

Strategies to Prevent and Treat Preeclampsia: Evidence From Randomized Controlled Trials

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Preeclampsia-eclampsia is a major cause of morbidity and mortality in mothers, fetuses, and neonates worldwide, most devastating in developing nations. Its cause is still uncertain, and many controversies exist concerning its management. The World Health Organization is aware of this and is coordinating a series of systematic reviews that focus on the etiology and the best strategies for the screening, prevention, and treatment of preeclampsia. This article summarizes results from systematic reviews of randomized trials to prevent and manage preeclampsia. There is a prophylactic role of modest magnitude for low-dose aspirin but the number to treat (90 women) to avoid one case of preeclampsia still is considered high. Antioxidant and calcium supplement trials remain to be completed before firm conclusions can be rendered on their efficacy for prevention. Magnesium sulfate is effective in preventing and treating eclampsia, while severe hypertension (with or without proteinuria) requires drug therapy, but there appears to be no benefits to treating mild to moderate hypertension without proteinuria in pregnancy. Finally, our review focuses on the quality of data reviewed, suggesting the need for better evidence, and discusses the use of systematic reviews as a strategy to focus future research on this important area of reproductive medicine.

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KEYWORDS preeclampsia prevention, randomized trials, antihypertensives, magnesium sulfate

Worldwide, hypertension complicates approximately 9% of all pregnancies.¹ Two percent to 3% of these complications will be pure or superimposed preeclampsia (5% to 7% nulliparous), of which almost 2% will progress to a convulsive phase, eclampsia.¹ Progress in prenatal and perinatal care have reduced the morbidity and mortality associated with preeclampsia-eclampsia substantially, primarily in the developed world, but the cardinal features of this disorder, hypertension (often severe), convulsion, and major systemic manifestations, such as intravascular coagulation and liver failure, still are difficult to prevent and/or treat. Thus, as of fall 2004, the major recourse to successful treatment remains delivery. Also preeclampsia may be a heterogeneous disorder, one reason that prevention and treatment have proven difficult.²

Prevention and management of preeclampsia has not only proven difficult, but recommendations frequently have been controversial. Thus, many a practitioner faced with therapeutic decisions may be confused when perusing the literature, and amazed as to how often experts' opinions disagree. This article, discussing systematic reviews of randomized trials of the effectiveness of interventions or treatment regimens for hypertension during pregnancy, preeclampsia, and eclampsia, aims at remedying such dilemmas, improving care, and pointing to areas requiring further trials.

Why Do We Focus on Randomized Controlled Trials?

There is an extensive review of literature on hypertension during pregnancy, including suggestions for prevention and management, but most of it fails to differentiate between randomized and nonrandomized trials, or to delve into the qualities of such studies, and very few focus on systematic reviews of the evidence. Evaluation of different forms of care outside the context of a proper randomization strategy is prone to major biases that can provide an incorrect assess-

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ment of effectiveness. Randomized trials are considered the most valid means of evaluating medical interventions. They are the only certain way of eliminating bias on how patients are allocated to the treatments (selection bias), and randomization controls for both known and unknown baseline factors that may influence outcome.³

The best way to summarize evidence from these trials in the least-biased manner is to conduct systematic reviews. These are literature reviews on a clearly formulated question that uses explicit methods described in a research protocol to identify, select, and critically appraise relevant primary research, and extract and analyze data from those trials that are relevant to the question of interest. Statistical methods for pooling trials' results, such as a meta-analysis, can be used.

Meta-analysis is the use of statistical techniques to pool results from trials addressing the same question into a summary measure such as the pooled relative risk or odds ratio within the corresponding 95% confidence interval (CI).⁴ This pooled estimate, because it has a larger number of cases, has more statistical power than the individual trials. The interpretation of this pool estimation is similar to the interpretation of a relative risk (RR) from single trials: $RR = 1$ indicates no difference between comparison groups, $RR > 1$ for increasing harmful or undesirable outcomes, and $RR < 1$ for treatment indicates that the intervention was effective in reducing the risk of that outcome. The CI is the range within which the true RR value is expected to lie with a 95% degree of certainty.

The most common scenario of these systematic reviews and meta-analyses in perinatology is a series of small trials or a combination of small trials with 1 or 2 large trials. Heterogeneity of results among these trials often is present and data should be presented stratified.⁵

Nutritional Interventions

Our more extensive review of the literature regarding the role of nutritional interventions in preventing and managing hypertension in pregnancy, as well as detailed description of the trials, their methodology, and types of interventions, are available elsewhere.⁶⁻⁸ Our summary emphasizes the practical implications of such trials.

Nutritional Advice in Pregnancy

Nutritional advice appears to be effective in increasing pregnant women's energy and protein intake, but the implications for fetal, infant, and maternal health cannot be judged from the available evidence. Among the trials included in the Cochrane review devoted to this area,⁹ preeclampsia prevention, was assessed only in one small trial involving 136 women that showed no beneficial effects (Table 1).

Protein and Energy Supplementation

The effect of balanced protein-energy supplements for pregnant women on gestational weight gain and pregnancy outcomes was assessed in another Cochrane systematic review.¹⁰ Preeclampsia prevention was evaluated in 3 trials involving

516 women, with no significant beneficial effect noted (Table 1). The reviewed trials must be interpreted cautiously because of several methodologic flaws such as the use of alternate treatment allocation instead of more reliable randomization methods, and the failure of many participants to complete the study. In another Cochrane systematic review,¹¹ a single trial (782 women) evaluated isocaloric balanced protein supplements to underweight pregnant women to prevent preeclampsia. It too showed no effect (Table 1).

Protein and Energy Restriction For Obese Women

Protein-energy restriction for high-weight-for-height, or for excessive weight gain during pregnancy (several definitions were used), was assessed by a Cochrane systematic review.¹² Preeclampsia was evaluated in 2 trials (284 women) that showed no reduction in risk for either preeclampsia or pregnancy-induced hypertension (3 trials, 384 women) (Table 1). Thus, the limited evidence available suggests that protein-energy restriction for overweight gravidas, or for women showing excessive weight gain during pregnancy, is unlikely to be beneficial and even may be harmful to the developing fetus (e.g., cause intrauterine growth restriction¹³). Therefore, it is surprising that some practitioners still recommend that pregnant women restrict their food intake in an attempt to prevent preeclampsia.

Salt Restriction

The effectiveness of dietary sodium restriction was evaluated in a Cochrane review.¹⁴ The analysis included 2 trials with data reported for 603 pregnant women, comparing nutritional advice to restrict dietary salt with advice to continue a normal diet. No effect was found in preventing preeclampsia or pregnancy-induced hypertension (Table 1). There was no information regarding restricted salt intake prescribed to treat preeclampsia. Women's dietary preferences were not reported, but it was presumed that a low-salt diet was not very palatable and was therefore difficult to follow.¹⁴

Calcium Supplementation

An older review regarding the effectiveness of calcium supplementation during pregnancy recently has been updated.¹⁵ The investigators conducted a prespecified stratified analysis taking into account women's risk for hypertensive disorders of pregnancy (low versus increased) and baseline dietary calcium intake (low: <900 mg/d, versus adequate: ≥ 900 mg/d). Ten trials involving 6,634 women were analyzed, focusing on the ability of supplementation to prevent high blood pressure with or without proteinuria. The rate of high blood pressure was lower with supplementation but there was heterogeneity in the magnitude of the effects across the subgroups, the effect being considerably greater in high-risk populations, and also increased in groups characterized by low baseline dietary calcium intake compared with those with adequate calcium intake (Table 1).¹⁵

Overall, the risk for preeclampsia was decreased significantly (11 trials; 6,894 women; typical RR, .70; 95% CI,

Table 1 Results of Systematic Reviews of Nutritional Interventions for the Prevention of High Blood Pressure during Pregnancy or Preeclampsia

	No of trials in systematic review (Ref.)	# of trials with outcome reported [#] = trials with population at risk of nutritional deficiency*	EXPT	CTRL	RR	95% CI	Heterogeneity ¹ of trial results	
							(P value) Statistical	Clinical
Preeclampsia								
Nutritional advice	4 ⁹	1	17/96	8/40	0.89	0.42–1.88	N/A	N/A
Balanced protein/energy	13 ¹⁰	3[3]	34/258	28/258	1.20	0.77–1.89	>0.1	Yes?
Isocaloric balanced protein	3 ¹¹	1[1]	23/391	23/391	1.00	0.57–1.75	N/A	N/A
Energy/protein restriction for obese	3 ¹²	2	17/142	15/142	1.13	0.59–2.18	>0.10	Yes
Salt restriction	2 ¹⁴	2	10/294	9/309	1.11	0.46–2.66	>0.10	No
Calcium, low risk of hypertension	6 ¹⁵	6	188/3146	240/3161	0.79	0.65–0.94	<0.10	Yes
Calcium, high risk of hypertension	5 ¹⁵	5	9/281	54/306	0.21	0.11–0.39	>0.2	No
Calcium, adequate intake	4 ¹⁵	4	169/2505	197/2517	0.86	0.71–1.05	<0.10	Yes
Calcium, inadequate intake	6 ¹⁵	6 [6]	27/907	90/935	0.32	0.21–0.49	>0.10	Yes
Magnesium	7 ¹⁶	2 [1]	34/235	40/239	0.87	0.57–1.32	>0.10	No
Fish oil	3 ¹⁷	2	100/2510	143/2511	0.70	0.55–0.90	?	?
Vitamins E and C	Not in a systematic review ¹⁸	1	11/141	24/142	0.46	0.24–0.91	N/A	N/A
Pregnancy hypertension (with or without proteinuria)								
Energy/protein restriction	3 ¹²	3	70/192	72/192	0.97	0.75–1.26	>0.1	No
Salt restriction	2	1	13/110	16/132	0.97	0.49–1.94	N/A	N/A
Calcium, low risk	6 ¹⁵	6	611/3146	732/3161	0.84	0.76–0.92	<0.10	Yes
Calcium, high risk	5 ¹⁵	4	25/156	65/171	0.45	0.31–0.66	<0.10	Yes
Calcium, adequate intake	4 ¹⁵	4	547/2505	614/2517	0.90	0.81–0.99	>0.10	No
Calcium, inadequate intake	6 ¹⁵	5 [5]	79/782	172/800	0.49	0.38–0.62	<0.10	No
Fish oil	3 ¹⁷	2	516/2553	537/2555	0.96	0.86–1.07	>0.10	Yes
Vitamins E and C	Not in a systematic review ¹⁸	1	11/141	24/142	0.39	0.17–0.90	N/A	N/A

Expt = experimental group; Ctrl = control group; RR = relative risk; N/A = not available.

All relative risk (CI) using fixed effect model.

¹Heterogeneity. Statistical: Test for heterogeneity statistically significant if $p < 0.10$. Clinical: No evidence means that there was no clinical heterogeneity in the results of the included trials, as judged independently by two authors. N/A: there is only one trial included in the meta-analysis.

*Populations were considered likely to be at risk of nutritional deficiency if from developing countries, low socioeconomic status, or if the authors of the systematic review reported any other relevant information. The Cochrane systematic review of Calcium supplementation during pregnancy already presents a stratified analysis by level of calcium intake.¹⁵

.58-.83), however, when predefined subgroups were considered, a significant reduction was noted, primarily in women with low baseline dietary calcium intake who, in addition, were in a population considered high risk for developing preeclampsia¹⁵ (Table 1). Thus, current guidelines suggest supplementing calcium intake in the latter group alone.

This recommendation has been evaluated recently in a large (8,300 women), double-blind, randomized, controlled trial that was organized by the World Health Organization and conducted in 7 locations worldwide where calcium intake is low (<600 mg/d). Pregnant women received an extra 1.5 g/d of calcium carbonate or a placebo, treatment commenced after gestational week 20. Results should be available in late 2004.

Magnesium

A Cochrane review of 2 trials (474 women) could not detect an apparent effect of magnesium supplementation on the prevention of preeclampsia (mean supplement dose, 365 and 500 mg) (Table 1).¹⁶ These results may have been confounded by the fact that in the largest trial all of the women received a multivitamin and mineral preparation that contained approximately 100 mg of magnesium. The methodologic quality of these trials also was poor, especially in relation to concealment of treatment. Therefore, the investigators saw no reason to recommend routine supplementation during pregnancy.¹⁶ This conclusion is unrelated to and differs from that of the effectiveness of parenteral magnesium sulfate for the treatment of preeclampsia and eclampsia (discussed later).

Fish Oil

Fish oil supplementation, rich in long-chain n-3 fatty acids, was discussed in a Cochrane systematic review in 1995.¹⁷ Two trials were analyzed (5,135 women) that showed no effect on pregnancy-induced hypertension, but did show a small but significant decrease in the incidence of preeclampsia¹⁷ (Table 1). This decrease, however, was influenced strongly by a large trial conducted in 1942 that used an alternate allocation of women (rather than randomization) to vitamins and minerals, in addition to fish oil. Subsequently, 4 additional trials have appeared that included more than 2,000 women that, as of this November 2004, had not been added to the Cochrane database. These more recent trials found no differences in the incidence of hypertension during pregnancy or preeclampsia between supplemented and control populations.⁸

Vitamins E and C

An imbalance between circulating oxidants and substances, antioxidant in which the former predominate, has been postulated as a pathogenetic mechanism in preeclampsia, and considerable research interest now focuses on vitamins C and E as well as circulating levels of lipids peroxides in preeclampsia (see the article, "Antioxidant Therapy to Prevent Preeclampsia", by Roberts et al in this issue). In this respect,

supplementation with nutrients with antioxidant properties has been proposed to prevent preeclampsia.

In a recent controlled trial, 283 pregnant women were randomized to receive vitamin C (1,000 mg/d) and E (400 IU/d) supplementation or placebo.¹⁸ All were considered at high risk for developing preeclampsia on the basis of abnormal uterine artery Doppler waveform patterns detected at 18 to 22 weeks of gestation, or because they experienced preeclampsia in a previous pregnancy. Investigators found a large statistically significant decrease in the risk for preeclampsia in the supplemented group compared with the control group (Table 1). We underscore that these results, although promising, are from a trial limited to 283 very high risk women. The preventative potential of vitamins C and E currently is being evaluated in several large, multicenter, double-blind, randomized trials in North America (Roberts J, University of Pittsburgh, personal communication, 2002), in several institutions in the United Kingdom, and in a new World Health Organization multicenter trial in India, Peru, and Vietnam. Results are expected during 2006.

Nutritional Interventions for the Treatment of Hypertensive Disorders of Pregnancy or Preeclampsia

In a published review of interventions for management of mild to moderate chronic hypertension during pregnancy, no trials were found that compared nonpharmacologic interventions with either pharmacologic agents or no intervention in pregnant women.¹⁹ This comprehensive search identified 50 randomized controlled trials, but they involved either normotensive or hypertensive women both with a history of preeclampsia.

In general, weight reduction during pregnancy, even in obese women, is not recommended to improve pregnancy outcomes.¹³ Although obesity may be a risk factor for superimposed preeclampsia, there is no evidence that limiting weight gain during pregnancy reduces its occurrence.¹²

The physiologic volume expansion of uncomplicated pregnancy and the association of chronic hypertension, preeclampsia, and intrauterine growth restriction with plasma volumes lower than those measured in normal gestation are the reasons given for why sodium restriction generally is not recommended to treat hypertension during pregnancy. However, sodium restriction (and even diuretic therapy) can be considered if patients whose high blood pressure, determined to be salt-sensitive, has responded to such therapy before conception. We emphasize, however, that there are no data supporting the ability of such an approach to prevent preeclampsia, nor do we know how it could influence fetal and neonatal outcomes.

High alcohol intake is related to hypertension in nonpregnant patients but is not associated with an increased risk for gestational hypertension, preeclampsia, or eclampsia.²¹ There is no conclusive evidence of adverse effects on pregnancy outcomes, including fetal growth, at levels of con-

Table 2 Treatment of Mild-Moderate Hypertension During Pregnancy

Comparison Outcome	Any antihypertensive drug versus none		
	No. of studies	No. of subjects	RR (95% CI)
Severe hypertension	17	2155	0.52 [0.41, 0.64]
Proteinuria/preeclampsia	19	2402	0.99 [0.84, 1.18]
Eclampsia	4	508	0.34 [0.01, 8.15]
Small for gestational age*	12	1346	1.36 [1.02, 1.82]
Fetal or neonatal death	23	2727	0.71 [0.46, 1.09]
Preterm birth (<37 weeks)	12	1738	1.00 [0.87, 1.15]

Reference: Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.³¹

*only beta-blockers trials (Reference 32)

sumption less than 120 g of alcohol per week.²² However, there are suggestions that excessive consumption of alcohol can cause or aggravate maternal hypertension.²³

In summary, we could not locate reliable information from well-designed, randomized, controlled trials that accurately assessed the best dietary approach for the management of preexisting hypertension during pregnancy.

Treatment of Mild to Moderate Hypertension During Pregnancy

Because it is unlikely that mild to moderate hypertension (defined as diastolic and systolic levels between 90-110 mm Hg, and 140-160 mm Hg, respectively) could lead to an immediate risk to mother or fetus, many see no need for pharmacologic treatment of such levels. Under such circumstances, it has been argued that the potential risks of drug therapy to the fetus, still unknown for many agents, outweigh the long-term risks of this short-term inadequate control, especially because this can be remedied by focusing on control postpartum.

These clinical opinions, however, reflect, in part, the inadequacy of available research information. The literature is skewed to studies in which drug therapy was commenced after midgestation, a time when virtually all the risks of congenital malformations have passed. Furthermore, there is very little information about the long-term safety for the child after antihypertensive exposure during pregnancy.

A wide variety of drugs have been advocated to use during pregnancy and because each group has different pharmacologic actions, they could have potential side effects to mother and fetus. α -agonists inhibit vasoconstriction via a centrally mediated effect.²⁴ Methyldopa is the most commonly used α -agonist for hypertension during pregnancy. Clonidine is also an α -agonist, with the disadvantage that sudden withdrawal may cause a hypertensive crisis.²⁵ β -adrenoceptor-blocking drugs act on adrenoceptors in the heart, peripheral blood vessels, airways, pancreas, and liver.²⁶ Labetalol has an additional arteriolar vasodilating action that decreases peripheral resistance. Calcium channel blockers inhibit the influx of calcium ions to vascular smooth muscle, resulting in arterial vasodilatation.²⁷ Hydralazine has a direct relaxing

effect on smooth muscle arterioles.²⁸ (See Podymow et al, in this issue.)

Several reviews of existing randomized trials have been performed to assess the potential benefits and hazards of antihypertensive drugs for the treatment of mild to moderate hypertension during pregnancy.²⁹⁻³²

A recent Cochrane systematic review³¹ concluded, not surprisingly, that the main benefit of drug therapy in pregnant women with mild to moderate hypertension was to decrease the rate of progression to severe hypertension (RR, .52; 95% CI, .41-.64) (Table 2). Other anticipated findings were a decreased need for additional therapy (including a second agent), and a greater likelihood for the patient to experience more side effects (RR, 1.74; 95% CI, 1.04-2.91) than the controls.

Decreasing blood pressure would be more important if it were associated with benefits, such as a decrease in the incidence of preeclampsia, caesarean sections, decreased preterm labor, and/or small-for-gestational-age infants. No such benefits have been shown yet clearly. Specifically, better control of blood pressure does not seem to influence the appearance or the progression of preeclampsia (RR, .99; 95% CI, .84-1.18). There are insufficient data for any firm conclusions about other substantive outcomes, for example, the protective effect for eclampsia.

These results are consistent with the findings of another Cochrane review focused on β -blockers.³² However, when compared with placebo or no therapy, β -blockers seem to be associated with an increased risk for small-for-gestational-age infants (RR, 1.36; 95% CI, 1.02-1.82).³²

There are 2 possible hypotheses for why decreasing blood pressure during pregnancy might lead to small-for-gestational-age babies. First, higher blood pressure levels are protective and the drug-induced decreased blood pressure level decreases placental perfusion to below that necessary for adequate placental perfusion.³³ Second, this is a specific effect of certain classes of drugs. In this respect, 3 trials³⁴⁻³⁶ in the subgroup analysis for birth weight less than the 5th percentile as outcome, involved atenolol and labetalol (drugs with mostly β -blocker effects) and showed an increased risk in fetal growth retardation³⁴⁻³⁶ (subgroup meta-analysis: RR, 3.04; 95% CI, 1.25-7.40).

The question of which antihypertensive drug to use is less

Table 3 Treatment of Severe Hypertension During Pregnancy

Outcome Comparison	Eclampsia			Fetal or neonatal death		
	No. of studies	No. of subjects	RR (95% CI)	No. of studies	No. of subjects	RR (95% CI)
Labetalol vs. hydralazine	1	20	Not estimable	3	69	0.50 [0.05, 4.94]
Ketanserin vs. hydralazine	2	64	0.60 [0.08, 4.24]	1	36	0.16 [0.01, 2.87]
Urapidil vs. hydralazine	1	26	Not estimable	2	59	0.66 [0.08, 5.25]
Nimodipine vs. magnesium sulphate	2	660	1.02 [0.38, 2.72]	—	—	—
Nifedipine vs. chlorpromazine	1	55	2.52 [0.11, 59.18]	—	—	—
Nifedipine vs. prazosin	1	145	Not estimable	1	149	0.46 [0.18, 1.13]
Calcium antagonists vs. hydralazine	—	—	—	2	83	2.28 [0.35, 14.78]
Prostacyclin vs. hydralazine	—	—	—	1	47	1.14 [0.08, 17.11]
Labetalol vs. methyldopa	—	—	—	2	144	4.49 [0.22, 90.30]
Labetalol vs. diazoxide	—	—	—	1	90	0.14 [0.01, 2.69]

Reference: Duley L, Henderson-Smart DJ. Drugs for rapid treatment of very high blood pressure during pregnancy (Cochrane Review). In: The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.⁴³

relevant until it becomes clear whether attempting to control mild to moderate hypertension during pregnancy is worthwhile. In summary, treatment with antihypertensive drugs does not appear to prevent superimposed preeclampsia, abruption, or to decrease perinatal mortality, albeit these conclusions derive primarily from small trials from which the results vary considerably. There are also relatively unknown fetal and childhood risks for most of these drugs. Finally, the most important message from all these reviews, is “the need for large prospective trials specifically focused on the maternal and fetal effects of differing levels of targeted (and achieved) blood pressure control to decide if mild hypertension during pregnancy requires treatment.”²⁰

Treatment of Severe Hypertension

Severe hypertension, usually defined as systolic and/or diastolic blood pressures of 160 to 170 mm Hg or greater and 105 to 110 mm Hg or greater, respectively,^{37,38} is a more serious scenario posing a danger to both mother and fetus. Maternal risks are similar to those of nonpregnant subjects presenting with severe hypertension. In the mother, such blood pressure levels are associated with substantial end-organ damage including kidney and liver failure, as well as stroke. The unborn child is at risk both for fetal distress when vasoconstriction reduces placental perfusions and placental abruption.³⁹ Thus, all agree that pregnant women with severe hypertension require treatment with antihypertensive drugs.⁴⁰⁻⁴² There is some divergence as to the blood pressure at which therapy should be initiated, the general recommendation being to commence drug treatment when systolic and diastolic levels reach or exceed 160 to 170 and/or 105 to 110 mm Hg, respectively.²³ There is more disagreement on how aggressively to decrease blood pressure when faced with severe hypertension, especially when the increase is sudden, but given the absence of trials, the subject is not discussed here, but only to say the aim of treatment is a gradual reduc-

tion to levels considered safe for both mother and baby, care being taken to avoid sudden decreases that may cause placental perfusion problems as evidenced by acute fetal distress.

The question of which drug is best to treat severe hypertensive emergencies is considered in a Cochrane review⁴³ that included 20 studies (1,637 women). Most studies, although randomized, were very small, with 12 of them recruiting less than 50 women, and 1 study included women with severe preeclampsia for prevention of eclampsia as the primary outcome.⁴⁴ In other trials, hydralazine, nifedipine, labetalol, diazoxide, prostacyclin, ketanserin, and urapidil also were evaluated. All of them have been shown to decrease blood pressure, but there is no evidence that any one agent is better than another. Diazoxide, however, seems to be associated with a greater risk for excessive hypotension, and an increased risk for caesarean section, when compared with labetalol. On the other hand, the hypertension was more likely to persist when women treated with ketanserin were compared to those treated with hydralazine.⁴³ Because trials were small, the confidence intervals for outcomes such as perinatal mortality were all very wide, so the differences between drugs were not statistically significant (Table 3). Few trials reported side effects related to the different agents.

Therefore, until better evidence is available, the choice of antihypertensive drugs should depend on the experience and familiarity of an individual clinician with a particular drug and on what is known about maternal and fetal side effects. Large, well-designed, and properly conducted trials are needed to know reliably about the comparative effects of different antihypertensive drugs. Because these drugs cross the placenta and may affect the fetus directly or indirectly by their effect on uteroplacental perfusion, short- and long-term effects on the baby also should be evaluated.

Finally, plasma volume is reduced among women with preeclampsia, and some researchers suggested that plasma volume expanders could improve maternal and perinatal outcomes. Three trials enrolling a total of 61 pregnant

women were included in a Cochrane systematic review.⁴⁵ These trials compared a colloid solution with a no-plasma-volume-expansion regimen. For every outcome reported, the confidence intervals were very wide, therefore the evidence was insufficient to recommend the use of plasma volume expanders for treating preeclampsia.

Prevention and Treatment of Eclampsia

For years there was controversy, mostly in the United Kingdom, regarding the preferred treatment of the preeclamptic convulsion. Magnesium sulfate was hailed in obstetric texts, but criticized by the neurologists who recommended standard anticonvulsants such as phenytoin. The resolution of this controversy was signally important for 2 reasons. It ended an acrimonious controversy, at the same time confirming the importance of randomized trials in assessing treatment regimens in obstetrics and gynecology.

First, a landmark trial was published showing that magnesium sulfate is the anticonvulsant of choice for treating eclampsia.⁴⁶ Then systematic reviews, in which this large trial dominated the results,⁴⁶ convincingly showed that magnesium sulfate is substantially more effective than diazepam, phenytoin, or lytic cocktail for the treatment of eclampsia, particularly in reducing the recurrence of convulsions.^{47,48} The large seminal study alluded to⁴⁶ 1,680 women with eclampsia who were assigned randomly to 2 treatment arms, one of them comparing magnesium with intravenous diazepam, and the other comparing the cation with phenytoin. Magnesium sulfate significantly reduced the number of recurrent convulsions and there was a nonsignificant trend toward lower maternal mortality with magnesium in both arms of the study.

The recommended regimen was a loading dose of 4 to 6 g (infused over a 10-min period) followed by a maintenance infusion, preferably delivered by a constant infusion pump at a rate of 1 to 2 g/h. The aim was to maintain plasma levels at 5 to 9 mg/dL (2.1-3.5 mmol/L).

Whether or not all preeclamptic patients should receive prophylactic therapy also has been debated. This is because only a very small percentage of preeclamptic women will convulse. Thus, the widespread recommendation for its use as prophylactic (in contradistinction to efficacy after a life-threatening convulsion) should be supported by reliable evidence of safety for both mother and baby. In this respect, a large controlled trial assessing the advantages and disadvantages of prophylactic magnesium sulfate in women with preeclampsia recently has been published.⁴⁹ Dubbed the Magpie Trial, its investigators recruited 10,141 women with preeclampsia at 175 centers in 33 countries. The study, a blinded, randomized, placebo-controlled trial, showed that prophylactic magnesium more than halved the overall risk for eclampsia (RR, .42; 95% CI, .29-.60), and it was consistent across the subgroups. Because the effect was similar by a level of 70 and eclampsia is more common among women with severe preeclampsia than among those with moderate or

mild preeclampsia, the number of women who need to be treated to prevent one case of eclampsia is greater for nonsevere preeclampsia.

The risk for maternal death also was reduced, although this did not reach statistical significance (RR, .55; 95% CI, .26-1.14) and it is in accordance with the direction of the effect of magnesium sulfate for treatment of eclampsia. Also, no substantive harmful effects for the mother or baby were noted in the perinatal period. In particular, there was reasonable reassurance that there was no clinically important effect on the risk of the baby dying before discharge from hospital or being in a special care nursery for more than 7 days (RR, 1.02; 95% CI, .95-1.09). To assess whether these benefits persisted, and to provide adequate reassurance about long-term safety, a 2-year follow-up evaluation of these mothers and their children was completed during 2004 and will be published soon.⁵⁰

Is There a Role for Low-dose Aspirin in Preeclampsia?

It has been suggested that altering the metabolic balance in the prostacyclin-thromboxane relationship could prevent or delay the clinical development of preeclampsia. Aspirin is the logical candidate for such an effect. This possibility was evaluated in a comprehensive systematic review⁵¹ including 33 trials that mostly compared low doses of aspirin with placebo or no treatment. This review focused on a stratified analysis by the risk level of enrolled women with preeclampsia (hypertension and proteinuria), the primary outcome. Among women with moderate risk, low-dose aspirin (most of trials used doses ≤ 75 mg/d) was associated with a moderate reduction in preeclampsia (RR, .85; 95% CI, .77-.94) including a total of 25,738 women. There is a high degree of heterogeneity among the trial results ($P = .0014$), with the 2 largest trials showing overall no protective effect (RR, .88; 95% CI, .75-1.03 and RR, 1.14; 95% CI, .94-1.38).⁵¹ There were 3,593 women at high risk for preeclampsia, on whom the overall magnitude of the effect was similar (RR, .83; 95% CI, .72-.95), with no evidence of statistical heterogeneity. Overall, 89 women would have to be treated during most of their pregnancy to prevent 1 case of preeclampsia.

This review has been re-analyzed recently⁵² with only a few new inclusions and, as expected, shows similar effects as previously. However, there is a new stratified analysis indicating that for women at high risk (19 trials, 4,222 women) low-dose aspirin had a protective effect (RR, .73; 95% CI, .64-.83). It also showed a greater effect among women treated with higher doses than 75 mg/d of aspirin (RR, .49; 95% CI, .38-.63). The effect among women given a lower dose (21 trials, 28,352 women) was less dramatic and of borderline statistical significance despite the large sample size (RR, .86; 95% CI, .79-.93). Finally, current reassurances of safety apply mostly to low-dose trials and the overall number of events are small among the high-dose trials.

Implementation of these research results into routine clinical practice may require a better ability to identify a sub-

group of women on whom the benefit and compliance would be greater, and perhaps the use of higher doses if shown to be safer. Nevertheless, the high-risk strategy has the limitation that the largest total number of cases often occurs among the low-risk groups that are not covered by the treatment.

Conclusions

Preeclampsia-eclampsia was labeled “the disease of theories” over a century ago.⁵³ It is still an obscure disorder, but considerable information, mostly accrued during the past 2 decades, has led to a better understanding of its pathophysiology. An essential way to evaluate the scientific merit of data are through systematic reviews.

We believe this approach should help identify focused paths of future research in preeclampsia. In fact, we are surprised that such a logical approach had not been used earlier, given the many controversies that abound preeclampsia.

What are the clinical implications of the data reviewed in this article? First, prevention: low-dose aspirin has a modest protective effect, although 90 women would have to be treated throughout their pregnancy to prevent 1 case of preeclampsia. Furthermore, selecting only subgroups considered at high risk for preeclampsia for treatment does not change the number to treat because the effect appears similar at different risk levels. Higher doses may have a larger protective effect and are being evaluated. The preventive effects of supplemental calcium or of vitamins C and E still are under evaluation, although a definitive trial on calcium supplements in populations in whom dietary intake is low will be available in 2004.

Concerning treatment: severe hypertension should be treated with antihypertensive drugs, and both preeclamptic and eclamptic patients should receive parental magnesium to prevent a convulsion or its recurrence. The overall benefit of treatment for mild to moderate hypertension with drugs that reduce blood pressure is unclear and under evaluation.

Finally, we are broadening our approach and applying systematic reviews to areas other than clinical trials, such as predictive tests, and differences in circulating proteins and lipids in normal and preeclamptic subjects, because these studies relate to the theories on the pathogenesis of the disease. We believe that such an approach will help in establishing the cause of the disease with certainty and lead to better treatment and possible prevention of this disorder.

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