotensin II (Abdul-Karim, Assali, 1961; Chesley, 1971; Dieckmann and Michael, 1937; Gant et al, 1974; Gant et al, 1973; Gant et al, 1977; Talledo et al, 1968)(Figure 16). 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 17). This method of evaluating the vascular responsiveness in clinical research was pioneered by Dr. Kaplan 25 years ago (Kaplan and Silah, 1964).

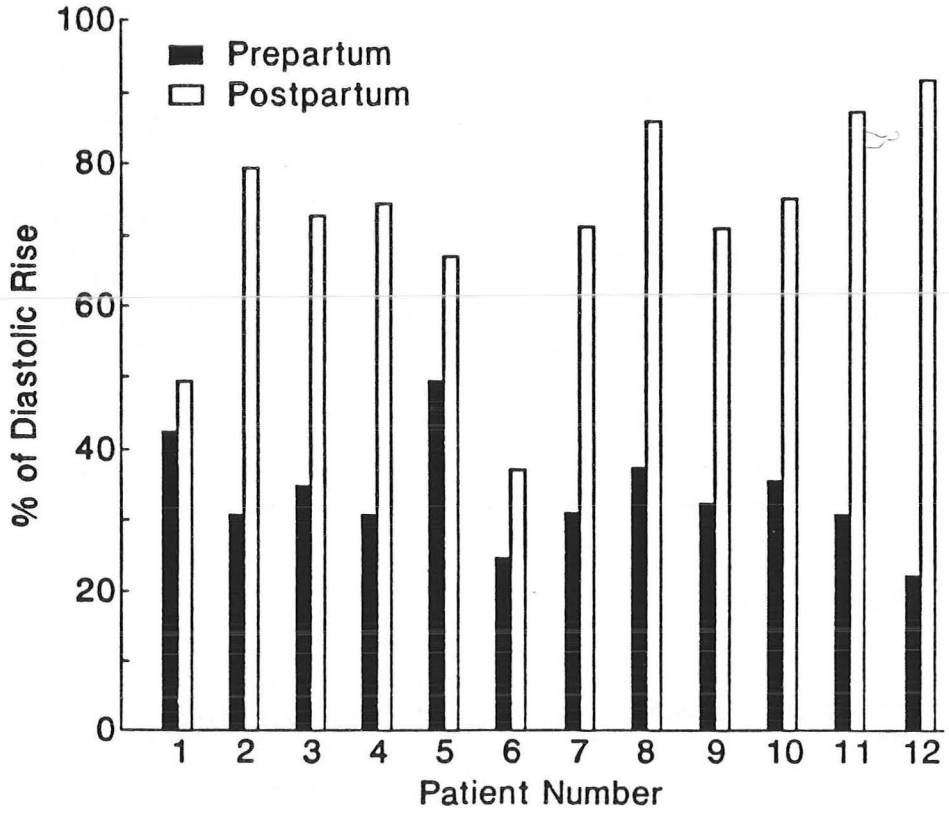


Figure 16: Diastolic blood pressure response to angiotensin of 12 subjects at term and post partum. The response was taken as a per cent of the control blood pressure. Note the striking difference between the prepartum and the postpartum response. (From Abdul-Karim and Assali, 1961).

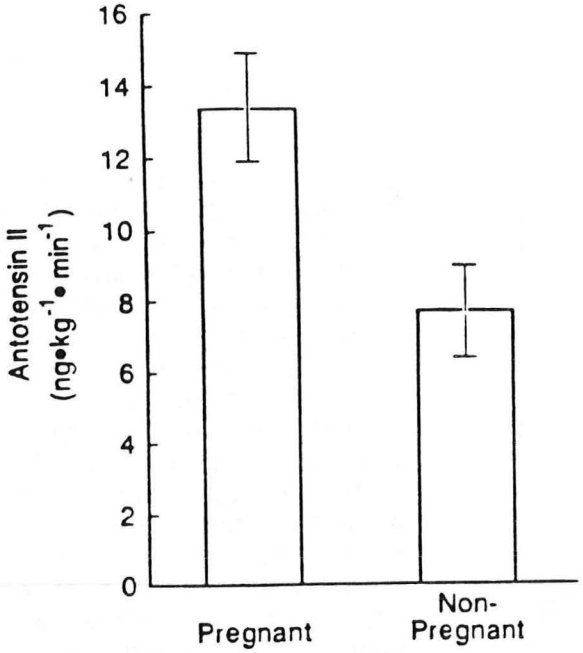
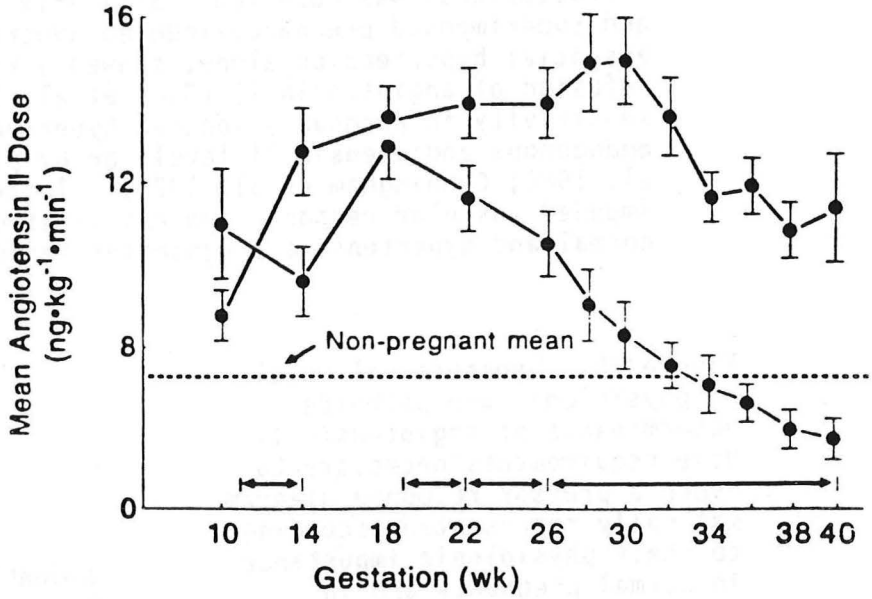


Figure 17: The dose of angiotensin II required in pregnant women to evoke a 20 mm Hg rise in diastolic blood pressure is nearly doubled by 15 weeks gestation in comparison with nonpregnant women. (From Broughton Pipkin et al 1982.)

Although it was shown more than 50 years ago that the pressor effect of a crude substance (vasopressin) is greater in toxemia than in normotensive pregnant women (Dieckmann and Michael, 1937), it was left for Abdul-Karim and Assali to firmly document that pregnant women were refractory to pressor doses of angiotensin II (Abdul-Karim and Assali, 1961). A few years later it was reported that preeclamptic women showed exaggerated reactivity to angiotensin II (Talledo et al, 1968). Perhaps the most definitive studies on vascular responsiveness in pregnancy were performed at this institution by Dr. Gant and co-workers.

Figure 18: Comparison of mean angiotensin dose required to raise diastolic blood pressure 20 mm Hg in 120 primigravidae who remained normotensive (black circles) and 72 primigravidae in whom pre-eclampsia occurred (open circle). (From Gant et al, 1973).



Gant and co-workers conducted a 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 pressor doses are depicted in Figure 18. The women

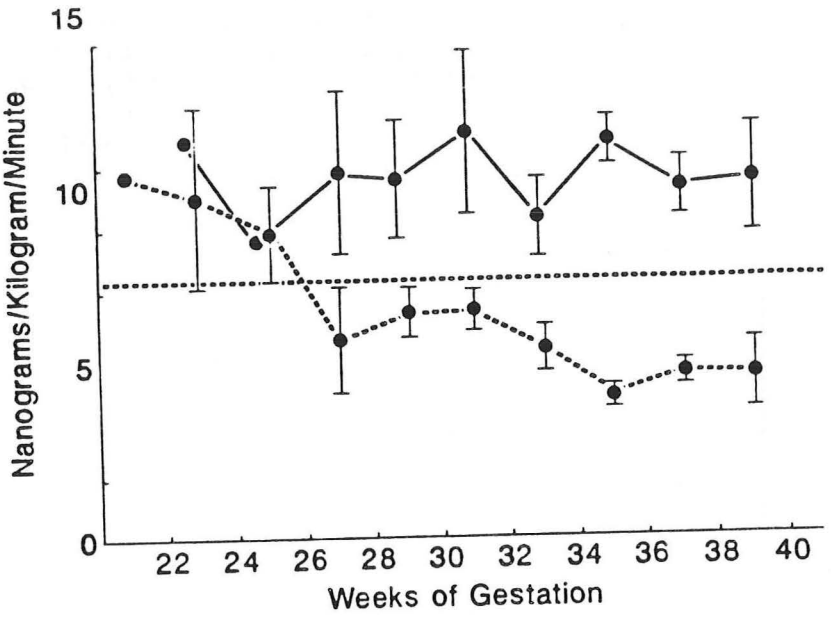


Figure 19: Comparison of angiotensin II responsiveness in 29 patients with uncomplicated essential hypertension and 34 patients with essential hypertension destined to develop super imposed PIH. The dose of angiotensin II (ng/kg/min) required to elevate resting diastolic blood pressure 20 mm Hg is shown on the vertical axis and is plotted as a function of weeks gestation. The results obtained in gravidas with chronic hypertension alone are indicated by squares connected by a solid line. The results obtained in gravidas with chronic hypertension destined to develop superimposed PIH are shown as dots connected by a broken line. The vertical bars represent the standard error of the mean. (Gant et al, 1977).

destined to develop pregnancy induced hypertension showed an augmented sensitivity to the pressor effects of angiotensin II after the 18th week of gestation. The data further suggested that between 28th and 32nd weeks 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)(Figure 19). 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 20).

Figure 20: Hypothetical model of physiologic and pathologic determinants of angiotensin II dose requirements necessary to evoke a pressor response diagrammatically represented according to their physiologic importance in normal pregnancy and in preeclampsia. (Gant et al, 1974).

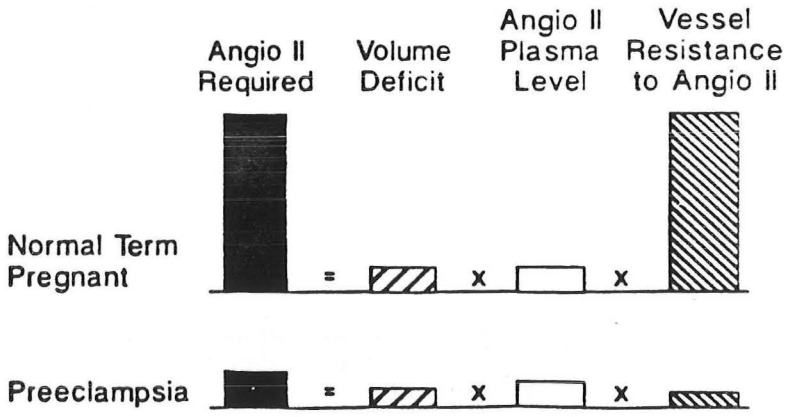


Table 6: Effective Pressor Dose of Angiotensin II* Before and After Indomethacin Treatment

Subject	Before Treatment	After Treatment†
1	25.0	12.7
2	25.5	13.0
3	7.7	2.8
4	25.0	6.5
5	52.7	13.7
6	12.7	4.6
7	19.2	9.8
8	17.5	4.5
9	9.8	6.9
10	12.9	9.2
11	13.9	3.5
	20.2	8.0
Avg ± SEM	± 3.8	± 1.2

*Angiotensin II dose (ng/kg/minute) required to evoke a 20 mmHg increase in diastolic blood pressure pressor.

†$p > 0.005$.

(From Semin Perinatol, 2:3-13, 1978, by permission of Stratton).

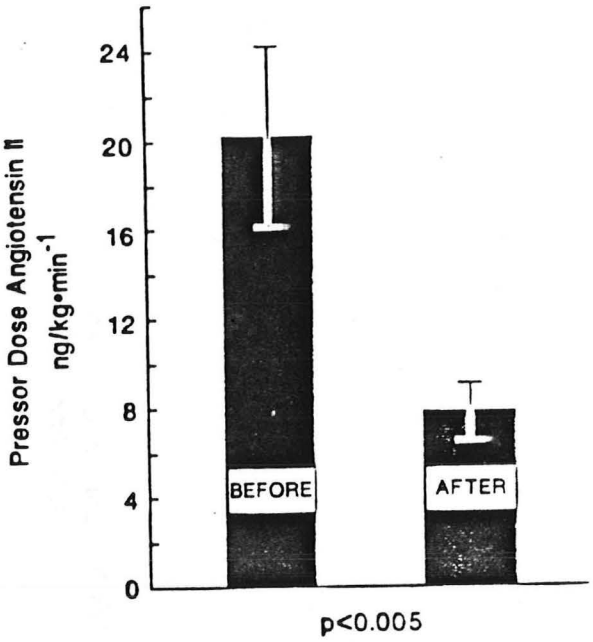


Figure 21: The mean effective pressor of angiotensin II before and during indomethacin treatment of normotensive women. (From Evertett et al, 1978a).

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, 1982; 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)(Table 6 and Figure 21). 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. Progesterone or its metabolites or cyclic AMP/phosphodiesterase activity may also influence the state of vascular tone in pregnancy (Everett et al, 1978a, Everett et al, 1978b). The vulnerability of the vascular smooth muscle in a gravida to the administration of prostaglandin inhibitors could be potentially harmful to the mother (↑ vascular responsiveness) and to the fetus (premature closure of ductus). 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)(Figure 22). Although there is no good explanation of the possible mechanisms, it remains to be seen whether prophylactic administration of calcium reduces the risk of pregnancy-induced hypertension.

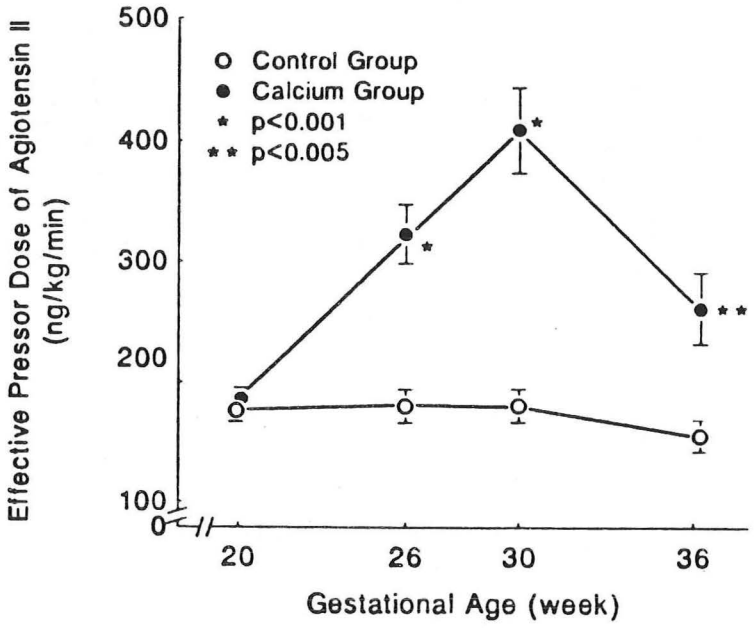


Figure 22: Values for the effective pressor dose of angiotensin II in the control gorup (o) (n=72) and the calcium-supplemented group (•) (n = 22) during pregnancy. The values are expressed as the means ± SEM. Signifi- cant differences compared to the control group: * = $p < 0.001$; ** = $p < 0.005$. (From Kawasaki et al, 1985).

In-vitro experiments with isolated omental blood vessels from pregnant and nonpregnant women have shown that vessels from women with preeclampsia clearly have an accentuated responsiveness to angiotensin II (Aalkjaer et al, 1985) and decreased rate of vascular relaxation (Figure 23). The sensitivity to norepinephrine did not reveal any differences between normotensive and hypertensive pregnancy. These elegant observations confirm the in-vivo findings and add credence to the notion of exaggerated vascular reactivity in pregnancy-induced hypertension. In addition to the functional changes, structural alterations in the resistance vessels have been noted in preeclampsia (Aalkjaer et al, 1984) (Figure 24).

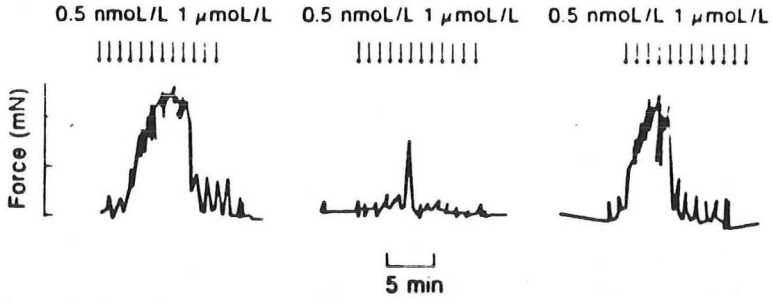
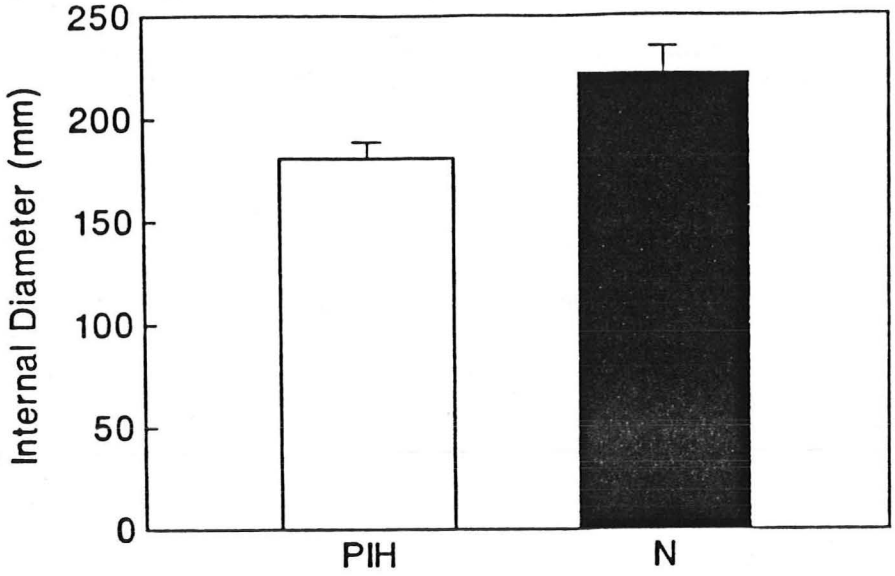


Figure 23: Typical responses in contractile force of a vessel from (a) a woman with preeclampsia, (b) a normotensive pregnant woman, and (c) a nonpregnant woman to stimulation with increasing concentrations of angiotensin II. At each arrow the concentration of angiotensin II was doubled. (From Aalkjaer et al, 1985).

Figure 24: The internal diameter of omental blood vessels in pregnancy-induced hypertension and in normal pregnancy. (From Aalkjaer et al, 1984).



V. 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). Preeclampsia and eclampsia represent serious manifestations of hypertension. I will devote a considerable proportion of my discussion to preeclampsia which is a true pregnancy induced hypertensive disorder.

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 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 time of the day when the blood pressure is measured has to be taken into account. In uncomplicated pregnancy, the blood pressures

decrease slightly at night (Redman et al, 1976; Lubbe, 1984)(Table 7). However, this normal circadian rhythm is disrupted in pregnancy induced hypertension resulting in persistent blood pressure elevation during the night (Seligman, 1971). It appears that the circadian variation in blood pressure is altered only in pregnancy induced hypertension but not in chronic hypertension associated with pregnancy (Murughan et al, 1978). These differences were documented with continuous 24 hour blood pressure recordings.

Table 7: Diurnal variability of blood pressure levels in pregnancy before and after the onset of hypertension. (From Redman et al, 1976)

	Noncturnal Change in Systolic (mm Hg)	Nocturnal Change in Diastolic (mm Hg)
20 Weeks		
Patient 1	-7.2	-1.7
2	-13.7	0.0
3	-22.7	-6.2
Before delivery		
Patient 1	+11.9	-0.7
2	+12.6	+8.5
3	+19.2	+21.1

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 (Chesley, 1978). 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.

Chronic Hypertension

Pregnant women may have chronic underlying essential or secondary hypertension. The clinician should distinguish chronic hypertension from pregnancy induced hypertension because of 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

Recently 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 25). Further clinical experience is warranted to determine the reliability of echocardiography in distinguishing chronic from pregnancy-induced hypertension. 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 (Abdella et al, 19084; Chesley, 1978; Gant and Pritchard, 1984; Redman, 1980). There are also considerable risks to the fetuses of hypertensive gravidas (Silverstone et al, 1980).

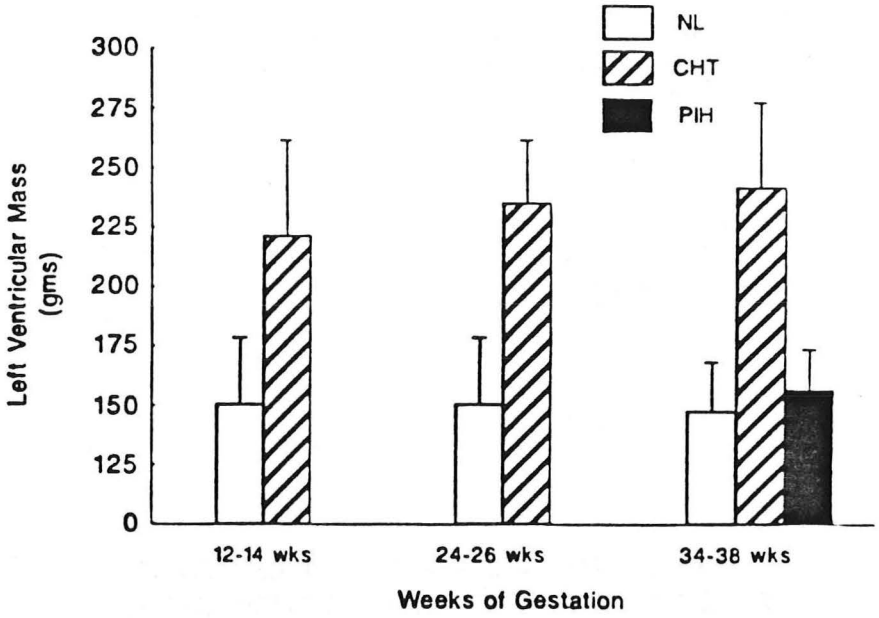


Figure 25: Left ventricular mass in grams according to weeks of gestation is depicted. NL = Normal pregnancy; CHT = pregnancy with chronic hypertension, and PIH = pregnancy-induced hypertension. *Denotes $p < 0.01$ in the CHT group in comparison with either the NL or the PIH group. (From Thompson et al, 1986).

Chronic Hypertension With Superimposed Preeclampsia

In patients with preexisting hypertension, there is 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.

Risks to the Mother and the Fetus From Hypertension in Pregnancy

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. Before going into an in depth discussion of hypertension in pregnancy, I want to outline the consequences of this disorder. Hypertension in pregnancy can be hazardous to the mother (Gallery, 1985; Department of Health and Social Security Report, 1979; Rubin, 1987; Maikranz and Lindheimer, 1987)(Table 8) and the fetus (Tables 9 and 10) (Browne and Dodds, 1942; Chesley and Annitto, 1947; Chesley, 1978). The situation is a true "double jeopardy." The maternal and fetal consequences are also listed in Tables 11 and 12.

Table 8: Deaths from pre-eclampsia per million maternities in England and Wales, 1952-1975 (From MacGillivray I, 1983.

Triennium	No.	Rate
1952-1954	90	43.8
1955-1957	99	46.8
1958-1960	62	27.0
1961-1963	64	25.4
1964-1966	27	10.4
1967-1969	12	4.9
1970-1972	18	7.8
1973-1975	18	9.4

Table 9: **FETAL DEATH RATE PER 1000 BY DIASTOLIC PRESSURE AND PROTEINURIA COMBINATIONS**

Diastolic Blood Pressure (mm Hg)	Proteinuria						
	None	Trace	1+	2+	3+	4+	Total
< 65	15.50*	13.64	6.20	–	–	–	13.60
65-74	9.30	8.06	5.58	32.86*	41.54	–	8.84
75-84	6.20	7.44	6.20	19.22*	–	–	6.80
85-94	8.68	9.30	23.56*	–	22.32	–	10.20
95-104	19.22*	17.36*	26.66*	55.80*	115.32*	143.22*	25.16
105 +	20.46*	27.90*	62.62*	68.82*	125.24*	110.98*	41.48*
Total	8.60	9.46	12.94	23.22*	41.96*	56.76*	

(From Freidman, Neff: In Lindheimer et al. (eds): Hypertension in Pregnancy, New York, Wiley, 1976.)

Table 10: From Friedman EA and Raymond NEFF. Pregnancy outcome as related to hypertension, edema and proteinuria. In: Lindheimer MD, Katz AI, Zuspan F, eds. Hypertension in Pregnancy. New York: John Wiley & Sons, 1975:17.

RATES OF FETAL MORTALITY (PER 1000) FOR DIASTOLIC BLOOD PRESSURE BY GESTATIONAL AGE

Gestational Age (Weeks)	Diastolic Blood Pressure, mm Hg				
	< 65	65-74	75-84	85-94	95+
13-16	9	8	12	13	18
17-23	8	8	11	12	16
24-27	6	8	10	9	26
28-32	6	7	8	8	21
33-34	6	6	6	6	19
35-36	7	4	6	5	16
37-38	2	5	4	5	9
39-41	4	5	3	5	9

Table 11: 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 uncontrollable bleeding develops
   c) A Capillary leak syndrome with heavy proteinuria, serous 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 12: Fetal complications

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

Patients at an Increased Risk for Hypertensive Disorders in Pregnancy

The following factors have been identified as predisposing to the development of hypertension in pregnancy.

1) Nulliparity

2) Genetic Factors

3) Plural Pregnancy

4) Chronic Hypertension

5) Hydatidiform Mole

6) Fetal Hydrops

7) Diabetes Mellitus

VI. 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 in the introduction, 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. Despite some considerations, it is probably irrelevant whether one uses 4th or 5th Korotkoff sound for diastolic blood pressure level. The blood pressure should be measured with the woman in the sitting, lateral, and semi-recumbent position. The relationships between the blood pressure level, proteinuria, and perinatal mortality are shown in Figures 26 and 27.

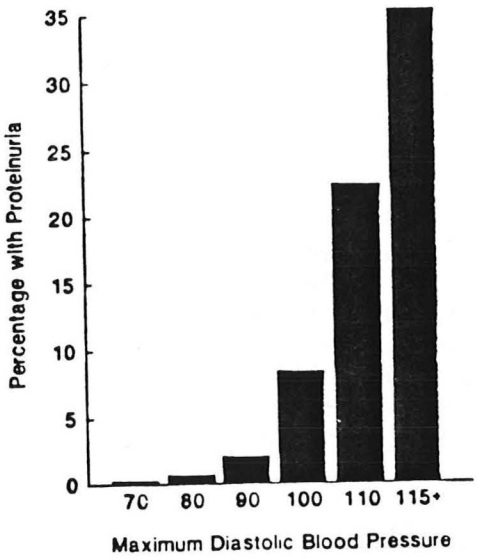


Figure 26: (From MacGillivray, 1983)

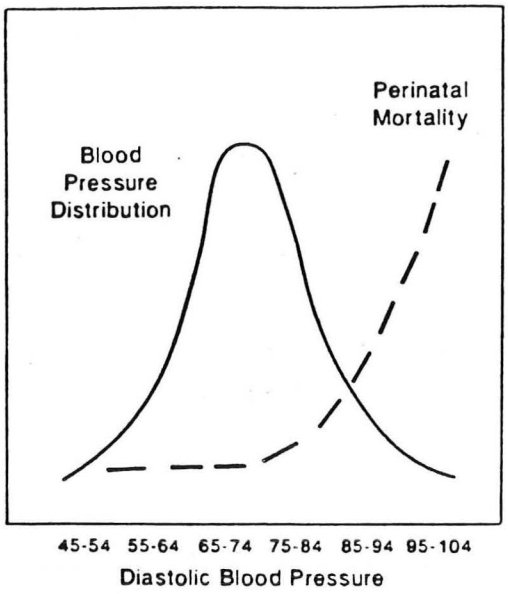


Figure 27: Relationship between diastolic blood pressure and perinatal mortality. (From Davey DA and MacGillivray I. Clin Exper Hypertens 1986;B5(1):97-133.)

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, 1974). 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 (MacGillvray, 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 at the present time as a screening test for pregnancy-induced hypertension.

Recently, continuous ambulatory blood pressure recordings have been increasingly used in the diagnosis and management of hypertension. Utilizing continuous intra-arterial blood pressure recordings, Murughan and co-workers noted that the normal diurnal variation of blood pressure was disrupted in pregnancy induced hypertension (Murughan et al, 1978). 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. Large scale data on the blood pressure variability in pregnancy are not available. Prospective studies utilizing the automated continuous blood pressure recorders are needed to profile the normal and abnormal ambulatory blood pressure levels in pregnancy.

3. PROTEINURIA

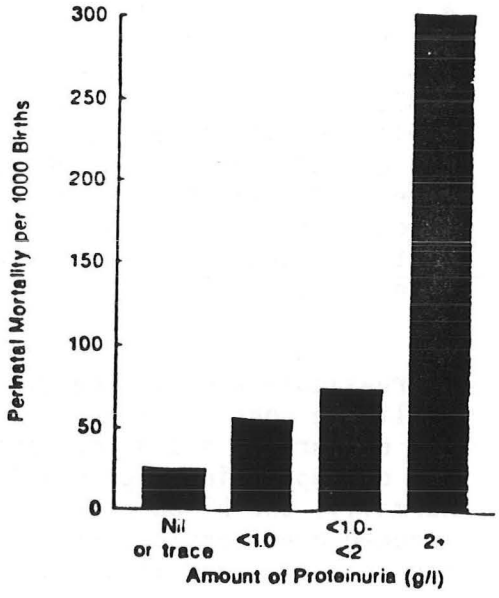
Proteinuria is a salient feature of preeclampsia. If proteinuria is detected on routine urinalysis, it should be followed by a 24-hour collection. Obviously, other causes of proteinuria such as urinary tract infection and kidney disease should be excluded. Total protein excretion of 300 mg/24 hours or more is abnormal (Table 13). The presence of proteinuria connotes bad prognosis for the mother as well as the baby (Taylor et al, 1954; Naeye and Friedman, 1979) (Figure 28).

Table 13: (From Cunningham and Pritchard, 1984).

SOME FACTORS THAT INDICATE SEVERITY OF PREGNANCY-INDUCED HYPERTENSION

Abnormality	Mild	Severe
Diastolic blood pressure	< 100 mmHg	110 mmHg or higher
Proteinuria	Trace to 1+	Persistent 2+ or more
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsions	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia	Absent	Present
Hyperbilirubinemia	Absent	Present
Serum liver enzyme elevation	Minimal	Marked
Fetal growth retardation	Absent	Obvious

Figure 28: (From MacGillivary, 1983).



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. OTHER FEATURES

Elevated uric acid level, decreased platelet count, visual changes, oliguria, and abdominal pain are associated features of preeclampsia. I will not discuss these features.

VII. 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. There is considerable evidence to suggest that hypertension can have serious consequences on the mother as well as the fetus (Redman, 1980). The occurrence of hypertension in a previously normotensive woman may cause substantial vascular damage. Moreover, untreated preeclampsia may deteriorate into eclampsia which is one of the most dreaded, preventable medical complications of pregnancy. Hypertension may also exert an unfavorable outcome on the fetus. Thus, it is prudent to treat hypertension in pregnancy. 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

A schema for the management of pregnancy-induced hypertension is shown in Table 14.

Table 14:

(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. Therefore, proper clinical trials have not been conducted despite the widespread recommendation of rest for patients with pregnancy induced hypertension. Bedrest is advocated to decrease the blood pressure, edema, and to prolong pregnancy until the fetus has reached viability. At Parkland Memorial Hospital, patients with pregnancy-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). To date, more than 3000 nulliparae with pregnancy induced hypertension have been admitted to the High-Risk Pregnancy Unit at Parkland and with bedrest and supervision, beneficial results have been obtained (Cunningham and Leveno, 1988) (Tables 15 and 16). The perinatal mortality rate for the infants of 545 nulliparous women who were hospitalized 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. Per Doany and Brinkman (1987), 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

Table 15: (From Cunningham and Leveno, 1988)

BLOOD PRESSURE RESPONSE IN 545 NULLIPAROUS WOMEN WITH PREGNANCY-INDUCED HYPERTENSION HOSPITALIZED IN THE PARKLAND HOSPITAL HIGH-RISK PREGNANCY UNIT

Response			Number	(%)
Good initially (diastolic decreased to < 90 mmHg)			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 16: From Cunningham and Leveno, 1988)

GESTATIONAL AGES AT ADMISSION AND AT DELIVERY IN 545 NULLIPAROUS WOMEN HOSPITALIZED FOR PREGNANCY-INDUCED HYPERTENSION IN THE PARKLAND HOSPITAL HIGH-RISK PREGNANCY UNIT

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

Salt Restriction

It has been widely believed in the past that 'excessive' weight gain during pregnancy predisposes the patient to preeclampsia. And attempts were made to vigorously restrict the salt intake by pregnant women. The salt restriction concept remained popular because it is not a difficult task to 'advise' the patient and moreover this modality was widely used to treat hypertension in the nonpregnant state. 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 (DeSnoo, 1937) met with an extraordinary rebuttal in 1958 when it was 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 (Peyser and Toaff, 1974). 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, 1979; Rubin, 1986), it does not make much sense to use diuretics in pregnancy (Tables 17 and 18). In a rather important study, diuretics reduced the incidence of edema but not pregnancy induced hypertension (Campbell and MacGillivray, 1975) (Table 19). The birthweights 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 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, fluid therapy may be required to improve the central hemodynamics (Figure 29).

Table 17: (From Pritchard et al, 1984)

BLOOD VOLUMES IN FIVE WOMEN MEASURED (^{51}CR) DURING ANTEPARTUM ECLAMPSIA, AGAIN WHEN NONPREGNANT, AND FINALLY AT A COMPARABLE TIME IN THEIR SECOND PREGNANCY UNCOMPLICATED BY HYPERTENSION

	Eclampsia	Nonpregnant	Normal Pregnant
Blood volume (ml)	3530	3055	4425
Change (%)	+ 16		+ 47
Hematocrit	40.5	38.2	34.7

Table 18:

PLASMA VOLUMES IN NORMAL AND PRE-ECLAMPTIC PREGNANCIES FROM VARIOUS STUDIES

Reference	Normal pregnancies		Pre-eclamptic pregnancies		Decrease (ml)
	No. of cases	Mean (ml)	No. of cases	Mean (ml)	
Cope (1961)	29	3470	14	2830	650
Honger (1967)	20	3800	19	3300	500
Brody and Spetz (1967)	46	4245	34	4010	235
MacGillivray (1967)	18	4040	35	3535	505
Blekta et al. (1970)	55	3133	14	2590	543
All cases	168	3738	116	3250	488

Table 19: (From MacGillivray, 1983).

INCIDENCE OF PRE-ECLAMPSIA FOLLOWING PROPHYLACTIC DIURETICS

	Thiazide (%) (n = 51)	Controls (%) (n = 51)
Normotensive	43.1	58.8
Mild pre-eclampsia	47.1	23.5
Proteinuric pre-eclampsia	9.8	17.7
Total pre-eclampsia	56.9	41.2

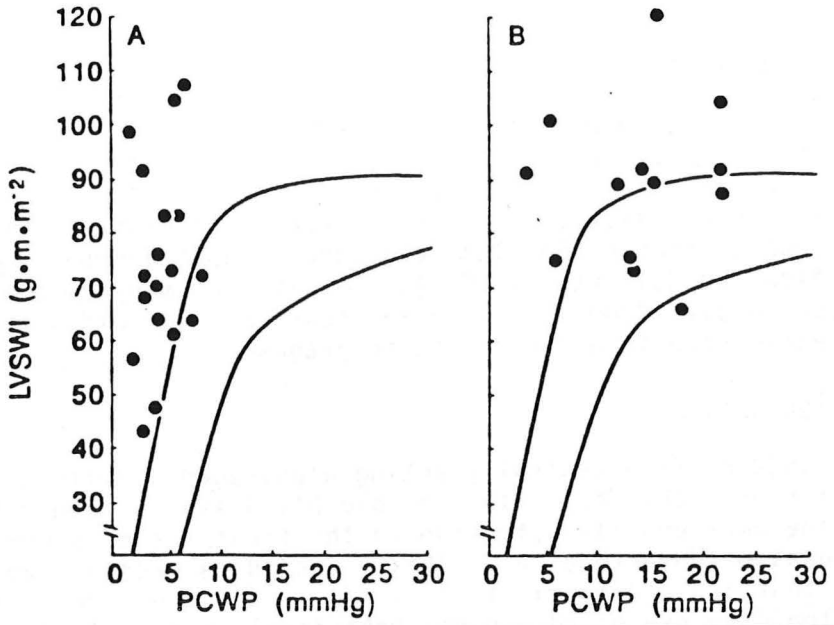


Figure 29: Ventricular function measured in women with severe preeclampsia or eclampsia. Left ventricular stroke work index (LVSWI) and pulmonary capillary wedge pressure (PCWP) are plotted. Restricted fluid therapy (A) and aggressive fluid therapy (B). (From Wallenburg HCS. Hemodynamics in hypertensive pregnancy. In Rubin PC, ed. Handbook of Hypertension, Vol 10: Hypertension in Pregnancy. New York: Elsevier Science Publishers B.V., 1988:66.)

Table 20: ANTIHYPERTENSIVE DRUGS USED IN PREGNANCY

- CENTRALLY ACTING AGENTS (Methyldopa, Clonidine)
- DIURETICS
- BETA BLOCKERS
- PRAZOSIN
- LABETALOL
- CALCIUM ANTAGONISTS
- SEROTONIN ANTAGONIST → KETANSERIN

Methyldopa

Methyldopa is the most popular drug at the present 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, 1976; Rubin et al, 1983). 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. The commonly used antihypertensives are shown in Table 21.

Table 21:

- HYDRALAZINE
- METHYLDOPA

- DIURETICS → CAUTION

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). Despite the many recent acquisitions in antihypertensive drugs, hydralazine continues to hold a prominent therapeutic role in hypertension in pregnancy.

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. The usefulness of beta-blockers is unrelated to their pharmacological differences. 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, 1981). 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 neonate-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) (Table 22). 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, 1983). Although beta-blockers with intrinsic sympathomimetic activity (ISA) - pindolol or oxprenolol - have also been shown to be effective in the treatment of hypertension in pregnancy (Ellenbogen et al, 1986; Gallery, 1985; Gallery et al, 1979), it is unclear whether the ancillary property (ISA) of these drugs provides an advantage. 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.

Table 22: (From Lubbe, 1984)

INCIDENCE OF DEVELOPMENT OF PROTEINURIA AND FOETAL MORTALITY IN WOMEN WITH DIASTOLIC BLOOD PRESSURE > 105 MM HG FOR 4 WEEKS OR LONGER IN PREGNANCY

	n	Incidence of proteinuria	Foetal mortality rate
Bed rest alone	72	17%	7%
Methyldopa	25	29%	4%
Oxprenolol ± prazosin	24	0	4%
Atenolol ± prazosin	36	2%	5%
Pindolol ± prazosin	39	3%	3%

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 more effective than methyldopa in some patients with pregnancy induced hypertension. 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.

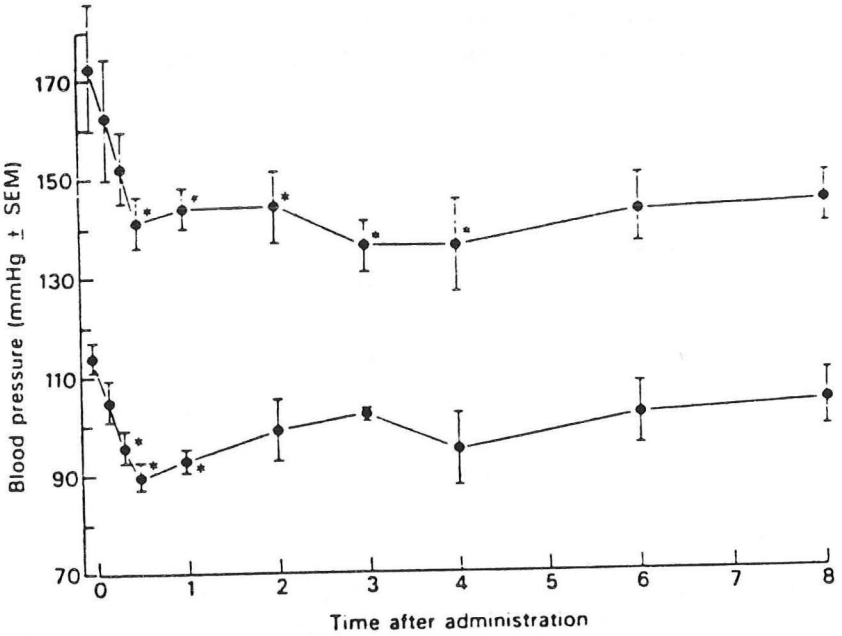
Prazosin

This alpha-receptor blocker has been used to treat severe pregnancy induced hypertension (Lubbe and Hodge, 1981; Rubin et al, 1983). 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; Constantine et al, 1987) (Figure 30). Although nifedipine is rapidly effective in controlling severe pregnancy induced hypertension, there is insufficient experience to warrant systematic use of these agents in pregnancy induced hypertension. One consideration is the potential (unproven) effects on calcium, bone metabolism, and hormonal influences on the fetus.

Figure 30: The effect of 5 mg of nifedipine given orally at time) on the blood pressure in the preliminary investigation (n=5). Significance of difference *p < 0.05.



Angiotensin Converting Enzyme (ACE) Inhibitors

At the present time, 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, 1982) (see Table 5). More recently, ACE inhibitors have been shown to provoke renal failure in the newborn (Schubiger et al, 1988). 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 23.

Table 23:

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). Therefore, I will not discuss this drug today. Diazoxide relaxes the uterus and therefore delays the labor. Some centers still use small doses of diazoxide to treat severe hypertension in pregnancy (Maclean et al, 1981; Morris et al, 1977; Dudley, 1985).

Sodium Nitroprusside

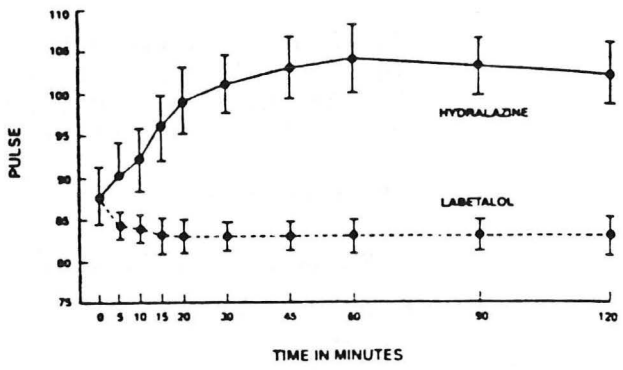
Experience with this rapidly acting, effective vasodilator in the management of hypertension in pregnancy is limited (Stempel et al, 1982). Whether it is safe for the fetus is not known. However, when maternal health is compromised as a result of severe hypertension, nitroprusside infusion should be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

Labetalol

As discussed earlier, labetalol a combined alpha plus beta-blocker can lower the blood pressure effectively in pregnancy. 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 (Figure 31). In contrast to diazoxide, the infusion of labetalol was better tolerated in one comparative study (Michael, 1986).

Figure 31: Change in maternal heart rate (mean ± 1 SD) with repeated boluses of intravenous labetalol (20-80 mg) or intravenous hydralazine (5 mg) given at ten-minute intervals starting at time 0. (From Mabie et al, 1987)



Ketanserin

Ketanserin, a peripheral serotonin receptor blocker has been successfully used in the control of hypertension in pregnancy (Weiner et al, 1984; Hume, 1986) (Figure 32). Serotonin may have an amplifying effect on vasoconstriction and platelet aggregation-features of preeclampsia. On this premise, ketanserin, which blocks the S_2 receptors has been shown to possess important effects on the circulation. Limited experience demonstrates its anti-hypertensive efficacy in pregnancy. Further experience is required to elucidate whether ketanserin offers any specific advantage over other hypotensive agents.

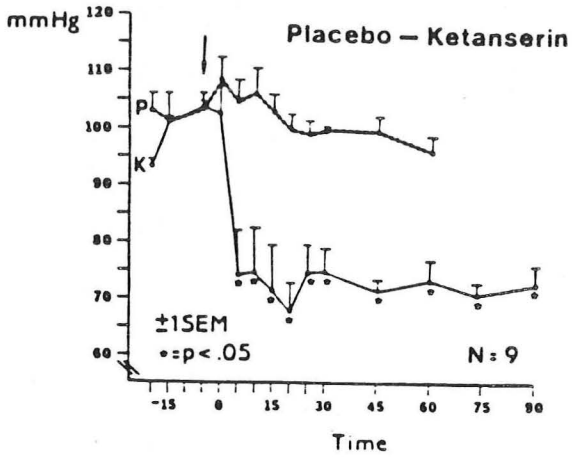


Figure 32: Change in diastolic pressure over time by sequence (K, ketanserin; P, placebo.) Ketanserin produces a significant decline in diastolic pressure regardless of drug sequence. (From Weiner et al, 1984).

VIII. FEW WORDS ABOUT THE 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 by Dr. Jack Pritchard 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; Hauth et al, 1976; Pritchard, 1979). I will not dwell on this aspect except to point out that the following therapeutic principles are responsible for Dr. Pritchard's remarkable results:

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

For a more detailed discussion, please refer to above cited publications.

IX. GOALS OF ANTIHYPERTENSIVE THERAPY IN PREGNANCY

Having discussed the clinical effects and actions of a variety of antihypertensive drugs in pregnancy, it is necessary to ask the question, 'What are the goals in initiating antihypertensive drugs in pregnancy?' The objectives are:

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

X. THERAPEUTIC TRIALS IN PREGNANCY

After having discussed the clinical effects of antihypertensive drugs in pregnancy. I would like to consider selected clinical trials of

treatment of hypertension in pregnancy. Leather et al, conducted the first randomized clinical trial ever undertaken of antihypertensive therapy in pregnancy (Leather et al, 1962). 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, 1983). 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). Michael (1986) compared labetalol with diazoxide, given intravenously and not surprisingly concluded that labetalol provided 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.

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 (Redman et al, 1977; Redman, 1980). The blood pressure level may not recede promptly in patients with chronic hypertension and superimposed preeclampsia. Of course, patients with preexistent chronic hypertension would require long-term therapy.

XI. ADVERSE REACTIONS TO ANTIHYPERTENSIVE DRUGS IN PREGNANCY

In this context, we have to consider the effects on the mother and the fetus. Prescribing any drug to pregnant patients is fraught with unknown risk and has become a subject of considerable public and professional interest. Efficacy is no longer a valid issue but questions remain concerning the safety of antihypertensive drugs, particularly the new agents. The fear is about the unknown consequences. The side-effects on the mother depend on the pharmacological effects of the drug but no such explanation can be offered for the fetal consequences. I have covered certain key points in my earlier discussion. Detailed analysis of the subject has been previously reviewed (Schonfeld et al, 1986).

There are bound to be some general concerns about prescribing antihypertensive drugs in pregnancy. For example, a new drug tested only in the nonpregnant population is sometimes given to a pregnant patient without consideration of the potential effects. One may get a false sense of security because of a notation in the package insert that no fetal or teratogenic effects have been reported. Of course, it is impossible to take too much comfort from statements like this because the drugs have not been previously used in pregnancy. By turning to the Physicians' Desk Reference, we will not get much relief because of statements like "...may be administered if potential benefits justify the risks." This advice is so vague and applied to so many medications that it is unlikely to provide prudent guidance to the practitioner. With certain limitations, there is a general agreement, however, that positive effects outweigh the negative aspects.

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 readily into milk than do water soluble drugs (Lien and Gadauskas, 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.

XII. THE CHILDREN OF MOTHERS 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 a strong indication that child development is unfavorably altered. 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).

XIII. CHRONIC ESSENTIAL AND SECONDARY FORMS OF HYPERTENSION IN PREGNANCY

Pregnancy can punctuate the course of chronic essential or secondary forms of hypertension. Certainly, a pregnant woman with a hypertensive disorder is at a greater risk compared to a normotensive pregnant person. 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 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.

Secondary Forms of Hypertension in Pregnancy

1. Renovascular Hypertension is not a common cause of hypertension in the general population. Renovascular disease has a bimodal distribution - the older men exhibiting atherosclerotic disease and the young women having fibromuscular disease (Ram, 1983). The latter problem, therefore, is more likely to be seen in pregnancy. Clinical examination may not give a clue to the presence of underlying renal artery stenosis. Abdominal bruits can be heard in any pregnant woman. However, if an impressive bruit is heard during the first trimester, it carries a significant diagnostic value. The maternal risk is not only from hypertension caused by renal artery stenosis but there is an enhanced risk of aneurysm formation and rupture in pregnancy (Cohen et al, 1972; Stanley et al, 1976). Although renal artery stenosis like other secondary causes is uncommon, its initial manifestation may be in pregnancy. Persistent postpartum hypertension in a young woman warrants work-up for secondary causes of hypertension.

2. Pheochromocytoma is an important secondary form of hypertension in pregnancy because it can cause serious, irreversible sequelae if not treated properly (Ram, 1988). Maternal mortality approaches 48% if pheochromocytoma is undiagnosed (Fudge et al, 1980; Schenker and Chowers, 1971). Although many patients may exhibit typical signs and symptoms of pheochromocytoma, the tumor can present as straightforward hypertension in pregnancy thus causing diagnostic difficulties. Because of potential errors in clinical recognition, some recommend routine screening for pheochromocytoma in all hypertensive pregnant women (Schenker and Chowers, 1971). Fetal wastage is very high in pregnant women with pheochromocytoma. If the diagnosis is suspected, specific pharmacological treatment is recommended, irrespective of the gestational stage. Pregnancy may unmask the manifestations of pheochromocytoma.

3. Primary Aldosteronism has been reported to occur in association with pregnancy (Crane et al, 1964; Hammond et al, 1982; Merrill et al, 1984). The manifestations of this condition are hypertension, spontaneous hypokalemia, volume expansion, and metabolic alkalosis. Since aldosterone levels are physiologically elevated in pregnancy, the diagnostic value of plasma/urine aldosterone levels is poor. If the potassium and blood pressure levels are well maintained, the gestation proceeds normally permitting detailed work-up and specific treatment to be undertaken at a later period.

4. Chronic Renal Disease can be present in patients with pregnancy-associated hypertension. This is a distinct, broad entity requiring interdisciplinary approach. This subject has been covered in this forum previously (Blachley, 1986).

XIV. 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 experiencing 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 controls. In some individuals, pregnancy may prematurely 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)(Figure 33). This finding underscores the notion that pregnancy induces a physiological stress on the cardiovascular system. In persons destined to develop hypertension ultimately, the gestaional physiology is converted to a pathophysiological state characterized by hypertension. On the other hand, continued normotension throughout pregnancy can be considered as an excellent indicator against the propensity to develop hypertension.

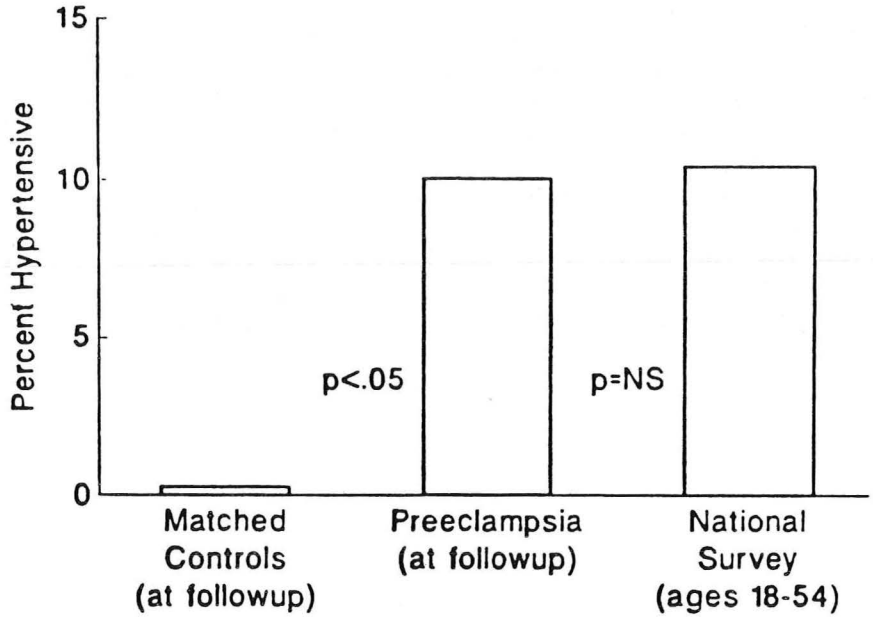


Figure 33: Prevalence of hypertension during follow-up of 53 preeclamptic women and in age matched subjects known to be normotensive during their pregnancy. Also shown is the National Survey. Note the prevalence is extremely low in subjects with recorded normotensive deliveries while the preeclamptics are no different from the population at large. (From Fisher et al, 1981).

XV. 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. Gestational hypertension generally manifests itself late in the third trimester and thus, any therapeutic approach is likely to yield acceptable outcome. If hypertension appears early in the third trimester, 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.

In the recent years we have witnessed considerable advances in our concepts of physiology of blood pressure control in pregnancy and how the regulatory systems are altered in hypertension. Fortunately, thorough clinical evaluation of a pregnant woman with continued antenatal care permits a logical approach to hypertension in pregnancy. 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 by the entire health care team. After all, this is reflected by the excellent outcome of patients with hypertension in pregnancy. Until a superior alternative is offered, the principles discussed in this grand rounds should be applied for the benefit of the mother and the fetus. In the meantime, the plaque on the wall of the Chicago Lying-in Hospital is still awaiting the name of the discoverer of the cause of preeclampsia.

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