Medical Grand Rounds - July 15, 1976

HYPERTENSION WITH PREGNANCY AND THE PILL

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"The hypertensive disorders in pregnancy are common complications of gestation, occurring in 6 or 7 per cent of all late pregnancies. They form one of the great triad of complications (hemorrhage, hypertension, and sepsis) responsible for most maternal deaths and they account for about one fifth of the maternal fatalities in the United States each year. As a cause of perinatal death they are even more important, for by a conservative estimate at least 25,000 stillbirths and neonatal deaths each year in this country are the result of the hypertensive disorders. Most neonatal deaths are caused by prematurity of the infant.

" The huge toll taken by hypertension in pregnancy of maternal and infant lives is largely preventable. Good prenatal supervision, with the early detection of signs and symptoms of oncoming preeclampsia, and appropriate treatment will arrest many cases and sufficiently ameliorate others that the outcome for baby and mother is usually satisfactory." (Chesley LC: Hypertensive disorders in pregnancy. In William's Obstetrics, 14th ed, Hellman LM and JA Pritchard, eds, Appleton-Century-Croft, New York, 1971)

I. Classification of the hypertensive disorders of pregnancy

A. Pre-eclampsia and eclampsia (the UTSWMS group prefer Pregnancy-Induced Hypertension or PIH). Toxemia seems a poor term. In the words of the editorial writer for Lancet "It is a judicious form of cowardice which eschews the term pre-eclamptic toxemia." (Sept. 13, 1975)

Preeclampsia: hypertension with proteinuria or edema, or both, developing after the 20th week of gestation

Eclampsia: the above with the addition of convulsions and coma

Hypertension: the blood pressure should be quite low in normal pregnancy; the levels found by Christianson (Am J Obstet & Gyn 125:509, 1976) in 6,662 white U.S. women whose pregnancies terminated in a single live birth are higher than those found by MacGillivray et al (Clin Sci 37:395, 1969) in 226 primigravidas, probably because the women in the latter study were handled with more care (Figures 1, 2 on page 2).

For the diagnosis of pre-eclampsia, hypertension is defined as a rise in pressure of 30/15 mm Hg or more or an absolute level >140/90. However, even less hypertension may be harmful: a sharp rise in perinatal mortality occurs when the blood pressure rises above 125/75 before the 36th week.

B. Chronic hypertension of whatever cause

C. Pre-eclampsia superimposed upon chronic hypertension

D. Late or transient hypertension: arises during pregnancy in a previously normotensive woman, disappears within 10 days after delivery and not associated with proteinuria or edema; most probably have pre-eclampsia.

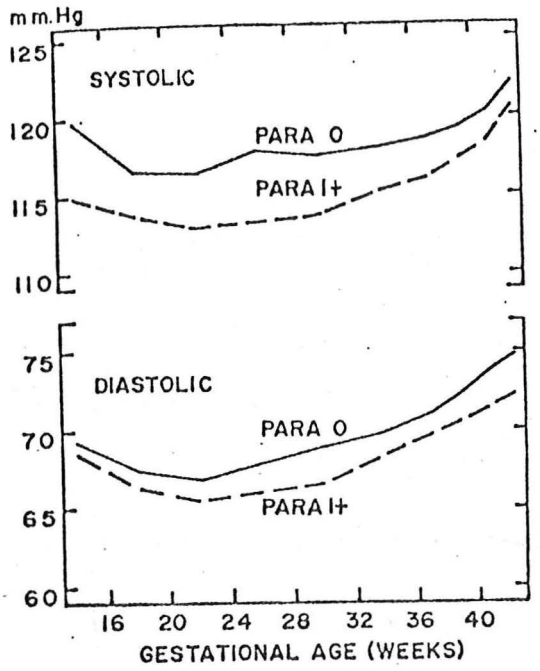


Figure 1

Mean blood pressure by gestational age and parity for white gravidas 25 to 34 years of age who delivered single live term births. (Christianson RE: Am J Obstet & Gyn 125:511, 1976)

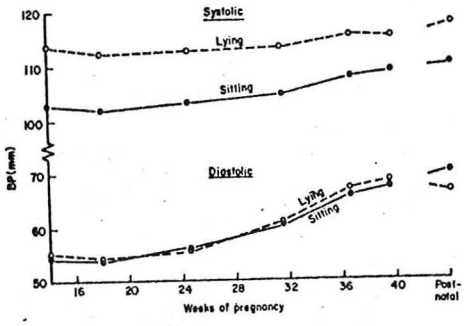


Figure 2

Mean blood pressures of 226 primigravidas seen at St. Mary's Hospital, London. These were all the patients seen at or before 20 weeks of pregnancy over an 18-month interval. (MacGillivray I, Rose GA and Rowe B: Clin Sci 37:395, 1969)

II. The differential diagnosis

	Pre-eclampsia	Chronic Hypertension
Age	Young (<20)	Older (>30)
Parity	Primigravida	Multipara
Onset	After 20 weeks	Before 20 weeks
BP during first pregnancy	Hypertensive	Not hypertensive
Proteinuria	Present	Absent
Systolic BP	<160	>160
Funduscopic	Spasm, edema	A/V nicking, exudates
Weight gain and edema	Sudden	Gradual
BP after delivery	Normal	Elevated
Plasma uric acid	Increased	Normal

III. The pathogenesis of pre-eclampsia

A. In addition to the clinical picture, the mechanism should explain these features

1. Occurrence almost exclusively during first pregnancy
2. Most common in young and in those with multiple fetuses, hydatidiform mole or diabetes
3. Rapid disappearance when pregnancy terminated
4. Increased incidence as term approaches
5. Characteristic renal pathology (Altchek A: Circulation 29-30 (Suppl II): 43, 1964)

   a. Swelling of the cytoplasm of the endothelial cell
   b. Deposits underneath the basement membrane and within the swollen endothelial cytoplasm
   c. Increase of intercapillary cells

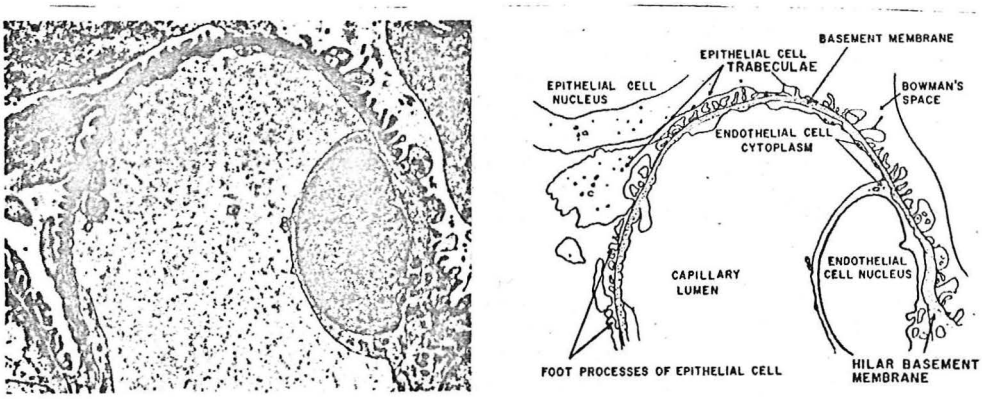


Figure 3

Electron microscopic picture of the cross section of the capillary loop of the glomerulus in a normal pregnancy, × 8,000 (left). Note the large open capillary lumen into which the nucleus of the endothelial cell protrudes, the thin endothelial cytoplasm, the epithelial cytoplasmic trabeculae which end in foot processes, and the folded, thickened basement membrane near the hilar area.

(Altchek A: Circulation 29-30 (Suppl II):43, 1964)

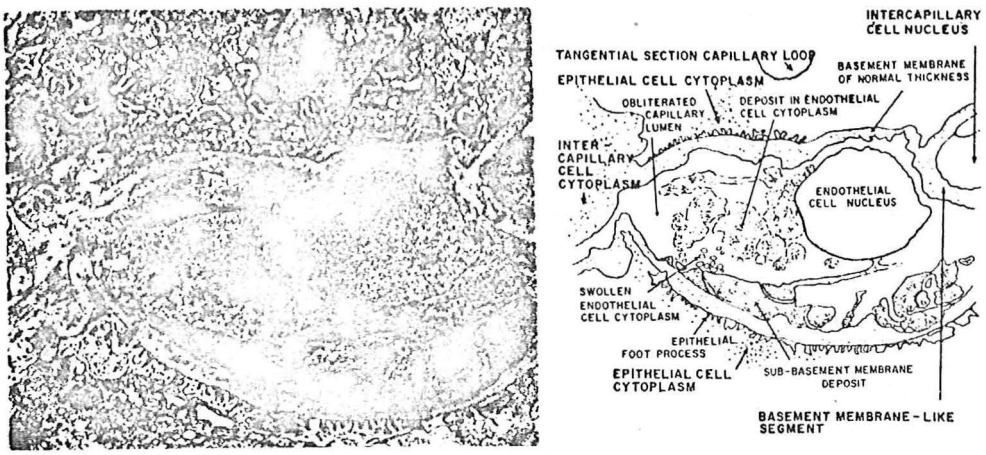


Figure 4

Electron microscopic picture of the cross section of the capillary loop of the glomerulus in toxemia of pregnancy, × 8,000 (left). The capillary lumen has been obliterated. Note the deposit in the cytoplasm of the swollen endothelial cell, the sub-basement membrane deposit, the increased intercapillary cell cytoplasm with its contained basement membrane–like segments, and the nucleus of the intercapillary cell. Note also that the basement membrane is of normal thickness and that the foot processes are essentially normal.

(Altchek A: Circulation 29-30 (Suppl II):43, 1964)

6. The familial tendency: Chesley followed 270 patients with eclampsia for 15 to 35 years; 26% of their daughters had pre-eclampsia in their first pregnancy compared to 8% of their daughters-in-law (Am J Obstet & Gyn 101:886, 1968).

B. The pathophysiological changes in pre-eclampsia

As shown in Table 1 on the next page, normal pregnancy is associated with a high cardiac output, increased blood volume and reduced peripheral resistance. The dilated peripheral vasculature is poorly responsive to the pressor effect of infused angiotensin (Abdul-Karim R and Assali NS: Am J Obstet & Gyn 82:246, 1961). High levels of renin-angiotensin-aldosterone are present presumably reflecting the response to high levels of estrogen, the natriuretic effect of progesterone and the need to keep the body fluid volume expanded and the blood pressure at an appropriate level.

In pregnant rabbits when the endogenous angiotensin effect is blocked with the competitive inhibitor, salarasin, the blood pressure falls 20 to 25 mm Hg; non-pregnant rabbits have no change in blood pressure (Bay WH and Ferris TF: Clin Res 23:468A, Oct, 1975; Douglas BH and Langford HG: Kidney Int 8:438, 1975).

The hypertension of pre-eclampsia develops from an increased peripheral resistance, tightening the vascular bed. Presumably as the pressure rises, baroreceptor reflexes mediate a fall in cardiac output and a suppression of renin release.

CHANGES IN PREGNANCY COMPLICATED BY PRE-ECLAMPSIA

	Normal Pregnancy	Changes Occurring with Pre-eclampsia*
Hemodynamics		
Plasma volume	Expanded	Decrease
Exchangeable sodium	Increased	Increase
Cardiac output	Increased	Decrease
Peripheral resistance	Reduced	Increase
Vascular reactivity		
to norepinephrine	Unchanged	Increase
to angiotensin	Reduced	Increase
Uterine blood flow		Decrease
Renal function		
Blood flow	Increased	Decrease
Glomerular filtration	Increased	Decrease
Plasma uric acid	Decreased	Increase
Excretion of sodium load	Normal	Unchanged
Hormonal changes		
Plasma renin substrate	Increased	Unchanged
Plasma renin activity	Increased	Decrease
Plasma renin concentration	Increased	Decrease
Plasma angiotensin-II	Increased	Decrease
Plasma aldosterone	Increased	Decrease
Plasma DOC	Increased	Decrease

*These changes are relative, as compared to those seen in normal pregnancy, and are not compared to those seen in non-pregnant women.

Table 1

Though the vascular bed is tighter and more responsive to exogenous angiotensin (Talledo OE: Am J Obstet & Gyn 96:141, 1966), the exaggerated excretion of a salt load that is characteristic of essential hypertension does not develop. In the study of Sarles et al (Am J Obstet & Gyn 102: 1, 1968), the patients with pre-eclampsia responded like those with glomerulonephritis and not like those with essential hypertension who maintained the exaggerated natriuresis of the non-pregnant hypertensive state. (see Figure 5 on page 6)

C. Evidence for an increased vascular reactivity

1. Increased pressor sensitivity to exogenous angiotensin

Gant et al have shown that women destined to develop pre-eclampsia have an increased pressor sensitivity to the infusion of exogenous angiotensin (J Clin Invest 52:2682, Nov, 1973). This occurs as early as the 26th to 28th week of gestation, often 10 to 12 weeks before hypertension appears (Figure 6, page 6).

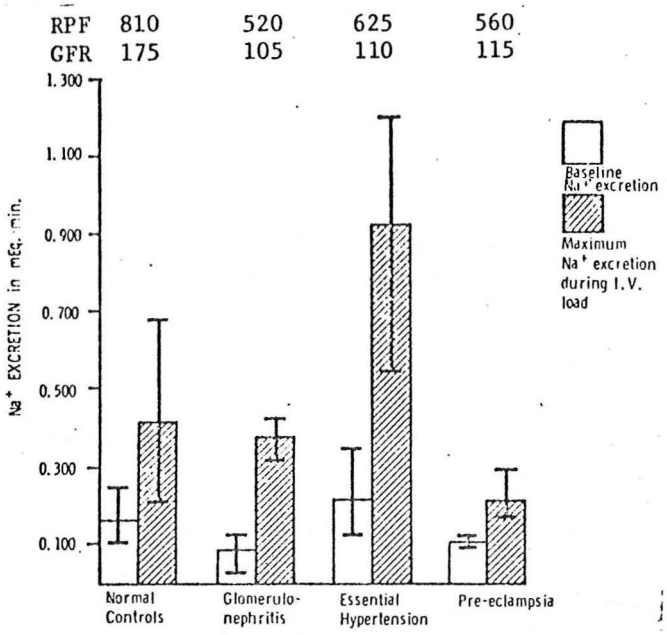


Figure 5

Base-line sodium excretion for each group represented by the open bars and the maximum sodium excretion achieved by the cross-hatched bars. The height of the bar pictures the mean value and the lines above and below the mean reflect the observed range.

(Sarles HE, Hill SS, LeBlanc AL, et al: Am J Obstet & Gyn 102: 1, 1968)

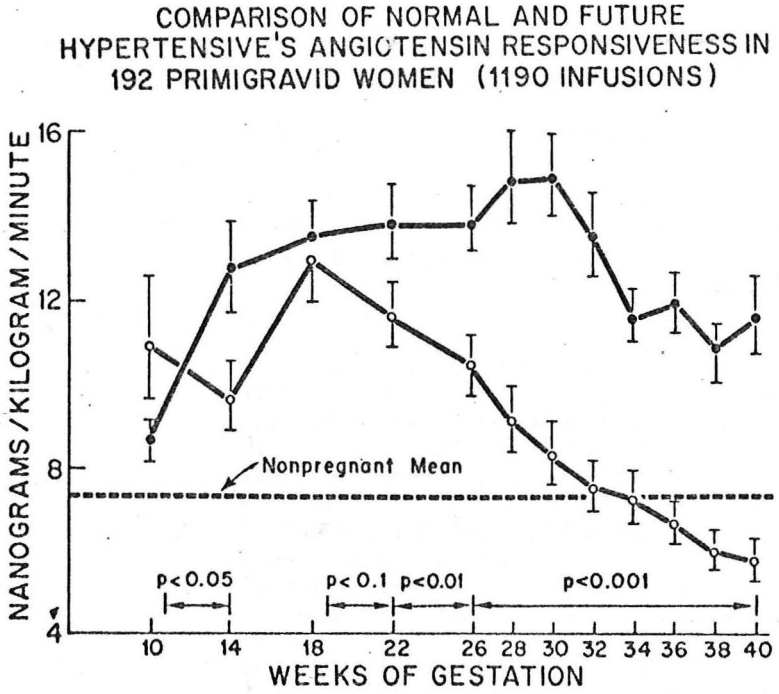


Figure 6

Comparison of the mean A-II doses (ng/kg/min) required to evoke a pressor response in 120 primigravidas who remained normotensive (●---●) and 72 primigravidas who ultimately developed pregnancy induced hypertension (o--o). The nonpregnant mean is shown as a broken line. The horizontal bars represent the standard error of the mean. The difference between the two groups became significant after wk 23 and the two groups continued to widely diverge after the 26th wk (Gant NF: 27th Postgraduate Assembly, Endocrine Soc, Dallas, Oct, 1975).

More recently, Gant et al have shown that this same phenomenon is seen in women with chronic essential hypertension (Am J Obstet & Gyn, in press). The figure below shows that, in 34 women with chronic hypertension who were destined to develop superimposed pre-eclampsia, (●---●), pressor sensitivity appeared at the expected time whereas in the 29 chronic hypertensives (■---■) who did not develop pre-eclampsia, resistance presisted.

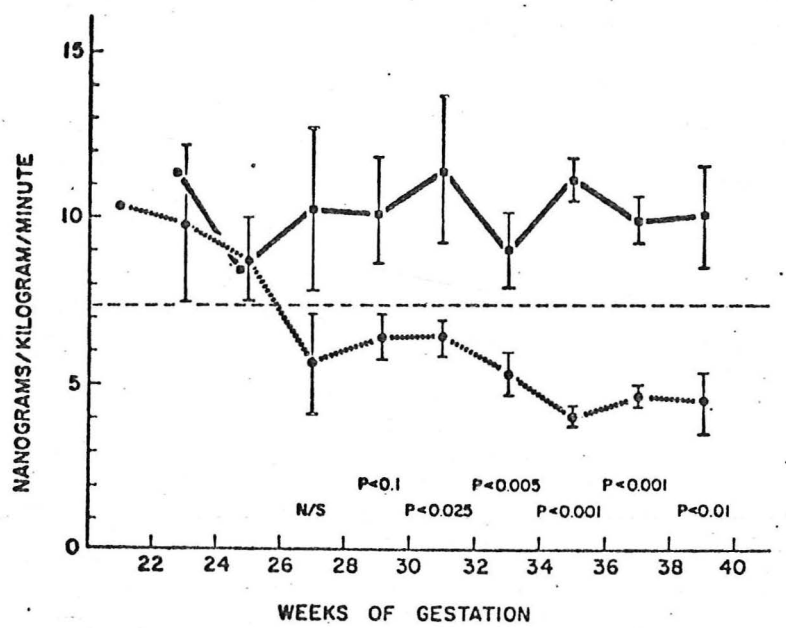
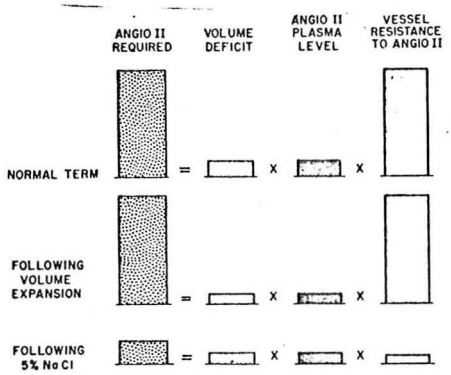


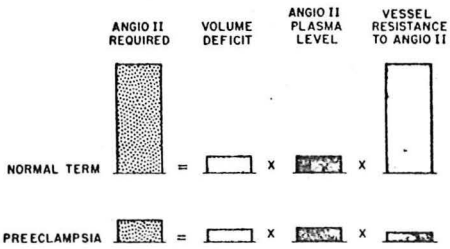
Figure 7
(Gant NF, Whalley PC, Chand S and MacDonald PC: Am J Obstet & Gyn, in press)

This increased sensitivity is thought to reflect an increased vascular responsiveness and not a better filled vascular bed. Volume expansion with a liter of isotonic saline or high-hematocrit blood did not decrease the resistance of normotensive women near term (Gant NF, Chand S, Whalley PJ, et al: Obstet & Gyn 43:854, June, 1974; Cunningham FG, Cox K, and Gant NF: Obstet & Gyn 46:581, Nov, 1975). On the other hand, rapid infusion of 200 ml of 5% saline did increase sensitivity. Sodium has been shown to increase pressor responsiveness in rats, presumably by increasing the avidity of angiotensin-II vascular receptors to the hormone (Brunner HR, Chang P, Wallach R, et al: J Clin Invest 51:58, 1972). The model for these experimental results is shown in Figure 8 (left side, page 8) and the natural findings in pre-eclampsia is shown in Figure 9 (right side, page 8).



Hypothetical model of physiologic and pathologic determinants of angiotensin II dose requirements necessary to evoke a pressor response, diagramatically represented according to their apparent physiologic importance in normal pregnancy, in normal pregnancy following volume expansion, and after hypertonic saline administration.

Figure 8

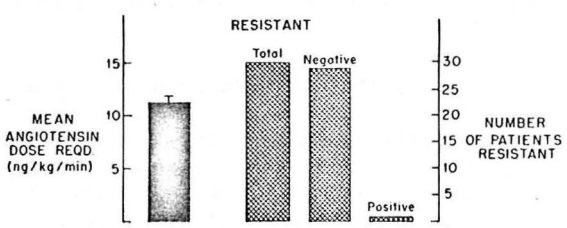


Hypothetical model of physiologic and pathologic determinants of angiotensin II dose requirements necessary to evoke a pressor response, diagramatically represented according to their physiologic importance in normal pregnancy and in preeclampsia.

Figure 9

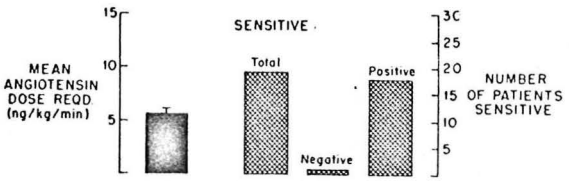
(Gant NF, Chand S, Whalley PJ, et al: Obstet & Gyn 43:86, 1976)

A possible hormonal clue to the difference in sensitivity to angiotensin has been uncovered: progesterone increased the sensitivity to angiotensin in normotensives but decreased the sensitivity in PIH women. The plasma levels of 5α-pregnane-3,20-dione (5α-DHP) parallelled angiotensin pressor responsiveness in both groups (Chand S, Andersen GJ, Worley RJ, et al: Gynecol Invest 7:86, 1976). This increased sensitivity to exogenous angiotensin might offer a useful diagnostic test but the hormone is no longer available and there is a potential for harm. Fortunately, while doing the above studies the UTSWMS investigators observed a difference in the blood pressure response to a change in posture from lateral recumbency to supine in women who were or were not destined to develop pre-eclampsia (Gant NF, Chand S, Worley RJ, et al: Am J Obstet & Gyn 120:1, 1974). The rollover test is positive if a 20 mm Hg or greater rise in blood pressure occurs within a few minutes after the patient turns to the supine position after having achieved a stable BP in the lateral recumbent position. This test correlates closely with angiotensin responsiveness (Figures 10 and 11) and with the subsequent course of the patient's blood pressure (Figure 12).



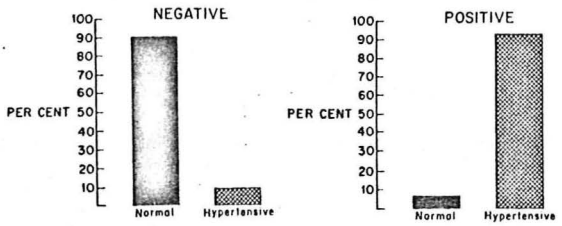
Correlation between angiotensin resistance and results of the supine pressor test. The mean dose of angiotensin required to elicit a pressor response in these 30 patients was 13.0 ng. per kilogram per minute. Of the total of 30 patients studied, 29 exhibited a negative test and only one had a positive test.

Figure 10
(Gant NF, Chand S, Worley RJ, et al: Am J Obstet & Gyn 120:1, 1974)



Correlation between angiotensin sensitivity and results of the supine pressor test. The mean dose of angiotensin required to elicit a pressor response in these 20 patients was 5.9 ng. per kilogram per minute. A total of 15 patients had a positive test, and only one had a negative test.

Figure 11



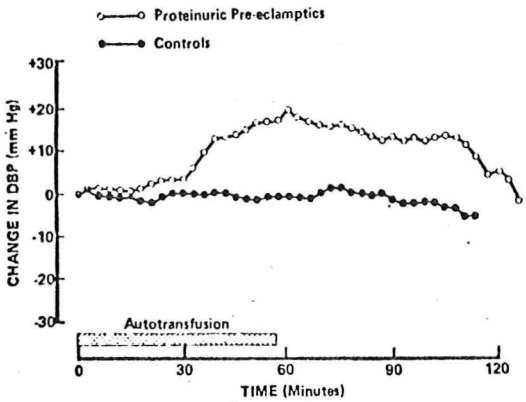
Left, Clinical outcome in patients with a negative supine pressor test. Ninety-one per cent of patients with a negative test remained normotensive throughout pregnancy. Nine per cent or 2 of 22 patients, despite a negative test, developed pregnancy-induced hypertension. Right, Clinical outcome in patients with a positive supine pressor test. Only 7 per cent or one of 16 patients failed to develop pregnancy-induced hypertension while 93 per cent or 15 of 16 patients with a positive test ultimately developed pregnancy-induced hypertension.

Figure 12
(Gant NF, Chand S, Worley RJ, et al: Am J Obstet & Gyn 120: 1, 1974)

Other's experience with the test is not as good: Gusdon has reported that only 50% of primigravidas with a positive test developed pre-eclampsia; however, a negative test predicted that it would not develop 93% of the time (Gynecol Invest 7: 9, 1976).

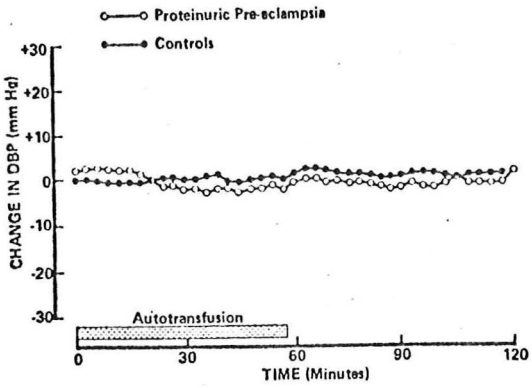
2. The effect of plasma re-transfusion

Two papers have shown a pressor effect from re-transfusion of blood or plasma taken before delivery from patients with pre-eclampsia (Tatum HJ and Mulé JA: Am J Obstet & Gyn 83:1028, 1962; Pirani BBK and MacGillivray I: Am J Obstet & Gyn 121:221, 1975). The latter study went further, re-infusing an aliquot of the same plasma at 6 days and 6 weeks post-partum. A pressor response occurred at 6 days, but not at 6 weeks. The authors interpret this as a hypersensitivity to normal amounts of circulating pressor substances that persists for 6 days after delivery but is lost by 6 weeks (Figures 13 and 14, page 10).



Change in diastolic blood pressure in proteinuric pre-eclamptic patients and control subjects following plasma autotransfusion six days post partum.

Figure 13



Change in diastolic blood pressure in proteinuric pre-eclamptic patients and control subjects following plasma autotransfusion six weeks post partum.

Figure 14

(Pirani BBK, MacGillivray I: Am J Obstet & Gyn 121:221, 1975)

D. Renin-prostaglandin interrelationships

1. Systemic renin

Almost everyone finds that plasma renin activity (PRA) is reduced when pre-eclampsia appears (Chesley LC: J Reprod Med 15:173, 1975). However the levels in the maternal systemic circulation may be inappropriately high for the higher blood pressure and more constricted vascular bed. Moreover, some find higher PRA or plasma angiotensin-II levels:

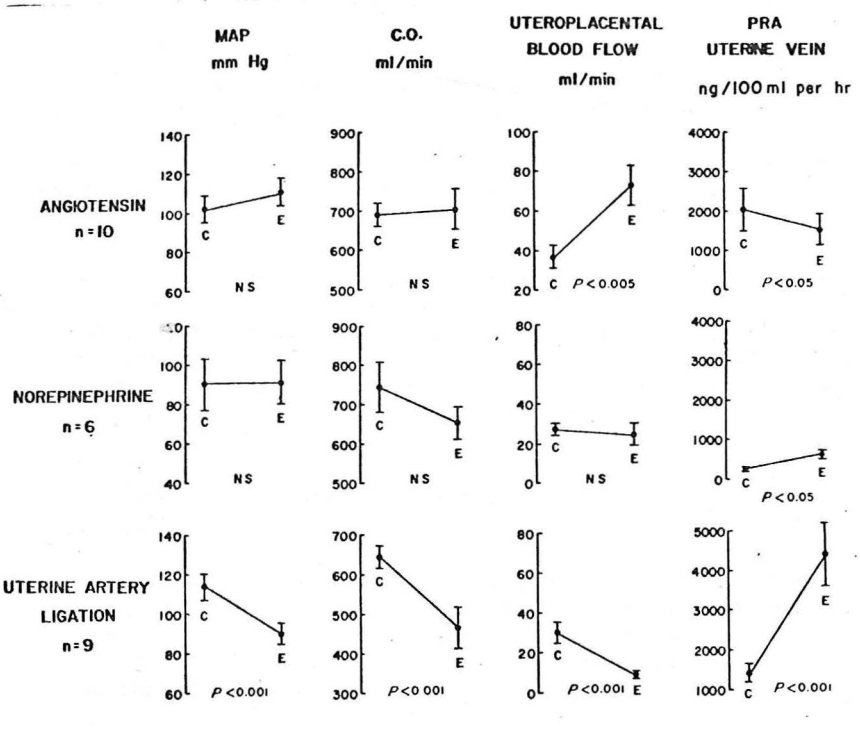
Tapia HR, Johnson CE, Strong CG: Lancet 1:847, 1972
Gordon RD, Symonds EM, Wilmshurst EG, et al: Clin Sci 45:115, 1973
Symonds EM, Pipkin FB, Craven DJ: Brit J Obstet & Gyn 82:643, 1975
Weinberger MH, Kramer NJ, Peterson LP: Gynecol Invest 5:35, 1974
Hayashi RH, Becker RA: Gynecol Invest 7:27, 1976

2. Uterine renin

The systemic circulation may not be the right place to look for involvement of renin-angiotensin. The trophoblastic tissue of the uteroplacental unit makes renin (Gross F, Schaechtelin G, Ziegler M, et al: Lancet 1;914, 1964; Skinner SL, Lumbers ER, Symonds EM: Am J Obstet & Gyn 101:529, 1968). The release of this uterine renin is not affected by changes in sodium intake which suppress renal renin and continues after bilateral nephrectomy (Gorden P, Ferris TF, Mulrow PJ: Am J Physiol 212:698, 1967).

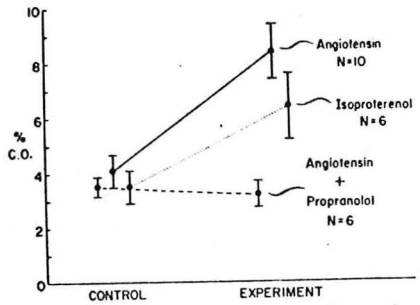
Uterine renin is increased by ligation of the uterine artery (Ferris TF, Stein JH, Kauffman J: J Clin Invest 51:2827, 1972) (Figure 15, page 11).

The released renin may be directly responsible for regulating uterine blood flow. Unlike the vasoconstrictor action of renin-angiotensin in the systemic circulation, non-pressor doses of angiotensin infused into pregnant rabbits or dogs increases uterine blood flow while decreasing vascular resistance (see Figure 15 and Assali NS, Holm LW and Segal N: Am J Obstet & Gyn 83:809, 1962). This vasodilatory effect of angiotensin is unique to the uterine circulation and does not follow pressor doses of norepinephrine. The effect appears to be mediated by beta-adrenergic stimulation since it is blocked by propranolol and a similar vasodilatory effect is produced by isoproterenol (Figure 16).



The effect of angiotensin, norepinephrine, uterine artery ligation, and hemorrhagic hypotension upon mean arterial blood pressure (MAP), cardiac output (C.O.), uteroplacental blood flow, and PRA in uterine vein and carotid artery. Values are expressed as mean ±SEM.

Figure 15
(Ferris TF, Stein JH, Kauffman J: J Clin Invest 51:2827, 1972)



A comparison of the changes in uterine blood flow, expressed as a percentage of cardiac output (C.O.), during an infusion of angiotensin, isoproterenol, and angiotensin with propranolol. Values are plotted as mean ±SEM.

Figure 16
(Ferris TF, Stein JH, Kauffman J: J Clin Invest 51:2827, 1972)

Thus, in pre-eclampsia, renal renin secretion may diminish secondary to salt retention whereas uterine renin may increase secondary to a reduction in uteroplacental perfusion.

3. Uterine hypoperfusion: A great deal of experimental and clinical evidence supports uteroplacental ischemia as a primary mechanism in pre-eclampsia

   a. Clinically, pre-eclampsia is seen where the growth of the uteroplacental unit is likely to outstrip the development of an adequate blood supply (e.g. first pregnancy, multiple pregnancies, hydatidiform mole) or where the vascular bed is compromised and incapable of the massive dilatation required (e.g. diabetes, chronic essential hypertension). The larger the placental mass, the greater is the likelihood of pre-eclampsia. The term "hyperplacentosis" has been introduced to describe the condition (Jeffcoate TNA: Proc Royal Soc Med 59: 397, 1966).

      The findings of the Dallas group, to be described subsequently, support this concept: in patients destined to develop pre-eclampsia, uteroplacental perfusion as measured by the placental clearance of dehydroisoandrosterone sulfate (DS) is increased; as the disease develops, DS clearance falls.

   b. Uterine arteriography shows a much poorer blood flow in patients with pre-eclampsia (Bieniarz J, Yoshida T, Romero-Salinas G, et al: Am J Obstet & Gyn 103:19, 1969).

   c. Experimentally, pre-eclampsia can be induced by reduction of uterine blood flow in rabbits (Abitbol MM, Gallo GR, Pirani CL, et al: Am J Obstet & Gyn 124:460, 1976), in dogs (Hodgkinson CP, Hodari AA, Bumpus FM: Obstet & Gyn 30:371, 1967) and in baboons (Cavanagh D, Rao PS, Tung K, et al: Obstet & Gyn 39:637, 1972). The evidence has been beautifully summarized by EW Page (J Obstet & Gyn Brit Commonwealth 79:883, 1972).

4. Uterine prostaglandin

   a. The uteroplacental unit synthesizes prostaglandins (Blatchley FR, Donovan BT, Poyser NL, et al: Nature 230:243, 1971). In the pregnant rabbit, uteroplacental secretion of PGE is greater than 5 times renal secretion (Venuto RC, O'Dorisio T, Stein JH, et al: J Clin Invest 55:193, 1975).

   b. In this model, when PGE synthesis is inhibited by meclofenamate or indomethacin, the systemic blood pressure rises 12 mm Hg and uterine blood flow falls from 16.5 ml/min to 7.8 ml/min (Venuto RC, O'Dorisio T, Stein JH, et al: Ibid).

   c. When angiotensin is infused in pregnant dogs (Terragno NA, Terragno DA, Pacholczyk D, et al: Nature 249:57, 1974) or pregnant monkeys (Franklin GO, Dowd AJ, Caldwell BV, et al: Prostaglandins 6:271, 1974), uterine venous PGE level rises.

   d. The obvious connection has been made: uterine ischemia → release of uterine renin → release of uterine PGE → vasodilatation in an attempt to maintain uteroplacental perfusion.

E. The basis for the MCR_{DS} and $PCDS_{E-2}$ as measures of uteroplacental perfusion

   1. The placenta, unable to synthesize estrogens de novo, utilizes plasma prehormones, mainly C_{19} steroids, produced in both the fetal and maternal adrenal glands:

      dehydroisoandrosterone sulfate (DS) → estradiol (E-2);
      16α-OH-DS → estriol (E-3)

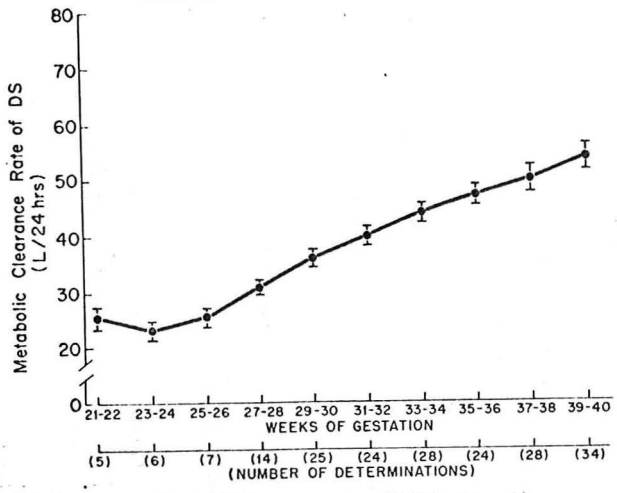
      (Siiteri PK and MacDonald PC: J Clin Endocrinol 26:751, 1966)

   2. The rate of estrogen formation by the placenta is directly dependent on precursor supply; the precursor, DS, reaches the trophoblast by simple diffusion (MacDonald PC and Siiteri PK: J Clin Invest 44: 465, 1965).

   3. The conversion of precursor DS to estrogen outside the placenta is insignificant. Therefore the clearance of DS, measured as the rate of disappearance of an isotopically labelled, miniscule quantity of the steroid, provides a direct measure of placental perfusion (Gant NF, Hutchinson HT, Siiteri PK and MacDonald PC: Am J Obstet & Gyn 111:555, 1971).

   4. The rate of clearance (Metabolic Clearance Rate or MCR_{DS}) of maternal plasma DS increases markedly and progressively during pregnancy, until delivery.

Figure 17



Metabolic clearance rates of DS in normal primigravidas who did not develop pre-eclampsia. MCR_{DS} is plotted against the weeks of gestation. The number of separate determinations comprising each point on the curve is shown just below the weeks of gestation. Note that the MCR_{DS} increases progressively throughout pregnancy in these 38 subjects who remained normal.

(Gant NF, Hutchinson HT, Siiteri PK, et al: Am J Obstet & Gyn 111:555, 1971)

5. Maternal plasma DS is metabolized through a variety of non-placental pathways with only 35% converted into estradiol; therefore a decrease in MCR_{DS} may not necessarily reflect a decrease in placental utilization or perfusion (Madden JD, Siiteri PK, MacDonald PC and Gant NF: Am J Obstet & Gyn, in press).

6. The conversion of DS to estradiol (E-2) almost exclusively occurs within the placenta and is irreversible. Therefore a more specific index of placental perfusion can be obtained by determining the placental clearance of DS to E-2:

   MCR_{DS} X % conversion DS → E-2 = Placental Clearance DS → E-2

7. The data in various states are shown on the next page (Figure 18). As expected, PCDS is doubled with twin pregnancy and markedly low with placental sulfatase deficiency.

F. Changes occurring with hypertension

1. In established pre-eclampsia, the MCR_{DS} and $PCDS_{E-2}$ are decreased and continue to fall until delivery or the patients are treated by bedrest.

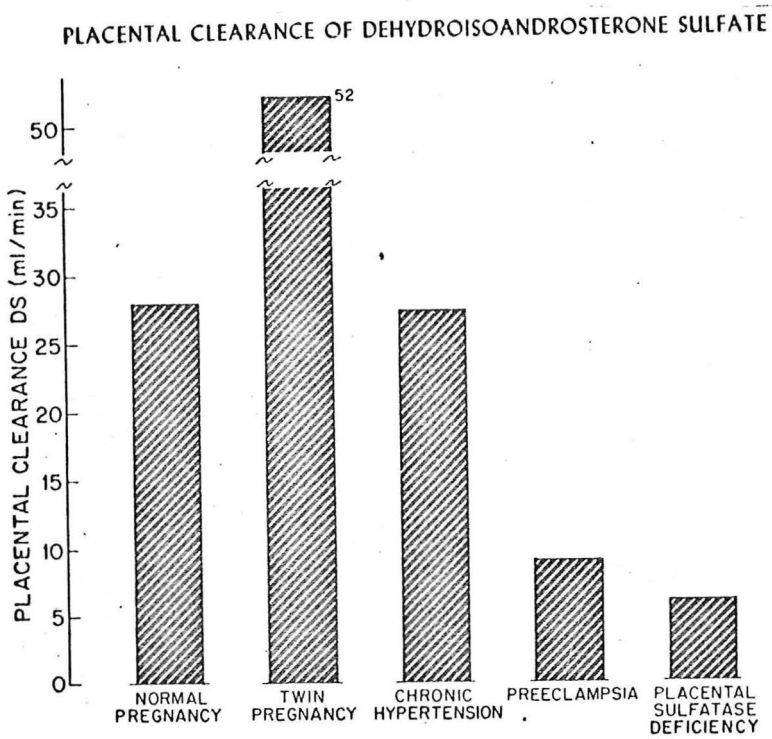
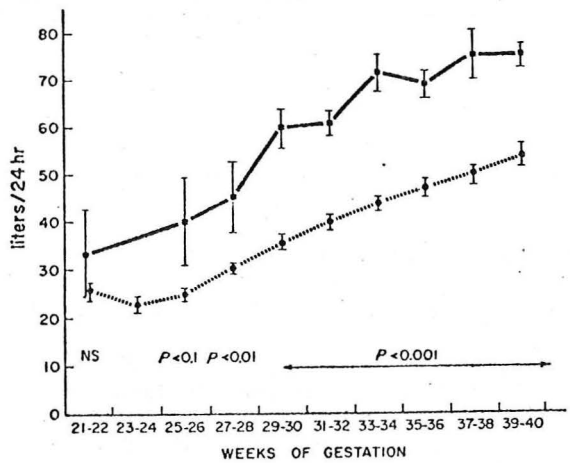


Figure 18
(Gant NF: 27th Post-graduate Assembly, Endocrine Soc, Dallas, Oct, 1975)

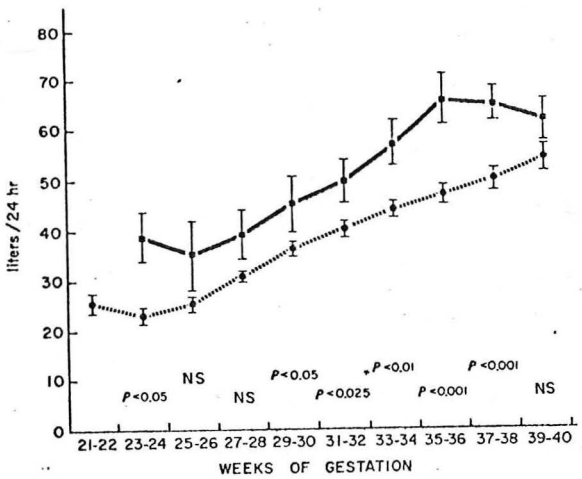


Comparison of the metabolic clearance rate of dehydroisoandrosterone sulfate (MCR_{DS}) in patients who did *not* develop pregnancy-induced hypertension. The results obtained in women with chronic hypertension are shown by squares connected by solid lines (■——■). The results obtained in normotensive subjects are shown by closed circles connected by broken lines (●- - -●). Vertical bars represent standard error of the mean. The MCR_{DS} (L/24 hr) is plotted as a function of weeks of gestation.

Figure 19
(Gant NF, Madden JD, Chand S, et al: Obstet & Gyn 47:319, 1976)

2. In women with chronic hypertension, the MCR_{DS} is higher than in normotensives (see Figure 19, page 15). The $PCDS_{E-2}$ is, however, decreased in such patients from 35.1% in normal pregnancy to 21.5% (Gant NF, Madden JD, Chand S, et al: Obstet & Gyn 47:319, 1976).

3. In women destined to develop pre-eclampsia the MCR_{DS} is higher prior to the onset of hypertension, as early as the 28th week of gestation (Figure 20).



Comparison of the metabolic clearance rate of dehydroisoandrosterone sulfate (MCR_{DS}) in normotensive primigravid patients (•- - -•) and in primigravid normotensive patients destined to develop pregnancy-induced hypertension (■——■). Vertical bars represent standard error of the mean. The MCR_{DS} (L/24 hr) is plotted as a function of weeks of gestation.

Figure 20

(Gant NF, Madden JD, Chand S, et al: Obstet & Gyn 47:319, 1976)

4. If treatment does not prevent progression into pre-eclampsia, MCR_{DS} and $PCDS_{E-2}$ will fall. The sequential changes in $PCDS_{E-2}$ in one woman followed prior to and after development of pre-eclampsia are shown in Figure 21, page 17.

G. The use of a DS loading test

1. In 1967 Lauritzen suggested that a DS load be given to pregnant patients and the subsequent rise of urinary estriol (E-3) excretion be used to assess the functional status of the placenta (Lauritzen CH: Acta Endocrinol (Suppl) 119:188, 1967).

2. The test proved invalid because urinary excretion may not reflect the rapidly occurring changes and the conversion of DS to estradiol (E-2), not estriol (E-3), is the unique and irreversible conversion occurring within the placenta.

SEQUENTIAL PLACENTAL CLEARANCE OF
DEHYDROISOANDROSTERONE SULFATE IN A PRIMAGRAVIDA
DESTINED TO DEVELOP PREECLAMPSIA

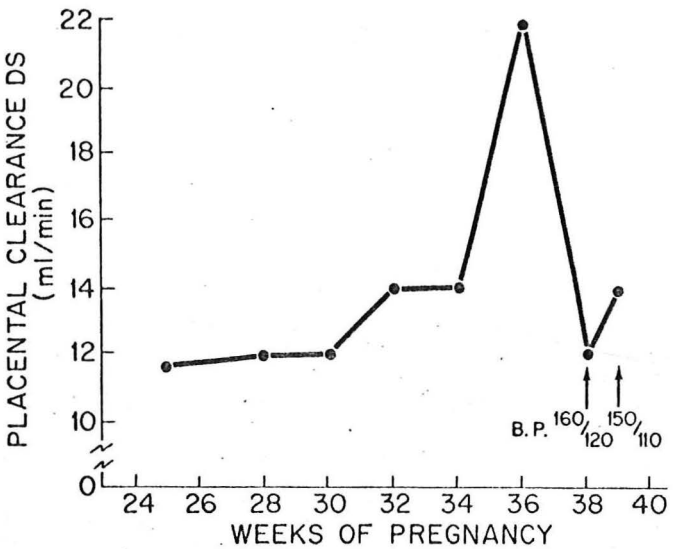


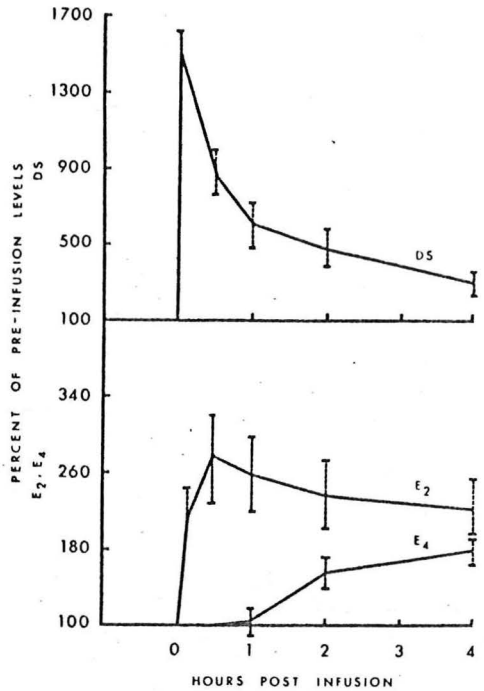
Figure 21

(Gant NF: 27th Post-graduate Assembly, Endocrine Soc, Dallas, Oct, 1975)

3. Using plasma estradiol the test may be a valid index of placental insufficiency. Tulchinsky et al have added a measurement of plasma estetrol (E-4), arising from fetal conversion from estradiol, as an additional index of fetoplacental function. The results are shown in Figures 22 and 23 on the next page.

   Note that subnormal plasma E-2 and E-4 levels were present in 9 of 10 pregnancies with fetal distress and subsequent delivery of infants small for gestational age. On the other hand only 1 of 10 with low urinary estriol (commonly advocated as indicative of placental insufficiency) who did not have fetal distress and whose infants were appropriate for gestational age had subnormal E-2 and E-4 after DS loading (Tulchinsky D: N Engl J Med 294:517, 1976).

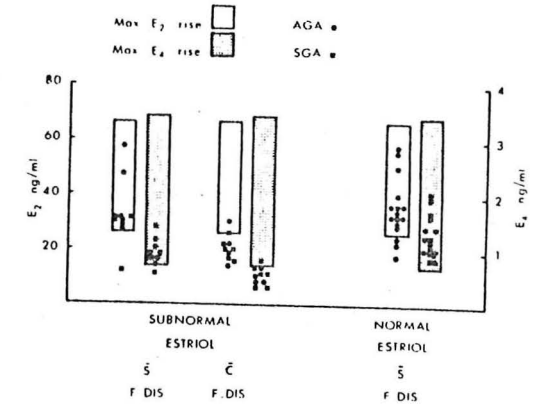
4. Some have found the procedure to be valid (Pupkin MJ, Nagey DA, MacKenna J, et al: Am J Obstet & Gyn 125:256, 1976); others have not (Fraser IS, Leask R, Drife J, et al: Obstet & Gyn 47:152, 1976).



Mean Plasma Concentrations of Dehydroepiandrosterone Sulfate (DS), Estradiol (E_2) and Estetrol (E_4) of 11 Normal Patients at 35 to 40 Weeks of Gestation after Infusion of 50 Mg of DS.

The mean values and standard errors (indicated by the bars) are expressed as percentage of mean pre-infusion levels.

Figure 22



Maximal Estradiol (E_2) and Estetrol (E_4) Levels after Dehydroepiandrosterone Sulfate Infusion in Complicated Pregnancies with ($\bar{c}$) and without ($\bar{s}$) Fetal Distress (F.DIS).

The open and shaded bars indicate the 95 per cent confidence limits of normal E_2 and E_4 levels, respectively. The dots represent plasma levels of patients with subsequent delivery of infants appropriate for gestational age (AGA), and the squares levels of patients with subsequent delivery of infants small for gestational age (SGA).

Figure 23

(Tulchinsky D, Osathanondh R and Finn A: N Engl J Med 294:517, 1976)

H. The renal lesion

1. The relation between uteroplacental hypoperfusion and the renal pathology and functional changes of pre-eclampsia seem best explained by the concept of degeneration of trophoblasts → liberation of thromboplastin → deposition into the renal glomeruli as schematized by EW Page (J Obstet & Gyn Brit Commonwealth 79: 883, 1972) (see Figure 24, page 19).

2. On the other hand, an immunologic mechanism has been suggested by the finding of IgM and IgG in the glomeruli of pre-eclamptic women, in proportion to the severity of the disease, with complement in arterioles and some glomeruli (Petrucco OM, Thomson NM, Lawrence JR et al: Brit Med J 1:473, 1974).

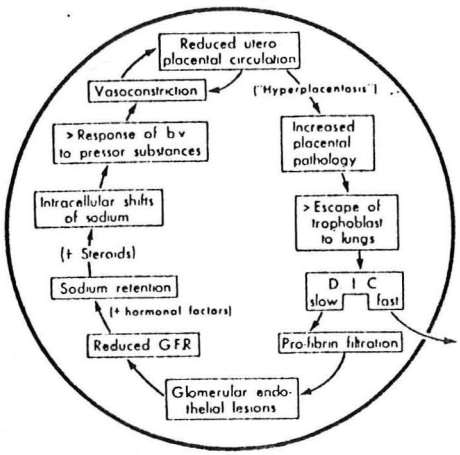


Figure 24

The inner vicious circle of pre-eclampsia and eclampsia. (D.I.C. = disseminated intravascular coagulation. G.F.R. = glomerular filtration rate.)

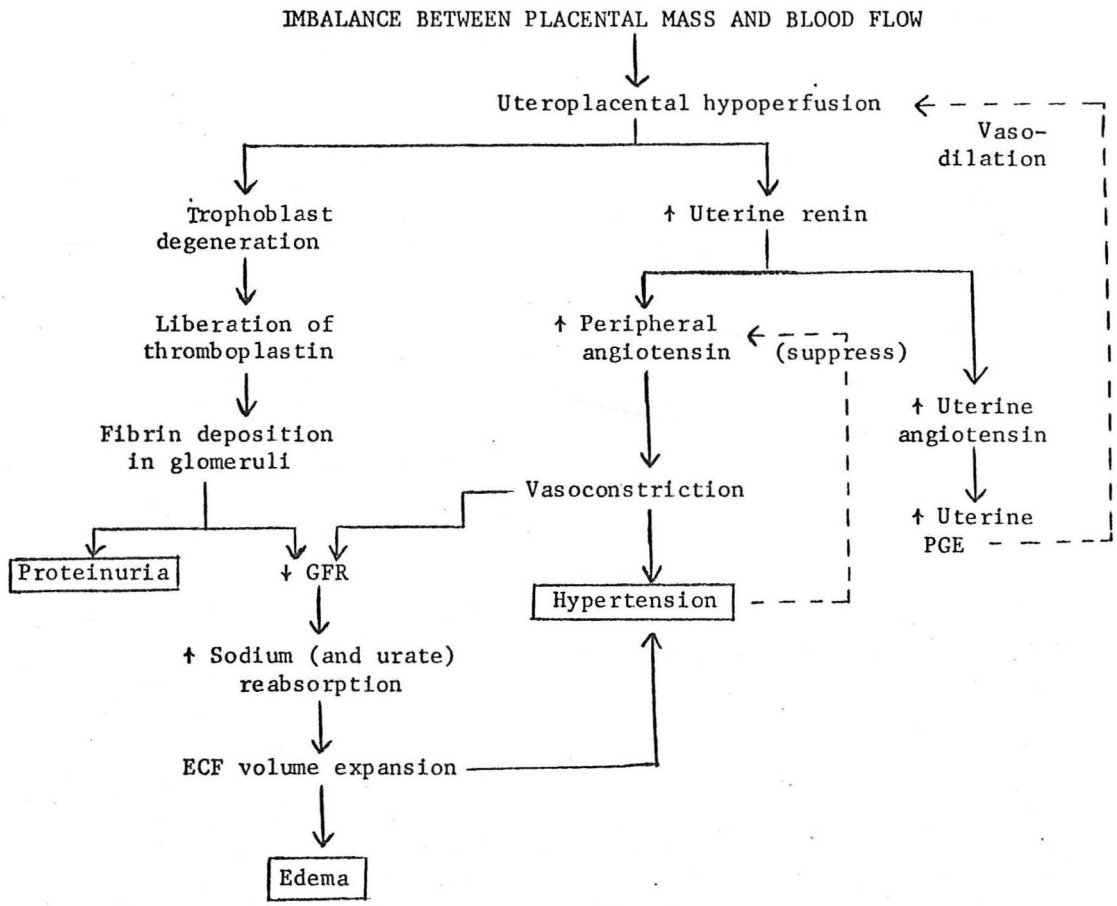
(Page EW: J Obstet & Gyn Brit Commonwealth 79:883, 1972)

3. There are other data supporting an immunologic basis for pre-eclampsia, beautifully summarized by JR Scott and Alan Beer (Am J Obstet & Gyn 125:418, 1976). The conclusion of their presentation is:

"These facts taken together could be interpreted as suggesting that pre-eclampsia may result when a young, often submaximally nourished, primigravida is confronted with a large placental mass, its size and extent of trophoblastic invasion determined by histocompatibility or organ-specific antigenic differences between the graft and host. Since not all primigravidas are affected, this premise would require the presence of placentas with certain unique or predisposing antigens or imply that unaffected women are "nonresponders" analogous to Rh negative individuals unresponsive to Rh antigens. If this were the situation, the normal maternal-fetal immunologic homeostasis may be overwhelmed in "responding" primigravidas so that effector lymphocytes or specific antibodies of maternal origin are then free to attack, resulting in damage to the trophoblast and basement membrane of the renal glomerulus producing placental insufficiency, maternal proteinuria, edema, and hypertension. The second pregnancy could indeed have the added advantage of sufficient blocking factors being evoked during or after the first pregnancy and therefore be unable to initiate the same process."

4. Disseminated intravascular coagulation may occur (Killam AP, Dillard SH, Patton RC, et al: Am J Obstet & Gyn 123:823, 1975), but the careful studies by Pritchard et al suggest that these coagulation abnormalities are the result and not the cause of eclampsia (Pritchard JA, Cunningham FG, Mason RA: Am J Obstet & Gyn 124:855, 1976).

I. A unified hypothesis (based upon the concepts of Page, Speroff, Ferris, Gant, MacDonald and many others)



IV. Management

A. Prevention

1. Contraception for young girls to prevent teenage pregnancies
2. Adequate nutrition: Poor nutrition predisposes to pre-eclampsia (Kaminetzky HA, Langer A, Baker H, et al: Am J Obstet & Gyn 115: 639, 1973); improved nutrition reduces the incidence (Primrose T, Higgins A: J Reprod Med 7:257, 1971). A weight gain of 25 lb should be encouraged with an intake of about 2,200 calories/day, including at least 65 grams/day of protein.
3. Early detection in susceptible women

   a. Roll-over test
   b. Attention to small rises in BP

c. Plasma uric acid: The plasma uric acid level was found to be a better indicator of the prognosis for the fetus in women with pre-eclampsia (Redman CWG, Beilin LJ, Bonnar J, et al: Lancet 1: 1370, 1976). Perhaps those with high uric acid levels should be more carefully observed and treated.

4. Sodium restriction and diuretic therapy

a. Since pre-eclampsia is often associated with edema, some advocated salt restriction and early institution of thiazide therapy as prophylaxis (Finnerty FA, Jr, Bepko FJ: JAMA 195:429, 1966).
b. However, these are of no benefit and may be harmful (Pike RL, Smiciklas HA: Internat J Gyn & Obstet 10:1, 1972). The incidence of pre-eclampsia is not reduced (Kraus GW, Marchese JR, Yen SSC: JAMA 198:1150, 1966); the infants may be small for gestational age (Campbell DM, MacGillivray I: Brit J Obstet & Gyn 82:572, 1975); neonatal thrombocytopenia may occur (Rodriguez SU, Leikin SL, Hilter MC: N Engl J Med 270:881, 1964). And using the MCR_{DS} technique, Gant et al have shown a decrease in placental perfusion in women given diuretics.

B. The Parkland approach to therapy

The treatment of the patient with established pre-eclampsia has changed markedly and for the better. The practices followed at Parkland seem to be eminently reasonable and amazingly effective, as described in a paper soon to be published (Hauth JC, Cunningham FC, Whalley PJ: Obstet & Gyn 48:--, Sept, 1976). The following is from the introduction of the paper:

"In October 1971 a high-risk pregnancy unit was established at Parkland Memorial Hospital. The purpose of this 28-bed unit was to provide long-term care for women whose fetuses were at high-risk, including those women with hypertension. Prior to the existence of the high-risk unit, the usual method of management of the nullipara with pregnancy-induced hypertension prior to term was termination of the pregnancy if hypertension persisted beyond 72 hours following hospitalization. Alternatively, if the woman's hypertension quickly responded to bed rest, she was discharged and followed in the obstetric complications clinic. However, most often the hypertensive process recurred, frequently was more severe, and usually prompted delivery. With this type management perinatal mortality increased due to stillbirths as did neonatal deaths from gross immaturity.

"With the establishment of the high-risk unit, an important alternative for the management of a significant number of nulliparous hypertensive women and their fetuses, remote from term, became feasible. Instead of terminating these patient's pregnancies resulting in the birth of a premature infant or discharging them to be followed as outpatients, they were admitted to the high-risk unit.

"Basic management following hospitalization consisted of close observation for evidence of those clinical signs and symptoms that would

indicate worsening of the hypertensive process, thereby mandating delivery. The objective of this approach was to allow gestation to continue safely until fetal maturity developed but to terminate it prior to the occurence of fetal death in utero or prior to serious maternal morbidity. During the first 3 1/2 years there were 372 nulliparas with pregnancy-induced hypertension admitted to the high risk pregnancy unit. The excellent results in maternal and fetal outcome demonstrate that this objective has been accomplished as indicated not only by a low perinatal mortality rate, but also by larger and apparently healthier infants."

The management of these patients follows these principles:

1. Patients with more severe hypertension (diastolic pressure > 110 mm Hg) and significant proteinuria are admitted to the delivery suite. If after 24 hours, there is no clinical improvement, delivery is promptly effected; if improvement occurs, the patient is transferred to the high-risk unit.

2. When admitted to the high-risk unit, the patients are allowed to ambulate as desired and given a general diet without salt restriction. Patients might be advised to lie in the left lateral position since the blood pressure may be lower in that position (Noble AD: J Obstet & Gyn Brit Commonwealth 78:110, 1971) and PRA higher when supine (Weinberger MH, Petersen LP, Herr MJ, et al: J Clin Endo & Metab 36:991, 1973); however, uteroplacental perfusion as measured by MCR_{DS} was not influenced by any positional change (Singley T, Madden JD, Chand S, et al: Obstet & Gyn 47: 419, 1976). No diuretics or other antihypertensives or sedatives are administered.

3. The following are performed:

   a. Blood pressure four times daily
   b. Weights three times a week
   c. Urine protein, random sample, three times a week
   d. 24-hour creatinine clearance weekly
   e. Ultra-sonography to measure fetal biparietal diameter, repeated every 3 weeks to assess fetal growth
   f. Oxytocin induction of labor is attempted if indicated.
   g. Amniocentesis for determination of the lecithin/sphingomyelin ratio is rarely performed.

4. Gestation is allowed to continue until spontaneous labor ensues or the cervix becomes favorable for induction of labor at or near term.

5. Delivery prior to term is considered in patients with persistent or recurrent hypertension and one or more of these:

   a. Rapid weight gain
   b. Decrease in creatinine clearance
   c. Appearance of significant proteinuria

d. Clinical or sonographic evidence of fetal growth retardation
e. Development of severe headache or scotomata

6. The results with this approach have been excellent: Of the 372 nulliparous patients, 346 remained in the unit until delivery, with these responses:

Response	Number of Patients	Percent
Good: Normotensive within 5 days	292	85%
Hypertension recurred prior to labor	121	42%
Hypertension occurred while in labor	137	47%
No recurrent hypertension	34	11%
Moderate: Less severe hypertension	32	9%
Poor: Severe hypertension, mandating delivery within 7 days	22	6%

A typical record of a patient who responded well is shown below.

LNMP: 8-21-73 Quickening: 12-30-73 EDC: 5-29-74 FHT 1st: 1-3-74

Complications: 15 year old Black Para 0-0-0-0 with PREGNANCY INDUCED HYPERTENSION

Dates		3-16	3-19	3-22	4-2	4-8	4-15	4-22	4-29	5-1	5-2
Weeks of Gestation		30	30	31	32	33	34	35	36	36	36
	Weight	136	129	129	130	130	130	131	132	134	136
	Blood Pressure	150/110	130/90	136/84	130/80	124/84	126/85	130/80	140/90	146/90	170/110
Renal Function	Plasma creatinine / urea	0.8 / 9				0.6 / 6			1.0 / 12		
	Urine total Creatinine mgs.	1000				1200			1000		
	Creatinine Clearance	123				124			69		
	Urine Protein	Trace	0	0	0	0	0	0	0	1+	2+
Ultrasound	Biparietal (mm)		73			82				89	
	Growth Rate (mm/wk)					3.2				2.1	
	Gestation (weeks)		28			32				36	
	Placental Location		post								
Other	Plasma Estrogen (µg%)	2.8	3.0	3.5	4.4	6.1	6.4	9.5	10.7	11.3	11.2
	L/S Ratio									<2	
	Estimated Fetal Weight (Pounds)		3		4.0			4.5			

DELIVERY 5/2/74 C-Section BIRTH WEIGHT 2320 gm Apgar 9/9

Figure 25

(Hauth JC, Cunningham FG, Whalley PJ: Obstet & Gyn 48:--, Sept, 1976)

The overall results are best described in the last two paragraphs of the paper:

"The ultimate test of the efficacy of this clinical study is pregnancy outcome. Among the group of patients who chose to continue hospitalization there were no maternal deaths and the perinatal mortality rate was only 9/1000. This perinatal mortality rate is much lower than that of the general obstetric population at Parkland Hospital, which was 29/1000 in 1974. More significantly, it is far lower than the perinatal mortality rate of 154/1000 occurring among those patients who left the hospital against medical advice and whose fetuses subsequently died as a direct results of hypertension.

"In conclusion, these data indicate that good maternal and fetal outcome is possible in nulliparous women who develop pregnancy-induced hypertension relatively early in pregnancy, only if the disease is recognized early in pregnancy and promptly treated with limited activity in a hospital setting. Only minimal laboratory monitoring is necessary, and good clinical judgment will dictate the timing for delivery. In the majority of pregnancies, continued fetal growth as indicated by clinical assessment and sonography, as well as the low fetal wastage and decreased incidence of low-brithweight infants, attest to the efficacy of the management that has been used. Contrarily, if pregnancy-induced hypertension is allowed to progress to the point of severe hypertension, proteinuria, oliguria, headache, and scotomata, the clinical course usually cannot be modified by hospital observation, and delivery is mandatory for both maternal and fetal reasons."

7. More aggressive and complicated regimens have been described, but the results are no better (Crane JP, Sauvage JP, Arias F: Am J Obstet & Gyn 125:227, 1976).

C. Assessment of fetal risk

1. A number of laboratory tests have been used in an attempt to improve the clinical detection of placental insufficiency and fetal distress. These include:

   a. Placental hormone levels in maternal blood or urine or amnionic fluid

      1) Protein hormones

         a) Human chorionic gonadotropin (HCG)
         b) Human placental lactogen (HPL)

      2) Steroid hormones

         a) Progesterone
         b) Estrogens, particularly estriol
         c) Dehydroisoandrosterone sulfate loading

b. Amnionic fluid analysis: enzymes, L/S ratio
c. Sampling of fetal scalp blood
d. Oxytocin challenge test
e. Plasma uric acid

2. Critical analysis of the value of these tests is rarely done. When it is, most have been found to be of little or no value. As an example, the UTSWMS group evaluated the plasma estrogen measurement and conclude that "the knowledge of plasma immunoreactive estrogen levels did not improve perinatal mortality in gravidas whose fetus is considered at high risk. Moreover, the results suggest that increased perinatal mortality and morbidity may occur if patient management protocols rely heavily or exclusively upon immunoreactive estrogen levels in determining the timing of intervention in these pregnancies" (Duenhoelter JH, Whalley PJ, MacDonald PC, in press).

   Elsewhere, they have stated "As yet there is no endocrine function test or endocrine measurement that will accurately reflect fetal well-being in such a way as to offer to the obstetrician data that is not already available. From clinical evaluation and careful monitoring of the patient with established techniques such as blood pressure monitoring, determination of creatinine clearance, serial determination of fetal growth rate by clinical and sonographic techniques, and sound clinical judgment, the best obstetric care is offered to the high-risk fetus and mother" (MacDonald PC, Gant NF, Duenhoelter JH, et al: In Diabetes and Other Disorders of Pregnancy. Alan Liss Co., New York, 1976).

D. Antihypertensive drug therapy

1. Though a few may still hold to a more aggressive stance, most believe that antihypertensive drugs should not be used in patients with pre-eclampsia unless the diastolic blood pressure is above 110 mm Hg with modified bed rest. This conservative view has been based upon empiricism. Leather et al found no improvement in the chances of a successful outcome to the pregnancy in patients given a thiazide and methyldopa (Lancet 2:488, 1968).

2. Using the MCR_{DS} technique to assess uteroplacental perfusion, Gant et al have shown that diuretics and antihypertensives may make things worse:

   a. Hydrochlorothiazide, 50 mg per day for 7 days → 18.5% decrease in MCR_{DS} (Gant NF, Madden JD, Siiteri PK, et al: Am J Obstet & Gyn 123:159, 1975)
   b. Lasix, 40 mg I.V. → 18.8% decrease
   c. Hydralazine → 23.5% decrease (Gant NF, Madden JD, Siiteri PK: Am J Obstet & Gyn 124:123, 1976)

3. Nonetheless, when the blood pressure needs to be lowered, repeated injections of hydralazine are favored. Uterine blood flow and

vascular resistance and fetal cardiovascular functions are little affected (Ladner CN, Weston PV, Brinkman CR: Am J Obstet & Gyn 108:375, 1970).

4. Others have reported good results, mainly in chronic hypertensives, with other drugs:

   a. Methyldopa (Kincaid-Smith P, Bullen M, Mills J: Brit Med J 1: 274, 1966)
   b. Bethanidine (Michael C: Aust N Zealand J Obstet Gyn 15:75, 1975)
   c. Diazoxide, orally (Pohl JEF, Thurston H, Davis D: Brit Med J 2: 568, 1972)
   d. Diazoxide, I.V. (Finnerty FA Jr: Obstet & Gyn 12:30, 1970)

5. Propranolol may cause various fetal problems: In a single 37 year-old patient taking 160 to 240 mg/day throughout pregnancy, the fetus had growth retardation, depression at birth, postnatal hypoglycemia and bradycardia (Gladstone GR, Hordof A, Gersony WM: J Pediat 86:962, 1975).

E. Therapy of eclampsia: Here again, the published series with the best results is from this Department of Ob-Gyn, with no maternal deaths in 154 cases and no fetal deaths in those alive when treatment was started and weighing 1,800 gm or more (Pritchard JA, Pritchard SA: Am J Obstet & Gyn 123:543, 1975). The regimen is:

1. $MgSO_4$ I.V. and I.M. to control convulsions
2. Hydralazine I.V. intermittently to lower diastolic blood pressure to below 110 mm Hg
3. Vaginal delivery as soon as the woman regains consciousness

Hypocalcemia has been reported in a patient treated similarly with $MgSO_4$ (Eisenbud E, LoBue CC: Arch Int Med 136:688, 1976).

V. The long-range consequences

Despite some evidence to the contrary, the immediate and remote prognosis of pregnancy-induced hypertension seems good. Since the diagnosis of pre-eclampsia may be tenuous, Chesley and others have looked at the later experience only in women who have had eclampsia.

A. Subsequent pregnancy: Fetal salvage in 466 later pregnancies in 189 with prior eclampsia was 76% overall and 93% in those carrying beyond 28 wks. Only 25% had recurrent hypertension during pregnancy and only 4 a second episode of eclampsia (Chesley LC, Annitto JE, Cosgrove RA: Obstet & Gyn 32:303, 1968).

B. Remote prognosis: Chesley has followed to 1974 all but 3 of 270 women surviving eclampsia in the period 1931 through 1951. The results of his latest survey are (Chesley LC, Annitto JE, Cosgrove RA: Am J Obstet & Gyn 124:446, 1976):

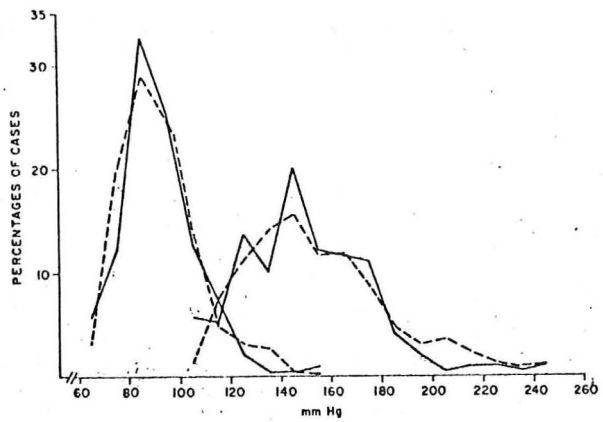
1. Mortality rate

   a. In white women having eclampsia in the first pregnancy, the remote mortality rate is not increased over that in unselected women.
   b. In white women having eclampsia as multiparas and in all black women, the remote mortality is from 2 to 5 times greater than expected.

2. Prevalence of later hypertension

   a. Primiparas are no different from women matched for age as shown below (Figure 26)
   b. Multiparas have a considerable increase. This may represent the much greater likelihood that these women had underlying, unrecognized, essential hypertension and not the "pure" syndrome. In a 2 month post-partum follow-up of 129 women with prior pre-eclampsia, a surprisingly large number (39%) had an abnormality by IVP or renogram, though most of these had just a slow transit time; only 4 had obvious renal parenchymal disease (Pystynen P, Laitinen S, Makkonen M et al: Acta Obstet Gyn Scand 55:7, 1976).

3. Diabetes: The prevalence is 2.5 times the expected in primiparas and 4 times in multiparas.



The distributions of systolic and diastolic blood pressures in women who had eclampsia in the first pregnancy carried to viability (solid lines) as compared with the distributions to be expected from the epidemiologic study of Hamilton and co-workers[18] (broken lines).

Figure 26

(Chesley LC, Annitto JE, Cosgrove RA: Am J Obstet & Gyn 124:454, 1976)

Chesley concludes that "Eclampsia neither is a sign of latent essential hypertension nor causes hypertension. Hypertensive pregnancies following eclampsia indicate the probability of later chronic hypertension, but do not cause it."

PILL-INDUCED HYPERTENSION

I. Clinical observations

A. Frequency

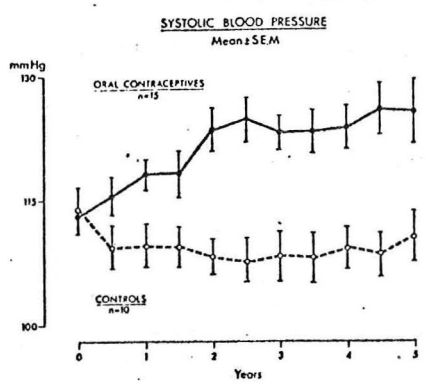
Since the first reported case of oral contraceptive-induced hypertension (Brownrigg GM: Canad Med Assoc J 87:408, 1962) the association has been amply confirmed. Perhaps the best study to establish the incidence is that of the Royal College of General Practitioners, since it involved over 23,000 users, compared to another 23,000 non-users (Oral Contraceptives and Health. Pitman Publishing Corp, New York, 1974).

	Takers	Ex-takers	Control
Rate/1000 women years	6.62	2.53	2.56
Ratio		2.59	

B. Time course

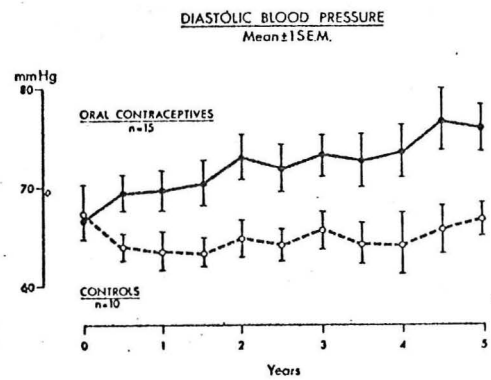
Hypertension has appeared within weeks to as long as 6 years after starting the pill. The carefully controlled study of Weir et al (J Steroid Biochem 6:961, 1975) shows that the pressure tends to progressively rise with longer pill usage (Figures 27 and 28). Similarly, the RCGP study showed an increasing incidence with time:

Years of pill use	1	3	5
Rate/1000 women years	3.8	8.9	15.2



Changes in systolic blood pressure after 5 yr in women taking oral contraceptives and in a control group of women using intra-uterine contraceptive devices or cervical diaphragms.

Figure 27



Changes in diastolic blood pressure after 5 yr in women taking oral contraceptives and in a control group of women using intra-uterine contraceptive devices or cervical diaphragms.

Figure 28

(Weir RJ, Davies DL, Fraser R, et al: J Steroid Biochem 6:961, 1975)

C. Relation to type of contraceptive

1. The culprit is probably the estrogen since, in most studies with progestogens alone, neither laboratory abnormalities nor rises in blood pressure have been observed. However the RCGP study found no relation between the incidence of hypertension and the dose of estrogen which varied between 50 and 150 µg/day, but did show a relation with the dose of progestogen:

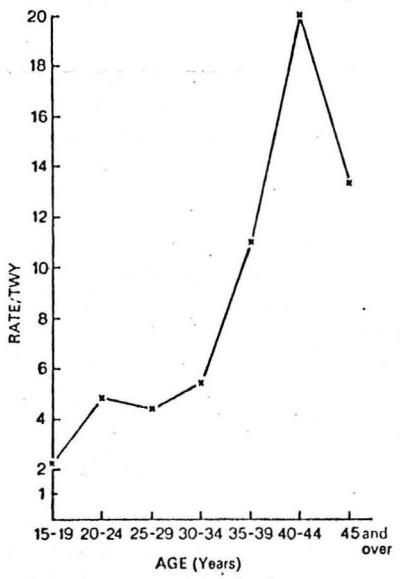
Progestogen dose	<3 mg	3 mg	>3 mg
Rate/1000 women years	6.0	7.2	10.7

These data may not be relevant to the U.S. since most oral contraceptives used here contain 1 mg or less of the progestogen.

2. The RCGP study did not include observations on women taking the currently used low-dose (20-30 µg) estrogen pills. Whether this will lower the incidence of hypertension remains to be seen.

D. Predisposing factors

1. Age: the older, the more likely (Figure 29)



Hypertension in relation to age corrected for parity

Figure 29

(Royal Col of Gen Practitioners. In Oral Contraceptives and Health. Pitman Publishing Corp, New York, 1974)

2. Obesity
3. Positive family history of hypertension
4. Previous pre-eclampsia: This association has been found by some (Mason B, Oakley N, Wynn V: Brit Med J 3:317, 1973; Spellacy WN,

Birk SA: Am J Obstet & Gyn 112:912, 1972) but was not observed among 150 primiparas in Dallas who had developed hypertension late in pregnancy (Pritchard JA, Crosby UD, Martin FG, et al: Gynecol Invest 5:26, 1974). Only 5.8% developed a diastolic BP > 90 on the pill.

5. Pre-existing hypertension: Though it seems prudent not to give the pill to women already hypertensive, the blood pressure was not aggravated in 33 hypertensive women given a combination oral contraceptive over the ensuing one year of observation (Spellacy WN, Birk SA: Fertility and Sterility 25:467, 1974).

E. The nature of the hypertension

1. In most, the blood pressure elevation is mild. In about half, the pressure returns to normal when the pill is stopped. The question remains: does the pill cause hypertension de novo or does it simply uncover the propensity toward essential hypertension that would eventually appear spontaneously? Among 14 women whose blood pressure reverted to normal after the pill was stopped, 7 developed spontaneous hypertension within the ensuing 6 years (Woods JW, Algary WA, Stier FM: Circulation 45-46 (Suppl II):82, 1972).

2. In some, the hypertension may be severe, rapidly accelerating into a malignant phase and causing irreversible renal damage. Examples include:

Harris PWR: Lancet 2:466, 1969
Zacherle BJ, Richardson JA: Ann Int Med 77:83, 1972
Dunn FG, Jones JV, Fife R: Brit Heart J 37:336, 1975
Schoolwerth AC, Sandler RS, Klahr S, et al: Arch Int Med 136:178, 1976

3. Considerable renal damage, demonstrable both by arteriography and by renal biopsy, was found in 9 women with pill-induced hypertension, even though most had reversible hypertension (Boyd WN, Burden RP, Aber GM: Quart J Med 46:415, 1975). Two of these had diffuse intravascular coagulation, so their renal changes may have been related more to that than to the hypertension per se.

II. Pathogenesis

A. Hemodynamic changes

1. Fluid volume: sodium retention of 100-150 mEq has been shown to follow estrogen administration (Crane MG, Harris JJ: In Oral Contraceptives and High Blood Pressure. Ed MJ Fregly, Dolphin Press, Gainesville, 1973). Since the progestogen may cause a diuresis, the overall effect from a combination pill may be less.

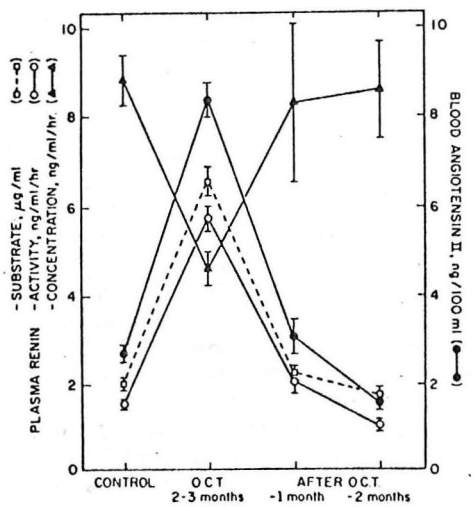
2. Two hemodynamic studies have been done on women before and after the intake of oral contraceptives for 2 to 3 months (Walters WAW, Lim YL: J Obstet & Gyn Brit Commonwealth 77:1007, 1970; Lehtovirta P: J Obstet & Gyn Brit Commonwealth 81:517, 1974). The results are

similar, showing an increase in blood volume and cardiac output despite the absence of a rise in blood pressure.

	Walters and Lim (30 Subjects)		Lehtovirta (21 Subjects)	
	Before	After	Before	After
Blood pressure	115/72	118/72	119/77	120/76
Weight	61.0	63.4	59.2	59.4
Blood volume	5.03	5.50	4.61	4.91
Cardiac output	7.04	8.10	5.69	6.15
Cardiac index	4.31	4.70	3.52	3.89
Stroke volume	107	126	79	86
Peripheral resistance			1308	1319

B. Renin-angiotensin-aldosterone: In view of the known effects of estrogen and the volume expansion seen with the pill, the logical assumption has been made that the hypertension reflects an activation of the renin-angiotensin system with a form of secondary aldosteronism. The changes in renin-angiotensin have been repeatedly shown (Figure 30). However, with few exceptions (Saruta T, Saade GA, Kaplan NM: Arch Int Med 126: 621, 1970), the changes seem to be identical in those who do and those who do not develop hypertension.

Blood angiotensin-II levels are increased and appear to induce renal vasoconstriction (Figure 31).



Levels of plasma renin substrate, activity, concentration, and blood angiotensin II before, during, and after 2 to 3 months of oral contraceptive therapy in 13 normotensive women. Cain MD, et al: *J Clin Endocrinol Metab* 33:671, 1971.)

Figure 30

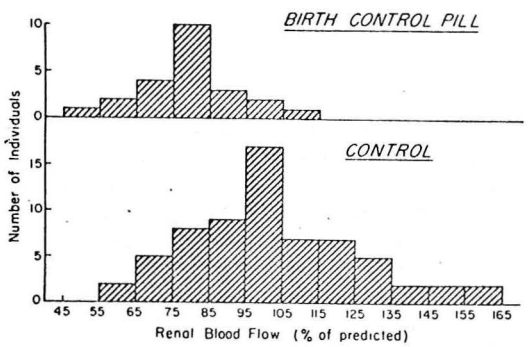


Figure 31

(Hollenberg NK, Williams GH, Burger B, et al: Circ Res 38: 35, 1976)

Moreover, the angiotensin blocker, saralasin, lowered the blood pressure from 145 to 117 mm Hg in rats made hypertensive with oral contraceptive, but had no effect in a normotensive group (Stubbs DH, Johnson JA, Keitzer WF: Fed Proc 35:398, 1976).

C. Sympathetic nervous system

The levels of plasma dopamine-β-hydroxylase activity, an index of sympathetic nervous system activity, were increased in 25 women who developed hypertension on the pill (Rockson SG, Stone RA, Gunnels JC, et al: Circulation 51:916, 1975). The changes in plasma DBH activity paralleled the changes in blood pressure, increasing little in the 16 women whose pressures did not increase, rising higher as did the blood pressure in the other women.

No studies of plasma catecholamine levels or other more direct indices of sympathetic nervous hyperfunction have been reported.

D. Differences in hormone metabolism

In an abstract, blood levels of the estrogenic component of the pill have been said to be significantly higher in a group of 9 women with hypertension than in a group of 20 normotensive pill takers (Ahluwalia B, Verma P, Gaines Q, et al: Clin Res 24:268A, 1976).

We are left then with inconclusive evidence for the pathogenesis of pill-induced hypertension. Various hemodynamic and hormonal changes occur but why only some women develop hypertension while most, with the same or similar changes, remain normotensive remains unknown. Perhaps only women with some intrinsic renal defect, similar to that presumably present in patients with essential hypertension, respond to the increased levels of angiotensin → renal vasoconstriction → sodium retention → hypertension.

III. Conclusions

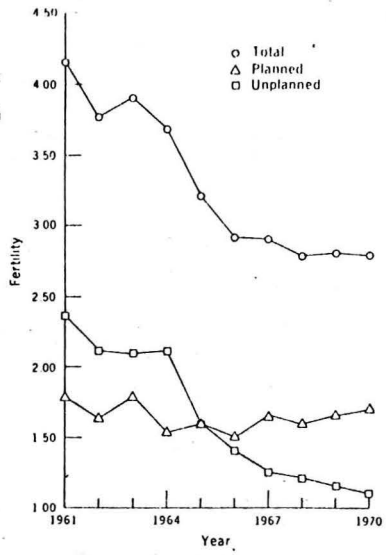
The pill is probably safe for most women for temporary birth control and family planning. However hypertension will appear in 5% of those taking it for 5 years and the frequency will likely rise with more prolonged use. Along with the changes in clotting, the rise in triglycerides, the abnormalities in glucose tolerance, hypertension may be an important risk factor, responsible for various cardiovascular catastrophes which occur with increased frequency, including myocardial infarction (Mann JI, Thorogood M, Waters WE, et al: Brit Med J 3:631, 1975), stroke (Collaborative Group for the Study of Stroke in Young Women: JAMA 231:718, 1975) and vertebral artery occlusion (Ask-Upmark E, Bickerstaff ER: Brit Med J 1: 487, 1976).

A recent paper from the Boston Collaborative Drug Surveillance Program (Rosenberg L, Armstrong B, Jick H: N Engl J Med 294:1256, 1976) found no increased association between current regular use of estrogens and nonfatal acute MI in either pre- or post-menopausal women. However the British have re-affirmed the association and one should remember that the Boston data

have not always held up (e.g. coffee drinking with MI, reserpine with breast cancer).

Before damning the presently available pills, alternatives should be considered. Newer forms of the IUD seem to be better tolerated and perhaps less hazardous. Unfortunately, the microdose progesterone-only minipill "has failed to live up to the expectations of those who once hailed it as the successor to combined estrogen-progestogen oral contraceptives and is being used by only a handful of the more than 50 million estimated to be using all forms of oral contraception" (Dept. of Medical and Public Affairs, George Washington Medical Center Population Reports, Series A, Number 3, Sept 1975).

In order to maintain the progressive fall in unwanted, unplanned pregnancies accomplished over the past 15 years (Figure 32) (Westoff CF: Science 191: 38, 1976) the combination oral contraceptives will continue to be needed.



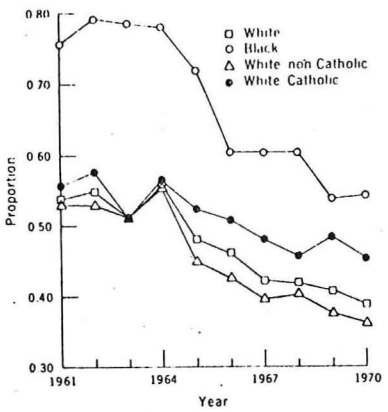


Figure 32 (left) Annual marital total fertility rates by planning status, 1961 to 1970. Figure 33 (above right) Proportion of marital total fertility rate that was unplanned, 1961 to 1970, by race and religion. (Westoff CF: Science 191:38, 1976)

At the least, all women given the pill should have to return for a blood pressure reading every 6 months. Those found to be hypertensive should be given other forms of contraception. If the blood pressure does not become normal within 3 months, appropriate work-up and therapy should be provided. If the pill must be continued, spironolactone may be the most effective therapy to control the blood pressure (Crane MG, Harris JJ: Program 58th Endocrine Society, p 149, June, 1976).