PART XXX

GUEST LECTURE

Chairmen: E Ritz
           G Rorive
PATHOPHYSIOLOGY AND MANAGEMENT OF HYPERTENSION DURING PREGNANCY

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Introduction

Hypertension complicates one out of every ten gestations and although advances in perinatal care have dramatically improved the maternal prognosis and fetal outcome in women with high blood pressure in pregnancy, the hypertensive disorders of gestation remain a major cause of maternal and fetal morbidity and mortality [1–3]. In addition, there is still substantial controversy regarding the aetiology, pathophysiology, and management of these disorders due in part to a lack of focused research in this important area of reproductive medicine, especially in comparison to investigative efforts on hypertension in non-pregnant populations. This article surveys the hypertensive disorders of pregnancy, focusing primarily on pre-eclampsia. It also discusses several controversies that continue to confuse the practitioner. The reader is referred to companion articles by Dal Canton [4] and Davison et al [5] that discuss, respectively, hypertensive pregnant animal models and hypertension in gravid women with underlying renal parenchymal disease.

Blood pressure and vascular reactivity in normal pregnancy

There are many physiological and hormonal alterations that accompany normal gestation, awareness of which should lead to early recognition of disease. The effect of pregnancy on normal blood pressure and vascular reactivity is a good example.

Mean blood pressure decreases early in gestation reaching a nadir by mid-trimester when diastolic levels are often 10–15 mmHg below values measured post-partum [6–8]. Blood pressure then increases gradually approaching non-pregnant values near term. These changes have been observed in patients surveyed under rigidly standardized conditions and housed in a quiet environment [6], as well as in large epidemiological surveys [7,8]. Since cardiac output rises quickly during the first trimester (to 140–160 per cent of non-pregnant values)
and remains relatively constant thereafter until term, the decrease in blood pressure is due to a marked decrement in peripheral vascular resistance. This is greatest in the uterine vasculature, which becomes a large ‘low resistance shunt’ but vasodilatation occurs in other organ systems including the kidney and skin. The return of mean blood pressure from a mid-trimester nadir towards non-pregnant values near term is of interest for it demonstrates that increasing vasoconstrictor tone is a feature of late pregnancy in normotensive gravidas as well as in women developing pre-eclampsia.

The physiological decrease in blood pressure which accompanies gestation raises the question of the upper limits of normal blood pressure during pregnancy. In this respect results of two large epidemiological studies are of interest. Page and Christianson [7] surveyed 12,954 pregnant women noting that perinatal mortality rates increased significantly when mean blood pressure exceeded 90mmHg in the second and 95mmHg in the third trimester respectively. In a survey of pregnancy in 38,636 women, Friedman and Neff [8] noted that the fetal mortality rate increased abruptly when diastolic pressure exceeded 84mmHg at any period of gestation, especially if such elevations were associated with qualitative proteinuria. Such data demonstrate that pregnancy outcome is jeopardized by levels of maternal blood pressure which are considered normal in non-pregnant subjects. In fact, some authors consider a gestation as ‘high risk’ and subject it to close scrutiny when diastolic levels exceed 70mmHg in the second trimester [9–11]. We consider diastolic levels of 75mmHg in mid-trimester and 85mmHg in the third trimester as upper limits of normal.

**Vascular reactivity**

Pregnant women are remarkably resistant to the pressor and renal actions of infused angiotensin II (AII) (Figure 1), and this vascular refractoriness occurs

![Diagram](image)

**Figure 1.** Dose response curves for infused angiotensin II (dashed line) and norepinephrine (solid line) in pregnant (x) and non-pregnant (o) women. At least twice as much angiotensin is required to elicit a given rise in blood pressure during pregnancy, while sensitivity to norepinephrine remains unchanged [12].
despite a 'physiological hypervolaemia' and renal hyperaemia [12–13]. (For a
detailed review of volume changes in normal gestation see references 12,14,15).
In humans the vascular resistance appears to be specific to angiotensin, as
reactivity to catecholamines is similar in gravid and non-pregnant subjects
(Figure 1). Of further interest, infusions of whole blood or isotonic saline, which
decrease renin activity and circulating angiotensin, fail to alter the pressor
refractoriness to All [13]. However, cyclo-oxygenase inhibitors administered to
gravidas increase their vascular reactivity to infused angiotensin to a degree seen
in non-gravid women [13].
Vascular reactivity during gestation has been studied in several species includ-
ing the rat, rabbit, and sheep. While results are often contradictory, a recent
report by Paller [16] is of interest. This author noted increased resistance to the
pressor effects of All, vasopressin, and norepinephrine during pregnancy in
Sprague-Dawley rats. Prior occupancy of vascular All receptors was not re-
ponsible for the blunted response, and All receptor affinity and number appeared
unaltered by gestation. Meclofenamate simultaneously increased the pressor
response to All, vasopressin, and norepinephrine. Thus the author concluded
that the vascular resistance during gestation in this species represented a prosta-
glandin effect on smooth muscle.

Classification, diagnosis and incidence

There are many classifications of the hypertensive disorders of gestation. In
1985 alone, a workshop has been convened by the World Health Organization,
and special committees are at work in the International Society for the Study of
Hypertension in Pregnancy and the World Federation of Obstetricians and
Gynaecologists, whose goals are to resolve the confusion created by the many
terminologies in current use. For the purpose of this review we will utilize the
terminology suggested by the American College of Obstetricians and Gynaeco-
logists, as we find it both sound and concise; it considers hypertension associated
with pregnancy in only four categories:
1. Pre-eclampsia-eclampsia
2. Chronic hypertension (of whatever cause)
3. Chronic hypertension with superimposed pre-eclampsia
4. Late or transient hypertension

A fifth category for 'unclassified hypertensive disorders' was also suggested, but
this appears to us of little use and is not recommended.

One reason the literature dealing with aetiological classification, course and
remote prognosis of hypertension in pregnancy is controversial and confusing
lies in the difficulty of distinguishing clinically between pre-eclampsia, essential
or secondary hypertension, renal disease, or combination of these entities. The
problem arises in part because certain women with undiagnosed essential hyper-
tension experience the physiological decrements early in gestation, and normal
levels may be recorded when they are initially examined. They are then er-
roneously labelled pre-eclamptics when frankly elevated pressures are recorded

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near term. In other instances, an accelerated phase of essential hypertension (albeit unusual in pregnancy) and certain forms of renal disease such as glomerulonephritis, and lupus erythematosus may mimic pre-eclampsia. These diagnostic dilemmas are best illustrated in reports where the cause of the high pressure complicating pregnancy was determined with the aid of renal biopsies [12, 17, 18]. In one study in which an academic obstetrician and renal physician recorded their impressions prior to biopsy, an exact diagnosis was made by clinical criteria in only 58 per cent of the patients [17]. Our own experience is summarized in Table 1, which demonstrates the pathological diagnosis on post-partum renal biopsy of 176 patients hospitalized at The University of Chicago Medical Center between 1958 and 1976 [18]. In most instances the clinicians thought the patient had pre-eclampsia (or 'toxaemia'), as proteinuria and oedema usually accompanied the hypertension, but such a diagnosis proved incorrect in 24 per cent of the nulliparas, and was wrong more often than not in multiparas. Of further interest was the presence of a substantial number of patients with unsuspected parenchymal renal disease. Such data underscore the problems inherent in interpreting reports in which diagnosis is based on clinical criteria alone; most suspect are series in which many of the patients labelled pre-eclamptic or 'toxaemic' were multiparas.

### TABLE 1. Renal pathology in 176 hypertensive gravidas

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of Patients</th>
<th>Primigravidae</th>
<th>Multiparae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-eclampsia:*</td>
<td>96</td>
<td>79</td>
<td>17</td>
</tr>
<tr>
<td>With nephrosclerosis</td>
<td>13</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>With renal disease</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>With both</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nephrosclerosis:</td>
<td>19</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>With renal disease</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Renal disease</td>
<td>31</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Normal histology</td>
<td>8</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

*Only glomerular endotheliosis on biopsy
From: Fisher, Luger, Spargo, Lindheimer [18]

Since there are few anti-partum indications for renal biopsy, investigators have attempted to differentiate pure or superimposed pre-eclampsia from other hypertensive disorders using biochemical markers such as plasma urate and antithrombin III [12, 19–21]. Others have analysed changes in platelet count, circulating Fe++, and most recently immunoreactive ouabain-like factors [19, 20, 22–24]. All these tests lack morphological correlations, which makes it difficult to assess their true sensitivity and specificity.

In summary, there are many problems in making correct diagnoses or in interpreting studies of pre-eclamptic populations in which diagnosis is based on clinical criteria alone. This is especially true of reports where many patients were
multiparas. As will be discussed below, when doubt exists it is always best to manage gravidas as if they had pre-eclampsia. Furthermore, clinical research of this disease should be restricted to primigravid women with hyperuricaemia and proteinuria whose mid-trimester diastolic pressure was less than 70mmHg.

**Pre-eclampsia-eclampsia**

Pre-eclampsia, a hypertensive disorder associated with proteinuria, oedema, and at times coagulation and/or liver function abnormalities [20] occurs primarily in nulliparas (Table I), usually after the 20th gestational week, and most often near term. When the disease progresses to a convulsive phase it is termed eclampsia. Although third-trimester hypertension is defined by diastolic pressures exceeding 85mmHg (sustained for at least 4 hours) increments in blood pressure of 30 and 15mmHg over previous systolic or diastolic levels are also considered abnormal, especially when such increases occur rapidly. These latter criteria are important as a young gravida may have had earlier diastolic levels of 50mmHg in which case a rise to 80mmHg could represent serious disease.

In the past excessive weight gain or oedema were considered ominous signs. As reviewed elsewhere [15] there are large variations in the weight increase considered normal for pregnancy, and leg oedema occurs in up to 80 per cent of normotensive women. Furthermore, in the large epidemiological survey analysed by Friedman and Neff [8] neither oedema nor maternal weight gain alone could be correlated with poor fetal outcome.

Eclamptic convulsions are dramatic and life threatening. Although these fits are usually preceded by various premonitory signs including headache, severe epigastric pain, hyper-reflexia and haemoconcentration, eclampsia can appear suddenly and without warning in a seemingly stable patient manifesting only minimal blood pressure elevations. This is why attempts to categorize pre-eclampsia as ‘mild’ or ‘severe’ (i.e. diastolic and systolic levels of 110 and 160mmHg or greater, heavy proteinuria and neurological symptoms) may be misleading. Many authorities stress that de novo third-trimester hypertension in a nullipara, whether or not other signs are present, is sufficient reason to proceed with hospitalization and treatment as if the patient were pre-eclamptic.

**Chronic hypertension (of whatever cause)**

Most gravidas in this category have essential hypertension, but in some the elevated blood pressure is secondary to such conditions as coarctation of the aorta, renal artery stenosis, primary aldosteronism, or kidney disease (for a detailed review of secondary hypertension and pregnancy see references, 5,12, 25). Pregnant women with chronic hypertension may be more prone to develop superimposed pre-eclampsia (see below), but otherwise gestation seems to have little influence on the course of their underlying disease. Fetal outcome in these patients appears related to the extent of end-organ damage prior to conception, and to the occurrence of superimposed pre-eclampsia, its timing and severity.

Exceptions to the predictions above are pheochromocytoma, scleroderma
with renal involvement, and periarteritis, in which gestation may have a devastating effect [25]. Fortunately these conditions are uncommon. The catastrophic potential of pheochromocytoma, in which mortality rates in excess of 40 per cent have been noted in unsuspected cases, can be reversed if the disease is diagnosed quickly and the patient treated with alpha adrenergic antagonists up to a point where gestation can be terminated successfully followed by resection of the tumour [25–27]. Because of these considerations we suggest screening for pheochromocytoma whenever hypertension predated conception or was discovered early in pregnancy.

Fetal outcome also appears poor in the rare patient with Cushing’s disease [28], whereas normalization of blood pressure and amelioration of potassium wasting have been described in patients with renal artery stenosis and primary aldosteronism, respectively [25]. In the latter instances the potassium sparing may be due to increases in circulating plasma progesterone which accompany gestation [25]. Finally, the guarded prognosis of pregnancy in women with aortic coarctation described in the older literature does not seem to have been borne out by the report of Deal and Wooley [29] who suggested that this disease is similar in pregnant and non-gravid subjects.

**Chronic hypertension with superimposed pre-eclampsia**

Patients with chronic hypertension may experience rapid rises in blood pressure late in pregnancy, often associated with proteinuria, and there is evidence from renal biopsy material that many of these cases are due to superimposed pre-eclampsia. However such a presentation may be misleading, especially in women with pre-existing kidney disease [18]. For example in a survey of pregnancy in 89 women with underlying parenchymal renal disease [30] ‘superimposed pre-eclampsia’ was diagnosed by their physicians on clinical grounds in 12 patients and eclampsia in one, all of whom underwent post-partum renal biopsies. The characteristic glomerular changes of pre-eclampsia were present in only seven of these gravidas, including the one with eclampsia.

In our experience, a substantial number of hypertensive patients with superimposed pre-eclampsia are multiparas, who often present early in the last trimester. If their gestations are allowed to continue they manifest extremes of hypertension frequently resistant to therapy, heavy proteinuria, coagulation abnormalities, oliguria and the fetus often succumbs. In elderly multiparas who already manifest end organ damage, superimposed pre-eclampsia can be life threatening and furthermore, if these patients conceive again there is a strong possibility that this acute syndrome will recur [12].

**Late or transient hypertension**

Some women develop hypertension alone (without proteinuria) in the last trimester or in the immediate puerperium but the blood pressure normalizes by the tenth post-partum day. The outcome of such pregnancies is usually good, but the hypertensive syndrome often recurs in later gestations. When blood
pressure increases during the third trimester in nulliparous women one cannot distinguish between early pre-eclampsia in women who have not manifested other signs of the disease and the more benign late gestational hypertension. In such instances it is prudent to manage the patient as if she were pre-eclamptic.

Patients with transient hypertension probably represent women destined to develop essential hypertension later in life, analogous to women with gestational hyperglycaemia who often become frank diabetics. In essence transient pregnancy hypertension defines a population in whom close scrutiny will lead to the early detection of high blood pressure one to three decades later.

One should also be aware of two uncommon entities: 'late post-partum eclampsia' (hypertension and convulsions occurring days to weeks after delivery), the existence of which is debated [31], and 'post-partum hypertension' in normotensive gravidae [32]. The latter condition characterized by abnormal increments in blood pressure two weeks to six months after delivery, is rather benign as the blood pressure increment rarely requires treatment and usually returns to normal within one year. Of note is a syndrome resembling both of the entities described above which has recently been reported to occur in women ingesting the dopamine agonist bromocriptine, a drug commonly used to suppress lactation [33].

The incidence of hypertension complicating gestation is about 5–10 per cent of all pregnancies, and approximately 50–60 per cent of the patients have pre-eclampsia (Table II) [12,25,34]. The increased frequency of pre-eclampsia in nulliparous gravidae has already been noted [12]. Other conditions which predispose to this renal disease, chronic hypertension, extremes of age, hydramnion, fetal hydrops and alpha thalassemia. The last three conditions are often associated with early pre-eclampsia, severe disease occurring before or at mid-pregnancy.

TABLE II. Combined incidence and prevalence of hypertension in pregnancy in Brooklyn, New York Hospitals participating in the obstetric statistical co-operative study during 1979

<table>
<thead>
<tr>
<th>Hospital</th>
<th>All hypertension</th>
<th>Pre-eclampsia</th>
<th>Perinatal mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>%</td>
<td>Cases</td>
</tr>
<tr>
<td>Kings County</td>
<td>434</td>
<td>10.1</td>
<td>255</td>
</tr>
<tr>
<td>University</td>
<td>163</td>
<td>8.8</td>
<td>79</td>
</tr>
<tr>
<td>Maimonides</td>
<td>123</td>
<td>2.7</td>
<td>69</td>
</tr>
<tr>
<td>Brooklyn-Cumberland</td>
<td>267</td>
<td>6.6</td>
<td>114</td>
</tr>
<tr>
<td>Brooklyn Jewish</td>
<td>221</td>
<td>10.9</td>
<td>162</td>
</tr>
<tr>
<td>Greenpoint</td>
<td>161</td>
<td>14.1</td>
<td>145</td>
</tr>
<tr>
<td>Totals and weighted means</td>
<td>1369</td>
<td>7.8</td>
<td>824</td>
</tr>
</tbody>
</table>

From: Chesley LC [34]

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Pathophysiology of pre-eclampsia

Frank hypertension in pre-eclampsia usually occurs late in gestation. Mid-term pressures, however, while still normal tend to be higher in many (but not all) gravidas who later manifest hypertension near term than in women who will remain normotensive throughout pregnancy [12]. Therefore it appears that in many gravidas destined to manifest pre-eclampsia peripheral vascular tone may be inappropriately elevated quite early in pregnancy [9,11,35]. Thus increased surveillance of all gravidas whose second trimester diastolic levels exceed 70mmHg could lead to earlier detection of frank pre-eclampsia later in gestation.

Pre-eclamptic women may show reversal of the normal diurnal blood pressure rhythm (i.e. morning peaks and night time nadirs) so that the highest levels may occur during the night [36]. Hypertension in pre-eclampsia is characteristically labile, reflecting the intense sensitivity of the vasculature to endogenous pressor peptides and catecholamines. Whereas normotensive gravidas are extremely resistant to the pressor effects of infused angiotensin, those who will develop pre-eclampsia manifest increased pressor responsiveness to this peptide many weeks before the appearance of clinical manifestations of the disease (Figure 2) [37]. In women with chronic essential hypertension, sensitivity to All also

Figure 2. Angiotensin responsiveness in 192 primigravid women (1190 infusions). Solid circles represent normotensive pregnancies, and open circles women who eventually developed hypertension before delivery. Note that differences in the two populations were detectable by mid-pregnancy (From Gant NF et al [37])
increases prior to the development of superimposed pre-eclampsia [38]. The vasculature of pre-eclamptics is quite sensitive to infused norepinephrine and vasopressin as well [12,39]. Thus even if circulating levels of these hormones appear unaltered, their concentrations may be high in relation to the augmented reactivity of the vasculature. For example, although angiotensin II has been described both as increased and decreased in pre-eclampsia (reviewed in 12,15,25) perusal of Figure 2 demonstrates that All sensitivity in this disease increases even above that of non-pregnant women during gestational weeks 34–40. At this point, the period when most patients first manifest symptoms, even if All levels are lower than in normal gravidas (in whom all components of the renin angiotensin system increase markedly [12,15,25]), they still are greater than those of non-pregnant subjects.

The alterations of vascular sensitivity in pre-eclampsia have been ascribed to decrements in production of prostaglandins of the E and I series, and increments in thromboxane production, while changes in the levels of eicosanoids have also been linked to the coagulopathies associated with pre-eclampsia [12,15,25,40].

The role of other hormones which might affect vascular reactivity, such as catecholamines and prolactin, is either controversial or poorly understood [12,15,25]. Urinary and uterine tissue norepinephrine increase during pre-eclampsia, dopamine excretion remains at normal pregnancy values, while most investigators find plasma norepinephrine to be decreased or unaltered. There is little consensus regarding plasma prolactin, which is reported to increase, decrease or remain normal during pre-eclampsia. Also, the literature abounds with references to unknown humoral substances, and there are instances where plasma obtained from pre-eclamptics has been shown to have vasoconstrictor properties when infused in non-pregnant subjects [12,25]. Such reports, however, await confirmation and further clarification.

Factors involved in membrane transport of cations (e.g. Na-K-ATPase, Na-Li Co-transport) have been implicated in hypertension. Data concerning their involvement in pre-eclampsia have been contradictory.

Disturbances in mineral homeostasis, such as low intake or increased excretion of calcium, and magnesium deficiency have been implicated in both human and experimental hypertension. Hypertension in pregnancy, too, seems inversely related to dietary calcium intake in certain populations [41].

There is disagreement concerning the incidence and significance of clotting abnormalities [12,25]. Evidence of disordered coagulation is usually easier to elicit in patients with severe disease, but there are also instances where signs of coagulopathy predominate when hypertension is only mild or moderate. Of interest are recent reports in which early antiplatelet therapy and thromboxane inhibitors have prevented or ameliorated the syndrome [42,43].

Pre-eclampsia may also affect the liver [44], but hepatic involvement is usually mild. There is however, a variant marked by severe signs of liver dysfunction combined with marked coagulation changes. Transaminase levels often exceed 1000–2000IU, the bilirubin may be elevated, while platelet counts are frequently below 40,000mm³ and evidence of microangiopathic haemolysis is present on the blood smear [45,46]. This uncommon form is life threatening, constitutes a medical emergency, and requires prompt termination of the

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of the pregnancy. Fortunately, most patients survive with supportive care, the abnormalities abating two days to one week after evacuation of the uterus.

The genesis of the eclamptic convulsion is poorly understood, the seizures being attributed to platelet thrombi within the cerebral circulation [47], or to intense, sometimes localized vasoconstriction [44]. There is also a high percentage of frank cerebral bleeding in autopsy material from women dying of eclampsia. However, according to Sheehan and Lynch [44] most of these episodes occur after the initial convulsion.

There is a mistaken tendency to equate eclampsia with hypertensive encephalopathy. Although seizures correlate with the severity of hypertension, they may also arise when blood pressure elevations are mild and differ little from that recorded 24 hours previously. In addition, retinal exudates, haemorrhages, or papillary oedema, hallmarks of hypertensive encephalopathy, are infrequent in pre-eclampsia-eclampsia, where fundoscopic changes are minimal.

The kidney and volume homeostasis in pre-eclampsia

Glomerular filtration rate (GFR) and renal plasma flow both decrease in pre-eclampsia [12]. The decrease in filtration rate averages 30 per cent in most cases, but since renal haemodynamics are usually increased 30–50 per cent during normal gestation, GFR in pre-eclampsics is still often greater than in non-gravid women. In fact the decrement may not be appreciated if one is unaware of norms for pregnancy and that values of creatinine and urea nitrogen of only 0.9 and 15mg per cent respectively are already suspect. In this respect mean creatinine levels in a large group of gravidas with diseases severe enough to warrant post-partum renal biopsies was only 1.1mg per cent [18]. It should be emphasized however, that although functional decrements in pre-eclampsia are usually mild and reverse rapidly post-partum, an occasional patient may progress to acute renal failure.

Uric acid clearance also decreases in pre-eclampsia, and these changes may predate and be more profound that decrements in GFR, resulting in decreased urate/insulin or urate/creatinine clearance ratios [12,17]. We consider plasma uric acid values exceeding 4.5mg per cent abnormal in pregnant women, and others have demonstrated that high urate values correlate with the severity of the renal lesion (see below) as well as with fetal outcome [12,17,25].

Abnormal proteinuria also accompanies pre-eclampsia. The increment in protein excretion may be minimal or severe; in fact pre-eclampsia is the most common cause of nephrotic range proteinuria in pregnancy [18,48]. The proteinuria which qualitatively correlates with the severity of the renal lesion is usually non-selective in nature [18]. Increments in tubular proteinuria have also been described, which seems surprising because the tubules are not involved in the morphological lesion [49].

The altered renal morphology has been detailed by others [17,44] and us [18,25] elsewhere. Briefly, the glomeruli swell due to a characteristic hypertrophy of the intracapillary cells involving mainly the endothelial, and less the mesangial cells (Figure 3). These swollen cells, which contain a variety of vacuoles and lipid clusters (Table III), encroach on the capillary lumen creating the appearance of bloodless glomeruli. on occasion, the glomerular swelling results in herniation of the tuft into the initial segment of the proximal tubule, a pattern termed by Sheehan and Lynch [44] as ‘pouting’.
Figure 3. The renal lesion in pre-eclampsia: a) Micrograph of an ischaemic glomerulus. Capillary lumina are encroached upon by swollen endothelial and mesangial cells (arrow). b) Ultrastructural appearance of post-partum renal biopsy in pre-eclampsia: Myelin-like figures are frequent in the cytoplasm of swollen endothelial cells. Note the presence of electron dense deposits (arrow) which have the periodicity of fibrin at higher magnification (Courtesy of Dr BH Spargo, University of Chicago)

<table>
<thead>
<tr>
<th>Vacuoles</th>
<th>Lipid clusters*</th>
<th>Electron dense deposits</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 1+ 2+ 3+</td>
<td>Granular Tactoid Both</td>
<td></td>
</tr>
<tr>
<td>No. Women</td>
<td>19 53 18 6 17</td>
<td>26 5 6</td>
</tr>
</tbody>
</table>

*Lipid in clusters reflects either droplets, myelin figures, or cholesterol clefts. From Fisher, Luger, Spargo, Lindheimer [18]

The basement membrane is usually normal and while some authors [50,51] have claimed that mesangial proliferation leading to interposition and a 'tramline' effect occurs in this disease, this has not been our experience. Similarly, we have not seen focal glomerular sclerosis [51] in pure pre-eclampsia, and believe such changes, when present, have predated the disease.

Occasionally, small endothelial deposits (thought to represent accumulation of protein) and tactoids of fibrin or a fibrin-like material may be seen (Figure 3).
Such images may in part be due to the accumulation of several basement membrane proteins including laminin, Type IV collagen, fibronectin, and a proteoglycan in the glomeruli [50].

The tubules are usually intact. Recently a marked decrease in renin-containing cells in the juxtaglomerular apparatus has been described in post-partum biopsies from pre-eclamptics [52].

The significance of immunoglobulins and fibrin deposition present in the glomeruli of pre-eclamptic patients is disputed. We find IgG, IgM, as well as evidence of fibrin only in a minority of the cases [18].

The ability to excrete sodium is decreased in pre-eclampsia, but the degree of impairment varies, and even severe disease can occur in the absence of oedema [12,14,15,25]. Of importance is that even when interstitial oedema is present, plasma volume is decreased compared to that of normal gravids, and haemoconcentration occurs [12,14,15,53].

The decreased plasma volume accompanied by sodium retention in pre-eclampsia underlies a major controversy concerning the management of the disease. Some authorities believing that the decreased intravascular volume is a primary event responsible for the rise in blood pressure (for example placental hypoperfusion may result in secretion of a vasoconstrictor substance, or intravascular volume depletion may lead to excessive instead of compensatory catecholamine release) avoid diuretics and even recommend vascular volume expansion as therapy. Others state that decreases in volume are secondary to vasoconstriction. They advocate use of diuretics in conjunction with vasodilating drugs and caution against treatment with volume expanders, stating that the latter therapy may aggravate the hypertension or lead to pulmonary oedema. Data in the literature currently favour the first view. First, it appears that the decrement in blood volume precedes the occurrence of hypertension [12, 14,53,54]. Also, when pre-eclamptics are studied prior to therapeutic intervention, cardiac output, central venous and pulmonary capillary wedge pressure are low and seem to vary inversely with the severity of the disease [55,56].

Management

Management of the hypertensive disorders of pregnancy remains an area of considerable controversy. For example, in the United States most academic obstetricians condemn the use of diazoxide combined with diuretic administration (usually frusemide) when treating acute rises in blood pressure near term, while many nephrologists advocate such therapy [25,57,58]. Other disagreements include the level to which the blood pressure should be decreased acutely, and what constitutes appropriate anti-eclamptic therapy. This section outlines our views.

Suspected pre-eclamptics should be hospitalized, an approach which diminishes the frequency of convulsions and other consequences of diagnostic error. Cunningham and colleagues [58,59] have shown the efficacy of such an approach, as in their experience ‘prophylactic’ hospitalization delays early termination of pregnancy, greatly improves fetal outcome, and actually reduces the extremely high costs incurred by very premature infants in intensive care nurseries.
In general, induction is the therapy of choice near term, whereas attempts to temporize can be made if pregnancy is at an earlier stage. If a decision is made to temporize there are several antihypertensive drugs that appear safe and effective during gestation [60] (Tables IV and V). When severe hypertension persists following 24–48 hours of treatment, delivery is indicated regardless of the stage of gestation, since the mother is at risk and further attempts at temporization rarely save the fetus [62]. Advances in neonatology are such that most infants weighing 1500g or more survive, and they are better off in a premature nursery than in the pre-eclamptic’s womb. Clotting or liver abnormalities, signs of impending convulsions, and deteriorating renal function, are indications for terminating the pregnancy.

**TABLE IV. Guidelines for treating severe hypertension near term or during labour**

| I. | Degree to which blood pressure should be decreased is disputed. Levels between 90–105mmHg are recommended (see text). |
| II. | a. Parenteral hydralazine is the drug of choice. Use low doses (start with 5mg, then 5–10mg q 20–30 minutes) in order to avoid precipitous decreases. Side-effects include tachycardia and headache. Neonatal thrombocytopenia reported. |
| | b. Diazoxide recommended for the occasional patient refractory to hydralazine. Use 30mg miniboluses as maternal vascular collapse and death have been associated with the customary 300mg dose. Side-effects include arrest of labour and neonatal hyperglycaemia. |
| | c. Do not use nitroprusside (fetal cyanide poisoning reported in animals), ganglion-blocking agents (meconium ileus), or loop diuretics (e.g. frusemide) (see text). (However, in final analysis, maternal wellbeing will dictate choice of therapy). |
| III. | Parenteral magnesium sulphate is drug of choice in the United States for preventing impending eclamptic convulsions. Therapy should continue 12 (and sometimes 24) hours into the puerperium as one-third of pre-eclamptics convulse post-partum. |

Modified from Lindheimer, Katz [61]

**Antihypertensive therapy**

Some investigators believe that reductions in maternal blood pressure tend to decrease uteroplacental perfusion (which is already compromised in pre-eclampsia) and caution against large or precipitous decreases in mean arterial pressure [12,25,63]. Others believe that uteroplacental blood flow is appropriately autoregulated and prefer a more aggressive approach in reducing blood pressure [12,25,57]. Until this controversy is resolved we prefer an intermediate approach (Table IV): Antihypertensive drugs are withheld when maternal pressure is only mildly elevated, and close maternal scrutiny and electronic fetal monitoring are instituted. Diastolic levels at or above 105mmHg are treated with parenteral hydralazine. This drug is administered cautiously and is successful in most instances, while diazoxide (in small 30mg boluses) is reserved for the occasionally resistant case. Preliminary successes recently reported using calcium channel blockers, bear watching, as these agents may have less side-effects than hydralazine [64].
<table>
<thead>
<tr>
<th>Category</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_2$ Receptor Agonists</td>
<td>Methyldopa (0.5–3g/d) is most extensively used in the US; safety and efficacy supported in randomized trials. Neonatal tremors have been reported; other side-effects as in non-gravid population. Trials with clonidine in progress. Embryopathy has been described in animals, and this drug is not currently recommended.</td>
</tr>
<tr>
<td>$\beta$ Receptor Antagonists</td>
<td>These agents, currently undergoing extensive testing, appear safe and efficacious. Atenolol (50–100mg/d), metoprolol (50–225mg/d), propanol (40–240mg/d) used most frequently to date. Fetal and neonatal bradycardia and hypoglycaemia reported, and animal data suggest the possibility of a decreased ability of the fetus to tolerate hypoxic stress.</td>
</tr>
<tr>
<td>$\alpha$ and $\beta$ Receptor Antagonists</td>
<td>e.g. labetalol – currently undergoing extensive testing, appear as effective as methyldopa. Possible association with premature separation of placenta under investigation.</td>
</tr>
<tr>
<td>Arteriolar Vasodilators</td>
<td>Hydralazine (50–200mg/d) used frequently as adjunct therapy with methyldopa and $\beta$ receptor antagonists. Fragmentary experience with minoxidil, thus not recommended at present.</td>
</tr>
<tr>
<td>Converting Enzyme Inhibitors</td>
<td>Captopril associated with fetal death in several animal species. Do not use in pregnancy.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Most authorities discourage their use, though some continue these medications if prescribed prior to gestation. We would prescribe diuretics when blood pressure control remains poor despite other agents, fetus is immature, and pregnancy termination is the only alternative.</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Calcium-channel blockers and serotonin antagonists (e.g. Ketanserin) are currently under investigation. Use of ganglion-blocking agents (causes meconium ileus) and nitroprusside (see text) should not be utilized.</td>
</tr>
</tbody>
</table>

From: Lindheimer, Katz [61]

Use of diuretics (e.g. frusemide) is condemned by most authorities [12,25], but some investigators [57] support such therapy. Since pre-eclamptics are susceptible to intra-partum hypotension and puerperal vascular collapse [12,25], we too are against their use.

Parenteral magnesium sulphate is the drug of choice in North America for impending convulsions or frank eclampsia, while anticonvulsants such as chloromethiazole and diazepam are used more frequently in Europe, Australia and Japan. This controversy and the reasons for our preference of magnesium sulphate is beyond the scope of this review and are discussed elsewhere [12,25, 34,58,65–67].

Monitoring of central venous or pulmonary capillary wedge pressure may be required in extremely severe and complicated cases especially during operative procedures. It is our opinion, however, that Swan-Ganz catheterization, which is not without morbidity [68], is currently overused in these patients. Epidural
block should preferably be avoided (or if used, should be administered by an
experienced obstetrical anaesthetist) as this form of anaesthesia in pre-eclamptics
is associated with sudden and marked falls of blood pressure and occasional
with vascular collapse.

Recently, volume expansion as a treatment modality has been repopularized.
Use of such therapy has been prompted by observations that pre-eclamptic
women show haemoconcentration, often manifest a low cardiac output with
decreased central venous and pulmonary wedge pressures, and that haemo-
dilution precedes the occasional improvement pre-partum. Of interest, too, are
reports by Gallery and colleagues [14,69] that rapid intravascular volume
repletion with commercial stable protein substitute decreased the blood pressure
of third trimester hypertensives for periods of 24 hours or more. Such results
appear impressive, but the majority of patients studied had mild disease. We
currently do not recommend such therapy for the following reasons: Myo-
cardial performance may be compromised in severe pre-eclampsia and volume
expansion, especially with saline, may enhance vascular reactivity. Furthermore,
infusion of crystalloids alone decreases the oncotic pressure, which is already
low in most pre-eclamptics (Figure 4) [70]. Since central volumes and pressures
tend to rise post-partum [71], the liberal use of saline may result in decrements
in oncotic levels to a point where pulmonary and cerebral oedema may then
ensue.

![Figure 4. Intra- and post-partum plasma oncotic pressure in nine normotensive women
(upper curve) and in nine patients with severe pre-eclampsia (lower curve). From:
Zinaman, Rubin, Lindheimer [70]](image-url)
The non-pre-eclamptic hypertensive

The increased risks associated with pregnancy in women with chronic hypertension have already been cited [12,25,34]. Complications include superimposed pre-eclampsia, placental abruption, acute tubular and cortical necrosis [72], intrauterine growth retardation, and mid-trimester fetal death. Such events correlate with age of the gravida and the duration of her high blood pressure. Thus it is not surprising that the most vulnerable group are chronic hypertensive women over the age of 30 and/or those with end organ damage. On the other hand, the majority of women with essential hypertension (approximately 85%) have successful gestations [12].

Women with chronic hypertension may experience mid-trimester reductions in blood pressure that actually exceed those observed in normotensive gravidas. Failure of a decrement to occur, or actual increments in blood pressure during mid-pregnancy are poor prognostic signs; it is the combination of chronic hypertension and pre-eclampsia that seems responsible both for the increased fetal loss and for most cases of cerebral haemorrhage in pregnancy [12]. This is why such patients should be promptly hospitalized, the hypertension controlled, and the gestation terminated rapidly when risk signs appear.

There is a controversy as to whether chronic hypertensive gravidas with only mild blood pressure elevations should be treated [60,73,74]. We withhold therapy unless diastolic levels are 15mmHg above borderline: That is we will consider treatment when levels exceed 90mmHg in the second and 95mmHg in the third trimester. The use and safety of antihypertensive agents in gestation, and a discussion of several controlled trials have been reviewed by Redman [60] and are summarized in Table V. Unfortunately, many of the reported studies have been limited in scope and often performed at the request and with the support of pharmaceutical companies. There is thus a critical need for large multicentre clinical trials using the combined expertise of obstetricians, hypertension specialists, epidemiologists and statisticians.

Remote prognosis

The remote cardiovascular prognosis of pre-eclampsia is disputed. Some authors claimed that pre-eclampsia increased the incidence of chronic hypertension and cardiovascular deaths later in life, while others suggested that pre-eclampsia per se had no influence on these events. The signal study in this area seems to be that of Chesley and his associates, who have periodically re-examined 267 of 270 women who survived eclampsia during the years 1931 to 1951 [12,24]. Because their last report included the years 1973 and 1974 some of these patients have been observed for over 40 years [75]. A special feature of this study is that it included only women with eclampsia; in the absence of a renal biopsy, a convulsion strongly suggests that the patient had pure or superimposed pre-eclampsia. Caucasian women convulsing as nulliparas had a remote mortality rate and blood pressure profile similar to that of age-matched unselected women. However, in those who convulsed as multiparas, the remote mortality was substantially increased, and these women had higher blood pressures than age-matched
subjects in several large epidemiological studies. In addition, the prevalence of hypertension was greater in eclamptic primiparas if any of their subsequent gestations was complicated by hypertension. Chesley concluded that eclampsia was not a predictive sign nor a cause of remote hypertension, and that hypertensive gestations in multiparas were probably predictive, but not the cause, of future essential hypertension. Similar conclusions were reached by Bryans [76] who studied black gravidas, as well as by our group [18], who investigated black women with renal biopsy evidence of pre-eclampsia.

Acknowledgments

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