Clinical Conference

Hypertension in Pregnancy

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High blood pressure, which complicates approximately 10% of all pregnancies, remains a major cause of morbidity and mortality for both mother and fetus. A relative paucity of investigative data, as well as the frequent difficulty in making an etiological diagnosis by clinical criteria alone, may be among the reasons why there are many conflicts about the management of hypertension during pregnancy. This clinical conference summarizes current concepts regarding the hypertensive disorders of gestation, focusing on the most dangerous cause, preeclampsia-eclampsia. It further highlights a recent report of the Working Group on High Blood Pressure in Pregnancy convened by the National High Blood Pressure Education Program at the National Heart, Lung, and Blood Institute (the Consensus Report). Among the Working Group's most interesting recommendations in controversial areas were a return to the classification schema suggested by the American College of Obstetricians and Gynecologists in 1972, use of the fifth Korotkoff sound to determine diastolic blood pressure levels, and institution of treatment with antihypertensive drugs for sudden elevations of blood pressure near term to diastolic levels greater than or equal to 105 mm Hg or for levels of 100 mm Hg or higher in pregnant women with chronic hypertension. The Consensus Report further recommended parenteral hydralazine and methyldopa as the drugs of choice for the acute hypertensive crisis and management of chronic hypertension, respectively, based on the long histories of safe use of these agents in gravidas. Parenteral magnesium sulfate remained the preferred therapeutic approach for avoiding or treating the convulsive complication, eclampsia, but the Working Group underscored the need for controlled trials of magnesium's efficacy. Finally, they noted that diuretics should be avoided in preeclampsia, but that these drugs can be continued during gestation if taken before conception, and may be prescribed to pregnant women with chronic hypertension who appear overly salt sensitive. (Hypertension 1993;22:127-137)

KEY WORDS • preeclampsia • eclampsia • hypertension, pregnancy-induced

Hypertension, which complicates approximately 10% of all pregnancies, remains a major cause of both fetal and maternal morbidity and mortality, the most serious problems being associated with a disorder peculiar to pregnancy, preeclampsia-eclampsia. (Space considerations limit citations; the reader is invited to consult References 1 through 6 for a more extensive bibliography.) Advances in maternal care and newer insights into pathophysiology have greatly reduced the incidence of maternal and fetal deaths (although to a lesser degree in the underdeveloped regions of the world), but large gaps still exist in our knowledge, as well as disagreements over managing pregnant women with hypertension. This conference, devoted to high blood pressure in pregnancy, will focus primarily on preeclampsia, highlighting the conflicts surrounding its management. Also, the recently reported recommendations of the Working Group on High Blood Pressure in Pregnancy, convened by the National High Blood Pressure Education Program (NHBPEP), will be summarized. I was privileged to be a member of this group, in which obstetricians and internists reached agreement, perhaps for the first time, on a number of controversial issues.7

Case Examples

I will digress from the customary inclusion of a single but detailed case report that serves to introduce the many facets and ramifications of the subject to be discussed. Instead, let me introduce the complexity of my topic by briefly summarizing three different pregnancies which illustrate that by clinical criteria alone one is never certain of the etiology of hypertension complicating pregnancy.

Case 1

A 22-year-old primigravida developed hypertension, edema, and proteinuria during her 18th gestational week and was transferred to Chicago Lying-in Hospital from an outlying facility 2 weeks later. She had no previous or family history of high blood pressure or renal or cardiac disease. Pertinent physical findings included a blood pressure of 180/120 mm Hg and ankle edema (3+). Laboratory results revealed the following serum levels: creatinine, 1.1 mg/dL (97 μmol/L); urea nitrogen, 17 mg/dL (6.1 mmol/L); and uric acid, 6.5

Dr Lindheimer was an invited speaker at the Cardiovascular Center, College of Medicine, University of Iowa, Iowa City, October 12, 1992.

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FIG 1. Light micrograph of two glomeruli (original magnification ×240) from patient 1 shows marked sclerotic changes and accumulation of hyalin material in Bowman's space typical of the McManus lesion seen in patients with severe hypertension. Not shown are marked sclerotic changes in the arterioles throughout the kidney.

mg/dL (387 μmol/L). Serum albumin was 2.1 g/dL (21 g/L), and 24-hour protein excretion was 5.6 g. Complement levels and antinuclear immunofluorescence were normal.

Attempts to control her blood pressure with parenteral hydralazine and oral methyldopa were unsuccessful, diastolic levels frequently exceeding 110 mm Hg, and her pregnancy was terminated 48 hours later. Six weeks postpartum her blood pressure range was 120-130/80-90 mm Hg, and serum creatinine and urea nitrogen were 0.8 mg/dL (71 μmol/L) and 9 mg/dL (2.3 mmol/L), respectively. Her 24-hour protein excretion was 700 mg. A renal biopsy was performed.

Clinical impression was that of preeclampsia, probably superimposed on mild essential hypertension, and if there were renal lesions, they were expected to be minimal, perhaps mild nephrosclerosis and perhaps resolving lesions characteristic of preeclampsia (see below). Fig 1, however, demonstrates a markedly sclerotic glomerulus demonstrating ischemic obliteration (the McManus lesion) usually observed in subjects with sustained severe hypertension. There were also striking lesions in the arterioles throughout the biopsy specimen but no evidence of resolving preeclampsia. Having reviewed the biopsy, most would counsel this woman that she is likely to develop high blood pressure in a subsequent gestation, although we cannot predict if its presentation will be as severe.

Case 2

A 16-year-old with no history of hypertension was admitted to Chicago Lying-in Hospital at term with a blood pressure of 140/100 mm Hg and qualitative proteinuria (1 to 2 or plus). During labor, diastolic levels increased to 120 mm Hg, blood pressure normalizing rapidly in the immediate puerperium to 120/80 mm Hg. All observers considered this presentation to be archetypical of preeclampsia in a teenaged gravida. Her postpartum renal biopsy, however, revealed sclerosis in several glomeruli, as well as in the arterioles (Fig 2), but no evidence of intracapillary cell swelling characteristic of preeclampsia.

The biopsy finding in this young girl is the initial indication that she is, or will become, chronically hypertensive and that high blood pressure may appear in subsequent pregnancies. This case resembles those described by Smythe et al in 1964 of young primiparas presenting with hypertension in late gestation whose blood pressure normalized postpartum; renal biopsies showed nephrosclerotic lesions only. Peyser and Fisher and their respective colleagues have demonstrated that most of these women will have developed sustained essential hypertension when examined a decade later.

Case 3

A 22-year-old primigravida was admitted to Chicago Lying-in Hospital during gestational week 34 with hypertension and leg edema. Pertinent history revealed recurrent streptococcal pharyngitis and hypertension in her mother. Her blood pressure was 170/110 mm Hg, and she had marked leg edema (4+). Laboratory results revealed serum creatinine and uric acid of 1.1 mg/dL (97 μmol/L) and 8.4 mg/dL (495 μmol/L), respectively. Her serum albumin was 2.4 g/dL (24 g/L), and 24-hour protein excretion was 13.6 g. Glucose, complement levels, and antinuclear immunofluorescence were normal. During the first hospital week, her blood pressures ranged between 150/100 and 170/100 mm Hg, and she continued to be heavily proteinuric (range, 5 to 11 g/d). One week later, a healthy but small for gestational age, 1500-g infant was delivered by cesarean section because of fetal distress.
A renal biopsy was performed on the sixth day of the puerperium. Three months postpartum, her blood pressure measured 140/66 mm Hg, and the serum creatinine level was still 1.1 mg/dL (97 μmol/L); a 24-hour urine collection contained 1.9 g of protein. The impression now was that her pregnancy complication was not that of preeclampsia (at most superimposed) but was that of another underlying renal disorder. Review of the biopsy, however, revealed morphological lesions consistent with preeclampsia only (see below). Ten months postpartum, still normotensive, her creatinine level was 0.7 mg/dL (62 μmol/L), and 24-hour protein was reported as negative.

The above examples were taken from the case histories of 176 women biopsied postpartum at Chicago Lying-in Hospital between 1958 and 1976.10 In almost every instance, the clinical impression had been preeclampsia (or "toxemia"), but this diagnosis was incorrect in one quarter of the primiparas and in the majority of the multiparas (Table 1); in addition, 31 patients, a surprisingly large number, had unsuspected parenchymal renal disease. I have begun this conference with these case examples and biopsy data primarily to underscore some of the initial problems a clinician faces when managing a pregnant woman who suddenly develops hypertension. These examples are also meant to alert one to the pitfalls inherent in interpreting reports in which diagnosis is based on clinical criteria alone. Most suspect are series in which patients described as preeclamptic or toxemic were multiparas.

### Interpreting Blood Pressure in Normal Gestation

Blood pressure normally decreases early in pregnancy, and by midtrimester diastolic levels are often 10 mm Hg lower than postpartum measurements.1-4 Pressures then increase gradually, approaching nonpregnant values near term, and some have even recorded transient rises in the immediate puerperium.2,11 Because cardiac output is also elevated, the decrease in blood pressure is primarily due to a marked decrement in peripheral vascular resistance. Some gravidas appear more sensitive than nonpregnant women to postural

### Table 1. Renal Pathology in 176 Hypertensive Patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Primigravida</th>
<th>Multipara</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia*</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>
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</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 was demonstrated on biopsy.
influences on blood pressure. They are more prone to syncope when standing in place, and late in gestation, they may develop a hypertensive syndrome, associated with the assumption of a supine position, the decrease in pressure being ascribed to the enlarged uterus obstructing the return of blood through the vena cava.  

There is considerable disagreement on how to measure blood pressure in pregnant women. Several national and international groups (eg, the World Health Organization) recommend use of Korotkoff phase IV (muffling) as the determinant of diastolic levels. However, phase IV may overestimate intra-arterial pressure by 7 to 15 mm Hg and appears more difficult to determine accurately. Furthermore, most health personnel in the United States are trained to recognize phase V (disappearance) as the sound by which they determine diastolic pressure in nonpregnant populations. These considerations led the NHBPEP Working Group to recommend use of Korotkoff phase V in pregnancy, reserving the fourth component for the 10% or fewer gravidae in whom there is a large discrepancy between muffling and disappearance (with the latter in Table 2 at times approaching zero). In addition, suggestions in the literature that pressure be measured with gravidae positioned in lateral recumbency were rejected as impractical in an outpatient setting, where quiet sitting remains the preferred approach.

The Working Group further retained the definition of hypertension in pregnant women as increments in systolic and diastolic levels of 30 and 15 mm Hg or greater or a diastolic pressure of 90 mm Hg or greater. However, given the physiological decrement in blood pressure described above, many consider the suggested diastolic cutoff to be too high, based on several studies demonstrating that diastolic levels of 70 mm Hg or greater or mean arterial pressures of 85 mm Hg or greater in early or midgestation are often associated with frank hypertension near term. Thus, I find it prudent to observe more carefully those pregnant patients whose diastolic pressures exceed 75 and 85 mm Hg in the second and third trimesters, respectively.

Classification of the Hypertensive Disorders of Pregnancy

The case examples should have revealed one reason why classification has been a confusing area in regard to the hypertensive disorders of gestation. Many schemes have been proposed, some complex and detailed, and perusing the literature one finds a multitude of terms to describe a single entity such as preeclampsia (eg, toxemia, EPH gestosis, and pregnancy-induced or pregnancy-associated hypertension). The Working Group recommended the precise and practical terminology proposed in 1972 by the American College of Obstetricians and Gynecologists. In it, high blood pressure in pregnancy is considered in only four categories: preeclampsia-eclampsia, chronic hypertension (of whatever cause), preeclampsia superimposed on chronic hypertension, and transient hypertension.

Preeclampsia, especially when superimposed on another hypertensive disorder, poses the greatest threat to both the mother and unborn child and is described below. Most gravidae with chronic hypertension have mild disease of the "essential" variety, and their gestations are usually uncomplicated except for a greater likelihood of developing superimposed preeclampsia. However, the hypertension rarely may be secondary to specific causes, such as renal disease, several endocrine disorders, renal artery stenosis, or hypoplastic aorta, as well as an emerging group of patients whose high blood pressure seems related to cocaine abuse. Some women with secondary forms of hypertension do poorly in pregnancy. Cushing's syndrome may be exacerbated, and fetal prognosis is guarded. Some collagen disorders, notably scleroderma and periarteritis nodosa, are also associated with poor fetal outcomes, as well as aggravated and sometimes fatal hypertension in the mother, and we have observed fatal cerebral hemorrhage in gravid cocaine abusers. Pheochromocytoma also can be lethal during gestation, especially if unrecognized, but when diagnosed in a timely fashion, this disorder can be managed pharmacologically until delivery, followed by resection of the tumor if operable. Incidentally, pregnancy has been reported to ameliorate the potassium loss due to primary hyperaldosteronism and to reduce blood pressure in women with renal artery stenosis.

Transient hypertension develops after midpregnancy, often near term or in the puerperium. Blood pressure elevations are usually mild, and gestational outcome is hardly affected. Pressure normalizes postpartum, but hypertension frequently reoccurs during subsequent pregnancies, and such women are believed to be destined to have essential hypertension later in life.

(When late pregnancy hypertension occurs in nulliparas, differentiation between preeclampsia and transient hypertension may be difficult and only apparent retrospectively; in such instances, it is prudent to manage the patient as preeclamptic.) The typically benign prognosis in this group was one reason the Working Group suggested abandoning the term pregnancy-induced hypertension (PIH), which fails to differentiate transient hypertension of pregnancy from the more ominous preeclampsia.

The Clinical Spectrum of Preeclampsia-Eclampsia

Preeclampsia occurs primarily in nulliparas, usually after midgestation and often near term. This disease, characterized by hypertension, proteinuria (≥300 mg/24 h or ≥2+), edema, and at times abnormal liver function, coagulation, or both, may progress to a convulsive phase termed eclampsia, a dramatic and life-threatening event. The eclamptic fit is often preceded by premonitory symptoms and signs including severe headaches, visual disturbances, hyperreflexia, epigastric pain, and hemoconcentration (Table 2); but on occasion, convulsions appear suddenly and without warning in an asymptomatic woman who appears to have only mild hypertension. In fact, the term eclampsia is derived from the Greek word ekklampsis, which means "lightning" or "a shining forth." Thus, attempts to categorize preeclampsia as mild or severe, based on criteria such as blood pressure levels, amount of proteinuria, and several other signs and symptoms, are misleading. This disease, regardless of apparent severity, always presents a potential danger to mother and fetus, although the signs and symptoms in Table 2 are particularly ominous. This is also why, when faced with diagnostic dilemmas, it is always prudent to "overdiag-
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TABLE 2. Ominous Signs and Symptoms in Women With Preeclampsia

Preeclampsia is always potentially dangerous but particularly ominous may be

- Blood pressure ≥160 mm Hg systolic or ≥110 mm Hg diastolic.
- Proteinuria of new onset at a rate of ≥2 g/24 h or ≥100 mg/dL (2+) in a random urine.
- Increasing serum creatinine levels (especially >177 μmol/L [2 mg/dL], unless known to be elevated previously).
- Platelet count <10×10^9/L, evidence of microangiopathic hemolytic anemia (eg, schistocytes and/or increased lactic acid dehydrogenase and direct bilirubin levels).
- Upper abdominal pain, especially epigastric and right upper quadrant pain.
- Headache, visual disturbances, or other cerebral signs.
- Cardiac decompensation (eg, pulmonary edema). Usually associated with underlying heart pathology or chronic hypertension.
- Retinal hemorrhages, exudates, or papilledema. (These are extremely rare in the absence of other indicators of severity and when present almost always indicate underlying chronic hypertension.)
- Presence of intrauterine growth retardation and decreasing urine volumes, which require added vigilance.

Modified from Cunningham and Lindheimer.

Causes of the enhanced vascular reactivity are obscure, but data support several interesting hypotheses. Some researchers consider the vasoconstriction the result of a relative or absolute deficiency of vasodilating prostaglandins. In this respect, there is evidence that renal excretion of prostacyclin metabolites or the production of this eicosanoid by the placenta or vasculature of preeclamptic women is decreased compared with that of normotensive pregnant women. There are also claims that thromboxane levels are increased in this disease. Another hypothesis is that preeclampsia is caused by vascular endothelial cell dysfunction, perhaps due to increases in circulating lipid peroxidases or in substances that influence cytokine production. Several other postulates—such as events during placentation; immune and genetic factors; and the roles of natriuretic and calcium-related hormones, alterations in or inhibitors of various membrane transport systems, and endothelin, all under study—are discussed elsewhere.

The kidney is one organ historically linked to and usually affected by preeclampsia. The kidneys increase in weight and size and reveal a characteristic lesion termed glomerular endotheliosis (Fig 3). There is diffuse enlargement of the glomeruli due not to hypercellularity but to swelling of the intracapillary cells (mainly endothelial but mesangial as well). These cells encroach on the lumina, giving the appearance of a bloodless glomerulus. The significance of immunoglobulins and fibrinlike deposits in the glomerular lesions of preeclamptic women is disputed. More recently, focal segmental glomerular sclerosis (FSGS) has been described in association with preeclampsia and has been claimed to be a consequence of the disease (see Reference 51). This finding, if confirmed, would alter the generally benign prognosis of pure preeclampsia and would suggest that clinicians may not have been sufficiently aggressive in controlling the rise in blood pressure (or have used antihypertensive therapy that failed to reduce glomerular pressure, which conceivably may be quite elevated in this disease). This concept also is disputed, but our own biopsy experience is consistent with the view that FSGS, when present, antedated conception or was due to hemodynamic factors present earlier in pregnancy. Such conclusions are consistent with the benign remote prognosis of pure preeclampsia, for FSGS lesions represent glomerular “scars” that are not apt to disappear spontaneously.

The Pathophysiology of Preeclampsia-Eclampsia

Current concepts of the pathophysiology of preeclampsia are detailed in several texts and reviews. There is still controversy over whether the cardiac output is normal (for pregnancy), decreased, or increased early in this disorder or even before overt manifestation of the hypertension. However, once established, the disease is usually associated with a decrease in cardiac output, the high blood pressure being the result of marked increments in peripheral resistance, especially compared with the vasodilation of normal pregnancy. The hypertension is often quite labile, reflecting the increased sensitivity of the vasculature to endogenous pressor hormones and representing a reversal of the vasopressor resistance (primarily to angiotensin) characteristic of normal gestation.
The enlarged ischemic glomeruli may be one reason for the 25% or higher decrease in glomerular filtration found in most preeclamptic women. However, because renal hemodynamics increase 35% to 50% in normal gestation, glomerular filtration rate may actually remain at or above nonpregnant levels. Thus, a serum creatinine level of 1 mg/dL (88 μmol/L), normal in nongravid populations, may actually indicate substantial dysfunction in preeclampsia. Furthermore, although unusual, some patients progress to acute tubular and even cortical necrosis.

The clearance of uric acid also decreases in preeclampsia, often early in its course and to a greater degree than glomerular filtration rate. Proteinuria, although usually minimal to moderate, can reach the nephrotic range. Finally, sodium excretion is compromised, leading to edema in some but not all preeclamptic women. It is of note, however, that even when edema is marked, plasma volume is decreased compared with normal gestation, the capillary wedge pressure may be normal or decreased, and there may be substantial hemoconcentration. In fact, some of the most severe cases occur in “dry” preeclamptic women.

The Prevention of Preeclampsia

Several approaches to the prevention of preeclampsia have been proposed and include salt restriction (and even prophylactic diuretics) and most recently low-dose aspirin and calcium supplementation. There is no evidence that restricting dietary sodium modifies the incidence or severity of preeclampsia, and nutrition advice to pregnant women stresses the importance of adequate sodium intake. In addition, a meta-analysis of randomized studies of more than 7000 gravidas failed to uncover differences in the incidence of hypertension with proteinuria (presumably preeclampsia) between women who received prophylactic diuretics and untreated control subjects.

Low-dose aspirin, 60 to 80 mg daily, starting shortly after gestational week 12, has recently been suggested as an approach to preventing preeclampsia. This is because at low doses aspirin primarily inhibits platelet thromboxane, sparing endothelial cell prostacyclin production, and it is hypothesized that this prevents both vasoconstriction and enhanced intravascular clotting. A meta-analysis (Table 3) of 13 trials performed primarily in “high-risk” patients revealed a significant reduction in the incidence of proteinuric hypertension. Furthermore, as of early 1993, several large randomized multicenter trials, including both “high-risk” and “low-risk” women, were nearing completion. Although some currently recommend the cautious use of prophylactic aspirin in high-risk populations (eg, among women whose previous pregnancies were complicated by early onset, especially those with HELLP-like syndromes, and who may be at risk for recurrent fetal death or severe intrauterine growth retardation), I suggest awaiting the results of these trials, especially in low-risk populations in which the benefit of use has not been demonstrated and aspirin is not a completely innocuous drug.

Insufficient dietary calcium intake has also been suggested as a cause of high blood pressure in pregnancy based on reports that hypocalciuria and perhaps abnormalities in ionized and intracellular calcium, parathyroid hormone, and vitamin D levels have been found in preeclampsia. Furthermore, reductions in the incidence of hypertension have been noted during several trials, one quite large, in which supplemental calcium was given to gravidas. The effects were minimal, however, and one should await the results of a large randomized multicenter study sponsored by the National Institute of Child Health and Development that began in 1992. One reason for this caution is that gravidas are normally hypercalciuric, and such a prophylactic approach could conceivably provoke renal stone formation in susceptible individuals.

Managing Preeclampsia-Eclampsia

When preeclampsia is suspected, consider hospitalization, an approach that diminishes the likelihood of convulsions, reduces the consequence of diagnostic error, and may improve fetal outcome. Near term, induction of labor should be undertaken, but temporization can be considered when the fetus is very immature. Delivery, however, is indicated regardless of ges-


<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental n</th>
<th>Control n</th>
<th>Odds ratio (95% CI)</th>
<th>Graph of odds ratios and confidence intervals</th>
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<tr>
<td>Wallenburg et al (1986)</td>
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<td>7/31 22.58</td>
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<tr>
<td>Sibal et al (1989)</td>
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<td>0/10 0.00</td>
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<td>Uzan et al (1990)</td>
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<td>8/73 10.96</td>
<td>0.24 (0.07-0.78)</td>
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<td>Benigni et al (1989)</td>
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<td>0/16 0.00</td>
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<tr>
<td>Railton et al (1988)</td>
<td>4/29 13.79</td>
<td>4/14 28.57</td>
<td>0.39 (0.08-1.95)</td>
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<tr>
<td>Dekker (1989)</td>
<td>0/3 0.00</td>
<td>1/5 20.00</td>
<td>0.14 (0.00-6.82)</td>
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<tr>
<td>Roberts et al (1990)</td>
<td>1/9 11.11</td>
<td>3/12 25.00</td>
<td>0.42 (0.05-3.63)</td>
<td></td>
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<tr>
<td>Typical odds ratio</td>
<td></td>
<td></td>
<td>0.20 (0.11-0.36)</td>
<td></td>
</tr>
</tbody>
</table>

Modified from Collins.34

There is controversy on when to treat and how aggressively to lower blood pressure, especially when levels rise rapidly near term.3-4 The Working Group advised beginning treatment when diastolic levels reach 105 mm Hg or higher, but some authorities permit withholding antihypertensive agents until these values reach 110 mm Hg.63 The ideal antihypertensive drug in these circumstances is one that will reduce blood pressure in a controlled manner and avoid precipitous falls that might compromise placental perfusion. The Working Group recommended parenteral hydralazine, a drug that has been used in pregnant women safely for several decades and one with which most obstetricians have considerable experience (Table 4). Given carefully, it will successfully lower pressure in most instances, surprisingly low doses being required to control pressure. Several alternatives are listed in Table 4. The Working Group's Consensus Report7 advised against administering diuretics, especially those of the potent "loop" varieties.

There is disagreement on the approach for preventing and managing convulsions, which is not surprising because the cause of eclampsia remains unknown.1-4,24 Magnesium sulfate remains the therapy of choice of obstetricians in North America, whereas neurologists and many European physicians recommend phenytoin and a variety of other anticonvulsants, including benzodiazepine.1-4,64-66 The Working Group endorsed paren-

### Table 4. Guidelines for Treating Severe Hypertension Near Term or During Labor

**Regulation of blood pressure:**
The degree to which blood pressure should be decreased is disputed. The Working Group's Consensus Report recommends maintaining levels between 90 and 105 mm Hg (see text).

**Drug therapy:**
1. Hydralazine administered intravenously is the drug of choice. Start with low doses (5 mg IV bolus), then administer 5 to 10 mg every 20 to 30 minutes to avoid precipitous decreases. Side effects include tachycardia and headache. Neonatal thrombocytopenia has been reported.
2. Diazoxide is recommended for the occasional patient whose hypertension is refractory to hydralazine. Use 30-mg miniboluses because precipitous hypotension may result with higher doses. Side effects include arrest of labor and neonatal hypoglycemia.
3. Experience with labetalol is growing, and some use this agent instead of diazoxide as a second-line drug (see also Table 5).
4. Favorable results have been reported with calcium channel blockers. However, if magnesium sulfate is being infused, the magnesium ion may potentiate the effect of the calcium channel blockers, resulting in precipitous and severe hypotension.
5. Refrain from using nitroprusside, because fetal cyanide poisoning has been reported in animal models. However, in the final analysis, maternal well-being will dictate therapy choice.

The Working Group retained parenteral magnesium sulfate as the drug of choice for preventing impending eclamptic convulsions. Therapy should continue for 12 to 24 hours into the puerperium, because one third of patients with eclampsia have their convulsion after childbirth.

teral magnesium sulfate but took care to note that, although the successful use of this agent has been documented in several large series, the efficacy of magnesium has never been evaluated in a definitive controlled trial. Subsequently, several limited studies comparing magnesium sulfate and phenytoin have appeared, and in 1992, the World Health Organization began a large multicenter trial designed to compare the efficacy of magnesium sulfate with that of diazepam.

Invasive hemodynamic monitoring using a pulmonary artery catheter may be necessary in severe and complicated cases, especially during operative procedures. I believe, however, that the frequently cited criteria for Swan-Ganz catheter use in preeclamptic women, which include severe hypertension and oliguria, are too broad. In our experience, indications for this invasive procedure, which is not without morbidity, are relatively uncommon, and most patients can be managed using clinical acumen alone. This conservative view echoes those of the Working Group and the American College of Obstetricians and Gynecologists. Anesthetic considerations are beyond the scope of this conference but are another area of disagreement. Epidural analgesia for labor and cesarean sections for women with severe preeclampsia is the choice of most obstetric anesthesiologists who fear the hypertensive response to laryngoscopy, intubation, airway suction, and extubation of these patients, but many obstetricians prefer general anesthesia for these patients. Concerning the epidural approach, the Working Group cautioned that it carries "the risk of extensive sympatholysis with consequent decreased cardiac output, hypotension, and impairment of an already compromised uteroplacental perfusion." I prefer the use of general anesthesia, and given the hemococoncentration characteristic of severe preeclampsia, use of epidural analgesia requires the presence of an experienced anesthesiologist, a view endorsed by the American College of Obstetricians and Gynecologists.

Finally, some thoughts on volume management of preeclamptic women. In the past, some have recommended the liberal administration of crystalloids and colloids, with the belief that these hemoconcentrated patients with decreased cardiac outputs and filling pressures, as well as suboptimal intravascular volumes, might benefit from volume expansion. However, such infusions, especially of crystalloids, have at most transient effects and reduce oncopletic pressure (already quite low in preeclampsia). Thus, infuse volumes during labor should be at or preferably less than 100 mL/h, even in the presence of oliguria (providing serum creatinine levels remain stable). This approach aims at avoiding postpartum pulmonary edema.

### Chronic Hypertension and Pregnancy

Gestations in women with essential hypertension are more prone than those in normotensive gravidas to complications such as fetal growth retardation, premature delivery, abruptio, acute renal failure, and, rarely, acute fatal hypertensive crisis. Much of this morbidity is associated with superimposed preeclampsia, correlates with increased age (>30 years), and the duration of the hypertensive disorder. Still, most (>85%) women with chronic hypertension experience uncomplicated pregnancies. There is uncertainty about whether mild hypertension should be treated during pregnancy, some claiming such an approach reduces the incidence of premature delivery, frequency of hospitalization, superimposed preeclampsia, and perhaps cesarean deliveries; others disagree and opt against treatment. The Working Group focused primarily on maternal well-being and recommended that antihypertensive treatment (Table 5) be commenced when diastolic pressures reach 100 mm Hg but treated at lower levels if risk factors such as renal disease or evidence of end-organ damage are present. Still, in 1993, the issue of whether or not to treat mild hypertension (diastolic levels between 90 and 100 mm Hg) remains unresolved; appropriately designed trials are required to resolve this question.

### Table 5. Antihypertensive Drugs Used to Treat Chronic Hypertension in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)-Adrenergic receptor agonists</td>
<td>Methyl dopa is the most extensively used drug in this group, its safety and efficacy supported in randomized trials, and there is a 7.5-year follow-up study of children born to treated mothers. Methyl dopa is the drug of choice recommended by the Working Group.</td>
</tr>
<tr>
<td>(\beta)-Adrenergic receptor antagonists</td>
<td>These drugs, especially atenolol and metoprolol, appear safe and efficacious in late pregnancy, but fetal growth retardation has been noted when treatment was started in early or midgestation. Fetal bradycardia can occur, and animal studies suggest the fetus's ability to tolerate hypoxic stress may be compromised.</td>
</tr>
<tr>
<td>(\alpha) and (\beta)-Adrenergic receptor antagonists</td>
<td>Labetalol appears as effective as methyl dopa, but there is little or no follow-up information on children born to mothers treated with labetalol, and there is concern for maternal hepatotoxicity.</td>
</tr>
<tr>
<td>Arteriolar vasodilators</td>
<td>Hydralazine is used frequently as adjunctive therapy with methyl dopa and (\beta)-adrenergic receptor antagonists. Rarely, neonatal thrombocytopenia has been reported. Trials with calcium channel blockers look promising. Experience with minoxidil is limited; this drug is not recommended.</td>
</tr>
<tr>
<td>Converting enzyme inhibitors</td>
<td>Captopril causes fetal death in diverse animal species, and several converting enzyme inhibitors have been associated with renal failure in the newborn when administered to humans. Do not use in pregnancy.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Many authorities discourage their use, but others continue these medications if they were prescribed before gestation or if a chronic hypertensive patient appears quite salt sensitive. The latter views have been endorsed by the Working Group.</td>
</tr>
</tbody>
</table>

Modified from Cunningham and Lindheimer. See References 4, 5, and 82 for detailed discussions.
Table 5 summarizes the Working Group's recommendations regarding the prescription of antihypertensive drugs during gestation. It is only during the past two decades that efforts have been undertaken to determine the safety and efficacy of these medications, but the majority of studies have been limited in scope, some being performed primarily at the request and by support of the pharmaceutical companies. Most of these studies do not meet the rigorous standards that good trials currently require, and there is a critical need for large multicenter studies using the combined services of obstetricians, hypertension specialists, and epidemiologists. Also needed are more rigorous requirements for animal testing that should be met before human trials can begin, including standardized means of evaluating effects of drugs on the fetus's ability to withstand hypoxic stress and more complete analysis of morphological and physiological variables in the newborn. For example, aminoglycosides administered to gravid rats have deleterious effects on the fetal kidney, only demonstrable by subtle tests of function and by histological examination of renal tissue, which reveal both developmental abnormalities and tubule damage. There are also no standards for long-term evaluation of the offspring in human trials. These concerns were one reason why many members of the Working Group preferred to withhold treatment until diastolic levels are 100 mm Hg or higher.

The Consensus Report lists the central adrenergic inhibitor methyldopa as the drug of choice to treat hypertension in pregnancy, noting its long record of use, apparent safety during gestation, and a 7.5-year follow-up study of infants whose mothers received the drug during one trial (Table 5). Clinical trials of other agents have failed (through 1992) to demonstrate the superiority of one or another antihypertensive drug, although comparable efficacy has been demonstrated for some newer medications. The association of angiotensin converting enzyme inhibitors with oligohydramnios and neonatal renal failure precludes their use in pregnant women (warnings to that effect are now clearly noted on the labels of these drugs when sold in the United States). There is concern that \( \beta \)-blockers may cause fetal growth retardation and that labetalol may be hepatotoxic. Finally, the most interesting pronouncement of the Consensus Report was the Working Group's recommendation, relating to an old controversy, that diuretic drugs taken before conception may be continued during pregnancy and even prescribed for the first time to gravidas whose hypertension appears overly sensitive to salt.

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Figs 1 and 3 are courtesy of B.H. Spargo, the University of Chicago (Ill). Fig 2 is from Lindheimer MD, Spargo BH, Katz AI (J Reprod Med. 1975;15:189-194).

Questions and Answers

Dr Gerald DiBona (University of Iowa, Iowa City): How long should proteinuria due to the glomerular endotheliosis lesion of preeclampsia take to clear? This becomes important in considering the timing of a renal biopsy for evaluation of underlying renal disease in the postpartum follow-up period.

Dr Lindheimer: That is a very good question for which data are inconclusive. Some state, anecdotally, that proteinuria should normalize in 3 weeks. I have observed a single case in which the abnormal proteinuria persisted for 3 months and then normalized; the biopsy had demonstrated glomerular endotheliosis only. Based on such poor data, I wait 12 weeks.

Dr Annette Fitz (University of Iowa, Iowa City): At what point should converting enzyme inhibitors be stopped in pregnancy, or should we entirely avoid these drugs in young women of childbearing age?

Dr Lindheimer: This is a very good question. The major reason for the warning is concern about the development and glomerular filtration rate of the fetal and neonatal kidney. It is also known that oligohydramnios may occur. There are anecdotal reports of anomalies and fetopathy. Thus, I really cannot think of anytime during pregnancy when a woman should receive angiotensin converting enzyme inhibitor therapy.

Dr Annette Fitz (University of Iowa, Iowa City): Does a low-sodium diet before pregnancy influence the frequency or severity of preeclampsia?

Dr Lindheimer: In 1957, Robinson actually reported that sodium loading prevented preeclampsia! In 1973, I concluded that access to normal dietary sodium intake was not harmful to such patients. I believe pregnant women need sodium. There also is evidence, especially in animal models, that too rigid a sodium restriction may not be beneficial to the fetus.

Dr John Stokes (University of Iowa, Iowa City): To what extent do serum uric acid concentration and plasma renin activity assist the physician in making the diagnosis of preeclampsia?

Dr Lindheimer: Everyone has been looking for a test that differentiates preeclampsia from other hypertensive diseases. The problem with most of the tests is their lack of sensitivity; it is never more than 70% to 80%. Serum uric acid concentration also has a questionable sensitivity, but it is still useful. Plasma renin activity is high in normal pregnancies and decreases in preeclampsia. However, the extent of overlap precludes clinical usefulness.

Dr William Lawton (University of Iowa, Iowa City): With desire to predict preeclampsia, please comment on current thoughts regarding the roll-over test.

Dr Lindheimer: The roll-over test has a poor sensitivity, but some feel that a negative test has good negative predictive value. This is arguable. One of the problems is that in reports of the test the blood pressure was not always taken with the same reference to the level of the heart.

Dr William Lawton (University of Iowa, Iowa City): What is the current thinking regarding the safety and efficacy in pregnancy of other drugs similar to methyldopa (clonidine, guanfacine) and \( \alpha \)-receptor antagonists (prazosin-like)?

Dr Lindheimer: There are only limited studies on these agents, and none includes the long-term follow-up on
infants similar to that performed in the Oxford methyl-
dopa investigation. As of 1993, there have been no major
differences in therapeutic efficacy when other
drugs have been compared with methyl-dopa.

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