This annotated bibliography is the result of an evidence review of nearly 200 articles on pre-eclampsia/eclampsia (PE/E) prevention, detection and management related topics. After an extensive technical review by members of the PE/E Task Force, the 20 most important articles were abstracted in December 2010 to highlight the key findings and implications for public health programming (Section 1). In November 2011, the bibliography was updated to add new resources. Other important articles are listed as references in Section 2.

To guide the use of this document, the following table identified where to find key evidence on various topics:

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<td>61</td>
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This annotated bibliography was prepared for MCHIP by Vandana Tripathi, from the Johns Hopkins University Bloomberg School of Public Health.
SECTION 1: ABSTRACTS

A. General Information About PE/E: Statistics, Guidelines, Risks and Strategies

<table>
<thead>
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<tbody>
<tr>
<td>Background:</td>
<td>“Hypertension, complicating 5 to 7% of all pregnancies, is a leading cause of maternal and fetal morbidity. PE is a major cause of preterm birth and an early marker for future cardiovascular and metabolic diseases.”</td>
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<tr>
<td>Objectives/ Aims:</td>
<td>To present a position paper on hypertensive disorders complicating pregnancy, addressing prediction, prevention and management, as well as recent breakthroughs on etiology.</td>
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<td>Key Points:</td>
<td>Normal changes in blood pressure during pregnancy can complicate diagnosis of hypertensive disorders. The authors classify blood pressure in pregnancy in four categories: “PE/E, chronic hypertension of any cause, PE superimposed on chronic hypertension, and gestational hypertension.” PE is characterized by hypertension and proteinuria, and “may also be accompanied by rapid weight gain and edema, appearance of coagulation or liver function abnormalities, and occurs most often in nulliparas, usually after gestational week 20, and most frequently near term.” Because distinguishing chronic hypertension and PE is not always possible, suggests managing unclear diagnoses as PE, which “is the more serious disorder with a broad clinical spectrum.” The review discusses attempts to classify the severity of PE, and differences between PE emerging before and after 34 weeks of gestation. Complications of PE, including HELLP syndrome, are discussed. The review discusses the lack of accurate prediction tools, but notes ongoing research involving assessment of circulating or urinary antigenic and antiangiogenic proteins. Prevention using low-dose aspirin and calcium is discussed. Recommendations are provided for management of PE near and far from term, as well as management of eclamptic convulsions using magnesium sulfate. Controversies in management of chronic hypertension in pregnancy are discussed, along with the limited evidence on antihypertensive therapy. The authors note that “PE is a risk marker of... future cardiovascular or metabolic disease” and recommend frequent checkups and behavioral interventions for these women.</td>
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1 HELLP stands for H (hemolysis or red blood cell damage), EL (elevated liver enzymes—indicating liver damage), and LP (low platelets in the blood leading to a bleeding tendency).

**Background:** PE and other hypertensive disorders of pregnancy complicate 2–8% of pregnancies worldwide. Their contribution to maternal deaths ranges as high as 26% in Latin America. Varying classifications exist regarding hypertensive disorders, differing in criteria such as “inclusion or exclusion of complicated nonproteinuric gestational hypertension as PE, use of early-onset PE as a severity criterion... and definition of severe hypertension.”

**Objectives/Aims:** To provide an overview of what is known about PE, specifically its pathogenesis, screening, prediction, clinical presentation, and management.

**Review Design:** The review searched PubMed and the Cochrane library, focusing on studies done in human beings in the past five years.

**Key Points:** Summarizes PE as “characterized by de novo development of concurrent hypertension and proteinuria, sometimes progressing into a multi-organ cluster of varying clinical features.” Notes that “predisposing cardiovascular or metabolic risks, as part of an exaggerated systemic inflammatory response, might dominate in origins of late onset PE.” References to the PE Community Guideline (PRECOG), which provides a summary of risk assessments that can be done early in pregnancy. Notes that later risk assessments (>20 weeks of gestation) should pay attention to the possible onset of PE by identification of any of the following signs and symptoms: new hypertension; new proteinuria; symptoms of headache; visual disturbance; epigastric pain; vomiting; reduced fetal movements; and an infant that is small for gestational age.”

Notes that, although dipstick testing for screening of proteinuria is prone to limitations in reliability, sensitivity, specificity, and predictive value, “it is... widely used, and might be the only test available in low-income and middle-income countries.”

As prevention and prediction are still not possible, “symptomatic clinical management should be mainly directed to prevent maternal morbidity (e.g., eclampsia) and mortality.” Describes clinical aspects of PE—including timing, probability, and presentation of different symptoms. Provides a management plan for antenatal PE based on gestational age at onset, noting caveats about the local availability of health care resources. Warns that “expectant management of women with early onset disease to improve perinatal outcome should not preclude timely delivery—the only definitive cure.”

Notes the risks of recurrence (“10% for previous mild disease and up to 40% for severe disease”) and discusses the importance of preconceptional care for women who have had PE in previous pregnancies. Finally, the authors note that “PE foretells raised rates of cardiovascular and metabolic disease in later life.”

**Conclusions/Discussion:** The authors discuss gaps in clinical practice and failures to apply evidence regarding PE management. They also note gaps in patient knowledge about risks and danger signs related to PE and other hypertensive disorders. This review calls for development and validation of disease severity criteria, additional research on management of early onset severe PE, and “audits of PE-related maternal mortality and severe morbidity” to improve care.

Background: “In this paper we review the evidence of the effect of health interventions on mortality reduction from hypertensive diseases in pregnancy (HDP). We chose HDP because they represent a major cause of death in low income countries and evidence of effect on maternal mortality from randomised studies is available for some interventions.”

Objectives/Aims: To summarize efficacy data from randomised controlled trials, separating effects on mortality from those on morbidity.
To review the literature on population models quantifying the effect of HDP-related maternal health interventions on mortality and examine the methods used.
To explore alternative methods to determine the effectiveness of comprehensive packages of health interventions on mortality by examining differentials in HDP-related mortality and case fatality over time and between countries or regions.

Key Points:
Five interventions were selected and reviewed. Two prevention strategies: routine calcium supplementation in pregnancy and antiplatelet agents during pregnancy in women at risk of pre-eclampsia. Three treatment interventions: Magnesium sulphate (MgSO4) for the treatment of eclampsia; MgSO4 for the treatment of pre-eclampsia, and hypertensive drugs for the treatment of mild to moderate hypertension in pregnancy.
“There are no randomized controlled trials for the combined medical treatment of eclampsia and pre-eclampsia, nor are there any trials quantifying the effect of a comprehensive package of obstetric care – including MgSO4, labour induction and caesarean section – on mortality from hypertensive diseases.”
“The 98% fall in HDP related mortality in the UK and Sweden over fifty years suggests that HDP-related deaths are highly avoidable. The fall in mortality from HDP has been largely attributed to a reduction in the number of cases of eclampsia, while the incidence of pre-eclampsia has been more resistant to change.”
“The low levels of HDP related mortality in rural China and Sri Lanka suggest that reductions of 85% or more are within reach, provided that most women give birth with a health professional who can refer them to higher levels of care when necessary.”

Table. Potential effect of prevention and treatment of HDP on maternal mortality from HDP using evidence from systematic reviews, historical trends and fatality rates in SAMM from HDP

<table>
<thead>
<tr>
<th>LEVEL WHERE INTERVENTION IS DELIVERED</th>
<th>INTERVENTION</th>
<th>RISK REDUCTION</th>
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<tbody>
<tr>
<td>Health centre</td>
<td>Calcium supplementation during pregnancy</td>
<td>20%</td>
</tr>
<tr>
<td>District or secondary hospital</td>
<td>Calcium supplementation during pregnancy</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>MgSO4 for pre-eclampsia</td>
<td>59%</td>
</tr>
<tr>
<td></td>
<td>MgSO4 for eclampsia</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>Antenatal screening for hypertension and proteinuria and treatment of PE/E with MgSO4 and early delivery in women with severe PE/E</td>
<td>84-99%</td>
</tr>
<tr>
<td>Tertiary hospital</td>
<td>All the above plus treatment of severe hypertension in pregnancy and referral to specialist intensive care for women with severe complications</td>
<td>99%</td>
</tr>
</tbody>
</table>
B. PE/E Prevention: Calcium, Aspirin, Vitamin D and Anti-oxidants


**Background:** Hypertension is associated with maternal deaths, preterm birth, neonatal mortality, and other adverse newborn outcomes. Ecological associations have linked high calcium intake and lower prevalence of hypertensive disorders of pregnancy for decades. Clinical and epidemiological studies have supported the association between calcium and hypertension as well as PE/eclampsia. Discrepancies in the results of recent trials, however, highlighted the need for "a systematic review of the current evidence concerning the effectiveness of calcium supplementation in pregnancy."

**Objectives/Aims:** "To determine... the effect of calcium supplementation during pregnancy on the risk of high blood pressure and related maternal and fetal or neonatal adverse outcomes." To determine whether "these effects were influenced by whether: 1. women had low or adequate dietary calcium intake prior to trial entry; and 2. women were at low or average risk of hypertensive disorders, or at high-risk."

**Review Design:** All randomized trials comparing "allocation to calcium supplementation during pregnancy versus placebo.” Quasi-random designs were excluded.

**Included Studies:** Thirteen studies were included. Four multicenter studies were included, of which one was international, and others were conducted in Argentina, Australia and the United States. Most trials used 1.5 to 2g of calcium per day. The majority of trials included low-risk women (n=15,143) and women with low dietary calcium intake (n=10,678).

**Results:** “The average risk of high blood pressure was reduced with calcium supplementation rather than placebo” (RR=0.65, CI: 0.53 to 0.81). This effect was greater for "women at high risk of developing PE (RR = 0.47, CI: 0.22 to 0.97) and for those with low baseline dietary calcium” (RR= 0.44, CI: 0.28 to 0.70). Calcium supplementation was also associated with a reduction in average risk of PE (RR = 0.45, CI: 0.31-0.65). “The effect was greatest for high-risk women” (RR=0.22, CI: 0.12 to 0.42) “and those with low baseline calcium intake” (RR=0.36, CI: 0.20 to 0.65).

Calcium supplementation was associated with a reduction in average risk of preterm birth (RR=0.76, CI: 0.60 to 0.97), particularly among women at high-risk of developing PE (RR= 0.45, CI: 0.24 to 0.83). “The composite outcome maternal death or serious morbidity was reduced” (RR= 0.80, CI: 0.65 to 0.97), but there was no overall effect on stillbirth or neonatal death before hospital discharge.

**Conclusions/Discussion:** Calcium supplementation (≥1g of calcium per day) “is associated with a halving in the risk ratio of PE.” Calcium supplementation is also associated with reductions in preterm birth and maternal death or serious morbidity taken together, as well as hypertension. Effects are generally greatest among women who are high-risk or have low dietary calcium intake.
### Background:
The results of trials regarding the effects of low-dose aspirin in the prevention of PE and intrauterine growth retardation (IUGR) are contradictory. This, however, may be due to “late initiation of treatment (after 18–20 weeks) and the inclusion of low-risk patients….” A recent study found that “low-dose aspirin started before 16 weeks of gestation in women with abnormal uterine artery Doppler was associated with a 50% reduction of PE.”

### Objectives/Aims:
“To assess and compare the influence of gestational age at the introduction of aspirin therapy on the incidence of PE and IUGR by performing a systematic review and meta-analysis of all women identified as being at risk of PE.”

### Review Design:
The review included prospective, randomized, controlled trials involving pregnant women at risk of PE. Quasi-randomized trials were excluded. The treatment dose had to range from 50–150mg of aspirin per day, alone or in combination with other antiplatelet agents.

### Included studies:
Thirty-four trials were included. Twelve started aspirin at ≤ 16 weeks of gestation and 22 started aspirin after 16 weeks of gestation. Studies used varying criteria to define risk for PE, including “nulliparity, previous history of PE or other hypertensive disorders, abnormal uterine artery Doppler.”

### Results:
“Daily low-dose aspirin initiated before 16 weeks of gestation was associated with a significant decrease in the incidence of PE, severe PE, IUGR and preterm birth in women identified to be at risk for PE.” This was among the first review to include sub-group analysis by the gestational age when aspirin was started.

“The diminution of PE” associated with the intervention was significant in women who began at ≤ 16 weeks of gestation (RR = 0.47, CI: 0.34–0.65). There was no significant reduction in PE associated with the intervention in women who began the intervention at >16 weeks. The difference in the effect of aspirin on women starting earlier versus later was significant. Other improvements in outcomes were also associated with aspirin among women who started the intervention at ≤ 16 weeks, including “decrease of severe PE, gestational hypertension and preterm birth,” as well as increase in mean gestational age at delivery. The reduction of IUGR associated with the intervention was only significant in women who started low-dose aspirin at ≤ 16 weeks of gestation.

### Conclusions/Discussion:
The authors conclude “that daily low-dose aspirin initiated before 16 weeks of gestation was associated with a significant decrease in the incidence of PE, severe PE, IUGR and preterm birth in women identified to be at risk for PE.” The authors note that these observations are consistent with recent studies regarding administration of low-dose aspirin in the first trimester and throughout in vitro fertilization treatment.

“The novelty of [this review] resides in sub-group analysis according to gestational age at the initiation of therapy.” Combining their findings with those of a previous meta-analysis, the authors suggest that: “1. women at moderate or high-risk for PE benefit from daily low-dose aspirin for the prevention of PE and IUGR; and 2. the earlier low-dose aspirin is started in pregnancy, the greater the benefits.” The authors recommend that a large randomized controlled trial is needed to validate their results.

**Background:** Clinical observations “led to the hypothesis that antiplatelet agents, and low-dose aspirin in particular, might prevent or delay the development of PE.” Previous reviews have suggested that “while low-dose aspirin appears to be safe, it is not usefully effective at protecting low-moderate risk women from developing PE.”

**Objectives/Aims:** “To assess the effectiveness and safety of antiplatelet agents, such as aspirin and dipyridamole, when given to women at risk of developing PE.”

**Review Design:** The review included “all randomized trials comparing antiplatelet agents with either placebo or no antiplatelet agent during pregnancy, and trials comparing one antiplatelet agent with another or with other interventions.” The review excluded Quasi-random study designs.

**Included Studies:** Fifty-nine trials were included (n=37,560 women). There was wide variation in sample size: 17 trials reported on <50 women, while nine trials involved ≥1000 women. Fifty-one trials compared aspirin alone with placebo or no treatment; five trials used a combination of aspirin and dipyridamole or dipyridamole. Other trials assessed other combinations of antiplatelets. Trials included women considered at risk of developing PE; this, however, included women with normal blood pressure, those with chronic hypertension, and those with gestational hypertension.

**Results:** Overall, the use of antiplatelet agents is associated with a 17% reduction in the risk of PE (RR = 0.83, CI: 0.77 to 0.89) among the primary prevention trials. The reduction was statistically significant across risk categories. The number of women who would need to be treated with antiplatelets to prevent one case of PE was significantly lower among high-risk women (n=19) than moderate-risk women (n=119). Although no trials directly compared the effectiveness of different doses of aspirin, “there is a significant reduction in the risk of PE in trials using higher-doses of antiplatelet agents” (RR = 0.88 for ≤75 mg of aspirin per day vs. RR = 0.64 for >75 mg of aspirin per day). There was a small reduction in the risk of small for gestational-age births among women receiving antiplatelets (RR = 0.90, CI: 0.83 to 0.98) across risk groups. Women receiving antiplatelets experienced a 14% reduction in the risk of fetal, neonatal and infant deaths taken together (RR = 0.86, CI: 0.76 to 0.98). There was no significant difference or insufficient evidence regarding other non-composite outcomes. Trials evaluating secondary prevention were smaller (n=1643), but observed a 40% reduction in the risk of PE (RR = 0.60, CI: 0.45 to 0.78).

**Conclusions/Discussion:** Administration of antiplatelet agents (largely low-dose aspirin) “to women at risk leads to a 17% reduction in the risk of developing PE... Starting aspirin before 12 weeks and/or using higher doses... cannot be recommended for clinical practice until more information is available about safety.” Further research is required on “which women are most likely to benefit, when treatment is best started, and at what dose.”

Background: Calcium is the only “dietary factor found to inhibit the absorption of both heme and nonheme iron.” Recommendations encouraging widespread use of calcium supplementation may “exacerbate the effects of marginal iron intakes.” The mechanism for the inhibitory effect of calcium on iron absorption is not known.

Objectives/Aims: “To test the hypothesis that calcium inhibition of the absorption of heme and nonheme iron occurs during the initial uptake step rather than during the serosal transfer step of the absorptive process. Additional objectives were to compare the two-week retention of heme and nonheme iron after their initial entry into the mucosal cell... and to ascertain the relation of serum ferritin² to the separate components of iron absorption.”

Study Design: Clinical experiment

Setting: United States

Sample: 27 males and females, ages 21–53

Intervention Healthy individuals (non-pregnant, no underlying disease, normal iron/hemoglobin) participated in one of two experiments. “Experiment A tested a meal with low iron bioavailability and moderate calcium content (n=15). Experiment B tested a meal with high iron bioavailability and low calcium content (n=12).” Both meals contained heme and nonheme iron radiotracers. Each experiment involved consuming the relevant test meal twice, six weeks apart. The meal was consumed once with a calcium supplement (450mg) and once without. “The entire gut contents were purged eight hours later with an orally administered lavage solution of polyethylene glycol. Initial mucosal uptake was estimated from isotope retention at eight hours, and absorption was estimated from retention at two weeks.”

Results: Experiment A found that adding calcium to the low-iron, moderate-calcium meal did not affect the uptake, absorption, and retention of nonheme iron. Added calcium, however, reduced initial mucosal uptake of heme iron from 49% to 39% (P=0.02) and reduced subsequent absorption of heme iron from 30% to 22% (P for trend=0.06). Supplemental calcium reduced the amount of total iron absorbed from the low iron meal by 25%, from 0.033 to 0.025 mg (P=0.06).

Experiment B found that adding calcium to the high-iron, low-calcium meal did not significantly reduce initial uptake of nonheme iron (13% vs. 10%) but somewhat reduced absorption of nonheme iron from 8% to 6% (P=0.07). Added calcium with this meal reduced initial mucosal uptake of heme iron (from 49% to 40%; P=0.02). It also reduced heme iron absorption (from 22% to 16%; P=0.01). Calcium supplementation of this meal significantly reduced the total amount of iron absorbed from by 27%, from 0.55 to 0.40 mg (P=0.01).

Conclusions/Discussion: Added calcium reduced the initial uptake of heme iron by 20%, from 49% to 40% from both meals (P=0.02), and reduced total iron absorbed from both meals by 25%. Nonheme iron absorption was not significantly affected. Most studies have evaluated short-term effect of calcium on iron absorption. While studies have shown that calcium supplementation for several months did not affect serum iron in premenopausal women, “the long-term use of dietary calcium supplements and fortificants may further increase the risk of iron deficiency in women who are having difficulty in meeting their iron requirements.”

² Associated with total body iron stores

<table>
<thead>
<tr>
<th>Background:</th>
<th>Serum concentration of 25(OH) D (a vitamin D metabolite) in early pregnancy is reduced in women who later develop PE. 1, 25(OH) 2 D (the active form of vitamin D) may play a role in immunologic tolerance during pregnancy, and adequate vitamin D may help in the prevention and management of PE.</th>
</tr>
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<tbody>
<tr>
<td>Objectives/ Aims:</td>
<td>The study aimed to estimate the association between Vitamin D intake (both through diet and supplements) and PE in primiparous women.</td>
</tr>
<tr>
<td>Study Design:</td>
<td>Prospective cohort study</td>
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<td>Setting:</td>
<td>Norway (national study)</td>
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<tr>
<td>Sample:</td>
<td>23,423 nulliparous women enrolled in the Norwegian Mother and Child Cohort Study (NMCCS) with registered food intake &gt;4500 kJ and &lt;20,000 kJ per day.</td>
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<tr>
<td>Method:</td>
<td>Women provided biologic samples and answered questionnaires at week 15, week 22, and week 30 of pregnancy. The first and third questionnaires assessed health, exposures, lifestyles, and background factors; the second was a Food Frequency Questionnaire (FFQ). The FFQ assessed dietary habits and supplement use in depth; the first and third questionnaires also assessed supplement use. PE was assessed through records from the Medical Birth Registry of Norway.</td>
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<tr>
<td>Results:</td>
<td>Among women included in the study, 5.4% (n=1267) developed PE. Intake of vitamin D and long chain n-3 fatty acids increased with increasing age, education, and height, and was lower in smokers and women with body mass index (BMI) &gt; 25. Women who developed PE did not have lower vitamin D intake from diet than women without PE. Women who developed PE, however, did have lower vitamin D intake from supplements. Daily vitamin D intake between 15–20g per day reduced the risk for PE by 25% when adjusting for maternal BMI. The risk reduction was slightly smaller when adjusting for additional factors such as maternal education and smoking. An intake of 10–15g per day from supplements reduced the risk of PE by 29% after adjustment for maternal BMI. No association was seen with vitamin D intake from diet alone. This may be because very few women (0.5%) received 15g per day of vitamin D from their diet. Of women whose supplement use could be assessed (n=22,057), 5.2% (n=1149) developed PE. Women reporting supplementary intake of vitamin D before pregnancy, in early pregnancy and in late pregnancy (all three time points) had a 29% reduced risk of PE compared with those never taking vitamin D supplements.</td>
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<tr>
<td>Conclusions/ Discussion:</td>
<td>The study did not find any benefit to a vitamin D intake above 20g per day. The study also did not find a reduced risk of PE among women who took supplements not containing vitamin D. This suggests that vitamin D supplementation was associated with reduced risk, rather than general good health behaviors that might be associated with taking vitamins. “Our results suggest that it may be possible to reduce the risk of PE through a sufficient vitamin D intake.” Other recent studies of vitamin D intake, however, show no effect on PE; these have been smaller trials, but were also in settings with higher total Vitamin D intake, “which might suggest that the upper level of vitamin D intake for impact on PE was reached.”</td>
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</table>
**Background:** Researchers have established the prevalence of vitamin D deficiency in pregnancy and identified associated adverse maternal and fetal outcomes. Among these are linkages to calcium absorption, which increases during pregnancy, peaking in the third trimester. Vitamin D, however, is a “key modulator of calcium metabolism” and its deficiency is associated with calcium reabsorption and bone loss.

**Objectives/ Aims:** To provide an overview of “the physiologic components of vitamin D, risk factors for vitamin D deficiency, and methods of supplementation to attain optimal levels in pregnant and lactating women.”

**Key Points:** Studies evaluating correlation between vitamin D levels and calcium absorption, as well as bone fracture/turnover, have led to a “classification of stages for vitamin D status in non-pregnant adults,” indicating that “32 ng/mL are required for adequacy.... These stages correlate with maternal and fetal outcomes, which suggest that they also apply in pregnancy and during lactation.” Despite the importance of vitamin D, its deficiency during pregnancy is a worldwide epidemic,” ranging from18–84%.

Several studies have found that Vitamin D deficiency is independently associated with PE risk. While noting the need for further research, the authors recommend “increased supplementation in all pregnant women to keep serum levels of active vitamin D in the normal range for adults (32 ng/mL).”

Studies have shown that women with PE have lower calcium and vitamin D levels compared with normotensive pregnant women. A recent study found that vitamin D deficiency before 22 weeks is an independent predictor of PE. Another trial showed that vitamin D plus calcium supplementation started at 20–24 weeks of gestation significantly reduced blood pressure, but not incidence of PE.

Studies have also identified independent associations between adequate vitamin D intake and infant birth weight. Maternal vitamin D deficiency may also “manifest as congenital rickets, craniotabes, or osteopenia in newborn infants,” due to poor skeletal mineralization in utero. Maternal vitamin D deficiency may also be associated with other adverse child outcomes, including asthma and diabetes.

**Conclusions/ Discussion:** “Current prenatal care does not include the monitoring of vitamin D levels, which is an unfortunate oversight because deficiency is easily treated.” Further research is needed to better understand the influence of vitamin D on calcium metabolism, and to “establish recommended daily doses of vitamin D in pregnant women.” However, the authors note that, because “vitamin D supplementation is simple and cost-effective with a low likelihood of toxicity, we recommend increased supplementation in all pregnant women to keep serum levels of active vitamin D in the normal range for adults (32 ng/mL).”

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Background: Oxidative stress has been proposed as a mechanism underlying PE/E. However, three prior double-blinded randomized controlled trials did not find a reduction in PE from anti-oxidant supplementation. These trials all took place in “well-nourished populations.” Antioxidants could prevent PE by either having “a pharmacological effect in well-nourished women... or may achieve benefit through correction of a deficiency secondary to low dietary intake.”

Objectives/ Aims: The trial evaluates “whether or not supplementation with vitamins C and E prevents PE and low birth weight among women at high-risk for PE from communities at risk of poor nutritional status in developing countries.”

Study Design: Multicenter, randomized, placebo-controlled, double-blind trial

Setting: Antenatal clinics serving low socioeconomic status populations with evidence of low nutritional status. Clinics were located in India, Peru, South Africa and Vietnam.

Sample: Pregnant women (n=1365) at high-risk for PE, randomized to vitamins (n=687) or placebo (n=678). Of women receiving vitamins, 681 women and their 753 infants were included in the analysis; of women receiving placebo, 674 women and their 762 infants were included in the analysis.

Intervention: Women in the vitamin group received vitamin C tablets (1000 mg) and vitamin E capsules (400 iu). Women entered the study between 14 and 22 weeks gestation and took supplements or placebo daily.

Results: The primary outcome was PE occurring after 20 weeks gestation and up to 72 hours postpartum. Eclampsia and neonatal outcomes (e.g., LBW) were also assessed. The incidence of PE was similar in both groups: 24.1% in the vitamin group and 23.3% in the placebo group (RR=1.0; CI 0.9-1.3). There were no significant differences between the groups in occurrence of eclampsia (RR=1.5; CI 0.3-8.9), gestational hypertension (RR=1.2; CI 0.9-1.7), or other maternal outcomes. Low birth weight, small for gestational age and perinatal deaths were not significantly different between the groups.

Conclusions/ Discussion: Vitamins C and E at the doses used did not prevent PE in these high-risk women. The results are consistent with two other recent, large studies, “demonstrating that independent of the study population, including its risk level and nutritional status, vitamins C and E supplements are unlikely to prevent PE, low birth weight, small for gestational age or perinatal death. Therefore, such supplements should not be recommended for clinical practice.”
## C. Detection, Screening and Prediction of PE/E

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<tr>
<td><strong>Background:</strong></td>
<td>The ability to predict patients at risk for PE would enable clinicians to identify women who require surveillance and enable early referral for treatment. Identification of at-risk women may also simplify research regarding the origins of PE and its prevention. “Although numerous tests have been proposed for the prediction or early detection of PE, their results... have been inconsistent and contradictory, with most deemed unreliable or unsuitable for routine use...”</td>
</tr>
<tr>
<td><strong>Objectives/Aims:</strong></td>
<td>The aim of the study was to “assess critically, from the best-available evidence, the clinical usefulness of promising clinical, biophysical, and biochemical tests in the prediction of PE.”</td>
</tr>
<tr>
<td><strong>Review Design:</strong></td>
<td>The review compiled studies conducted through February 2003 that meet inclusion criteria. The review assessed screening accuracy through likelihood ratios, and studies of the same test were pooled when possible. “As of early 2004, there is no clinically useful screening test to predict PE in either high- or low-risk populations.”</td>
</tr>
<tr>
<td><strong>Included Studies:</strong></td>
<td>A total of 87 studies (n=211,369 women) met inclusion criteria. Sixty studies focused on low-risk women, 24 focused on high-risk women, and 3 on both. The studies assessed Doppler ultrasonography (43), 24 hour ambulatory blood pressure (2), placental and fetal peptides (22), renal dysfunction-related tests (13), and endothelial and oxidant stress dysfunction-related tests (8).</td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td>Overall, among low-risk women, “there was a moderate predictive accuracy for anticardiolipin antibodies, presence of bilateral diastolic notches at Doppler ultrasonography, and urinary kallikrein.” However, because “a minimal increase in the pretest probability of PE was associated with a positive result... the clinical use of these tests in the general population was limited.” For Doppler ultrasonography, the “level of prediction of PE in both low-risk and high-risk populations was moderate to minimal,” with poorer predictive accuracy in high-risk women. The predictive accuracy of 24-hour ambulatory blood pressure tests was moderate in low-risk women and low in high-risk populations. The predictive accuracy of fetal and placental peptides tests “generally were quite low.” The authors could not draw conclusions about the accuracy of several other suggested tests because of the poor quality and limited number of studies.</td>
</tr>
<tr>
<td><strong>Conclusions/Discussion:</strong></td>
<td>“This review shows that, as of early 2004, there is no clinically useful screening test to predict PE in either high-risk or low-risk populations.” The authors note the methodological and data limitations of many included studies, and warn that the pooled estimates should be interpreted cautiously. The authors discuss emerging evidence regarding the possibly greater predictive accuracy of combinations of tests, but note that current data are limited. The authors provide guidelines for future research on screening tests for PE and discuss the need for an “ideal predictive test” that is “simple, innocuous, rapid, inexpensive, reproducible, and noninvasive, as well as easy to perform early in pregnancy to allow interventions” to prevent or mitigate disease development.</td>
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**Background:** Proteinuria is used as a marker for hypertensive diseases of pregnancy including PE. Hypertension with proteinuria is associated with poorer maternal and perinatal outcomes. Dipstick urinalysis is the most commonly used antenatal screening method for proteinuria. Recent reports indicate poor correlation between dipstick urinalysis and 24-hour protein measurements; some studies have found significant false negative rates and others have found significant false positive rates.

**Objectives/Aims:** The aim of the study is to "evaluate the accuracy of dipstick urinalysis in a single voided urine sample in assessing proteinuria in hypertensive women."

**Study Design:** Prospective study

**Setting:** A tertiary referral center in South Africa where 18% of all obstetric admissions have hypertensive disorders of pregnancy.

**Sample:** 198 pregnant patients presenting to the antenatal clinic with hypertension

**Intervention:** Routine dipstick urinalysis was performed by midwives for proteinuria and a 24-hour urine specimen was collected over the next day for quantitative protein assessment.

Urine dipstick analysis for protein was also performed by a laboratory technician on a mixed aliquot of the 24-hour urine collection. The predictive values, sensitivity and specificity for the dipstick analyses were calculated using the 24-hour urine protein as the gold standard.

**Results:** The dipstick analysis from antenatal clinic screening had 51.4% sensitivity, 84.1% specificity, 64.9% positive predictive value (PPV), and 75.2% negative predictive value (NPV). The laboratory dipstick analysis on the 24-hour aliquot had 68.1% sensitivity, 97.6% specificity, 94.2% PPV, and 84.2% NPV.

**Conclusions/Discussion:** The authors suggest that the inaccuracy of dipstick urinalysis may be related to inter-observer errors in interpretation, and the fact that tests on single urine specimens only reflect protein concentration at a given time. Time-specific measures may be affected by factors such as contamination and changes in posture. The authors note that the antenatal screening dipstick urinalysis had a false negative rate of 48.6% and suggest that all women with hypertension during pregnancy should have a 24-hour urine protein measurement. The authors also suggest that 6- and 12-hour urine collection may also be useful in screening, although further research is required.

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3 Exact fractions of each of the collected urine voiding over the 24-hour period
Background:
In 46% of maternal deaths and 65% of fetal deaths due to PE reported through the confidential enquiry system in the United Kingdom, “different management would reasonably have expected to alter the outcome.” These reviews suggested a “failure to identify and act on known risk factors at booking and to recognize and respond to signs and symptoms from 20 weeks’ gestation... No guidelines exist for the screening and early detection of PE in the community, and there is no uniformity in referral thresholds and assessment procedures.”

Objectives/Aims:
To provide an “evidence-based risk assessment [guideline], with criteria for early referral for specialist input, a... schedule for monitoring women in the community after 20 weeks’ gestation, and referral criteria for step-up care.”

Guideline overview:
The guideline recommends risk assessment early in pregnancy using thresholds derived from research data. Early assessment should identify the presence of predisposing factors including: first pregnancy; previous PE; ≥ 10 years since last baby; age ≥40 years; BMI ≥ 35; family history of PE; booking diastolic BP ≥ 80 mm Hg; proteinuria at booking; and underlying medical conditions. The guideline recommends that women be offered specialist referral before 20 weeks if they have: previous PE; multiple pregnancy; underlying medical conditions; pre-existing hypertension or booking diastolic BP ≥ 90 mm Hg; preexisting renal disease or booking proteinuria; preexisting diabetes; presence of antiphospholipid antibodies; or any two other factors from the risk assessment list above.

After 20 weeks, the guideline recommends that every assessment identify and act on the presence of any of the signs and symptoms of the onset of PE: new hypertension; new proteinuria; symptoms of headache and/or visual disturbance; epigastric pain and/or vomiting; reduced fetal movements; or small for gestational age infant.

Conclusions/Discussion:
“The guideline provides a framework by which pregnant women with PE are offered specialist care at the appropriate time for the best outcome for them and their baby.”

Note: The recommendations are made in the context of the United Kingdom, but the data guiding the risk criteria are based on generalizeable clinical research.
Background: Proteinuria is one of the essential criteria for the clinical definition of PE. It is part of the fundamental investigations performed by healthcare professionals... to monitor disease severity and predict complications in women with PE. However, studies documenting an association between levels of proteinuria and “maternal and neonatal outcomes have not generally been conducted with sufficiently large sample size to provide precise accuracy estimates... There are no systematic reviews exploring the accuracy of proteinuria to predict complications of PE.”

Objectives/Aims: To conduct “a comprehensive systematic review to obtain precise estimates of likelihood ratios of adverse maternal and fetal complications for various cut-off levels of proteinuria in women with PE.”

Review Design: The review included studies “which evaluated the accuracy of proteinuria in women with PE for the prediction of maternal or fetal complications.”

Included Studies: Sixteen primary articles were included (n=6749 women). Of these, eight reported estimation of proteinuria by laboratory method only, five by bedside dipstick urinalysis only, two by either of these methods, and one by spot urine protein:creatinine ratio.

Results: Likelihood ratios (LRs) for positive and negative test results were calculated for each study, indicating “by how much a given test result raises or lowers the probability of having the disease... All 10 studies predicting maternal outcomes showed that proteinuria is a poor predictor of maternal complications in women with PE. Seventeen studies used laboratory analysis and eight studies used bedside analysis to assess the accuracy of proteinuria in predicting fetal and neonatal complications. Summary LRs for positive and negative tests for the threshold level of 5 g/24 h were 2.0 and 0.53 for stillbirths, 1.5 and 0.73 for neonatal deaths, and 1.5 and 0.78 for Neonatal Intensive Care Unit admission.”

Conclusions/Discussion: “The magnitude of proteinuria in women with PE is a poor predictor of the major maternal and fetal complications.” This “calls into question the commonly used practice of making clinical decisions in women with PE based on the severity of proteinuria.” The authors note limitations due to heterogeneity between individual studies, and cite the need for both meta-analyses using individual patient data from past research and for “large, well-designed prospective studies” on this topic.

4 An LR >10 or <0.1 is... “very useful” test accuracy, an LR of 5 to 10 or 0.1 to 0.2 is... ‘moderately useful’, and an LR of 2 to 5 or 0.2 to 0.5 is... ‘somewhat useful.’ An LR of 1 to 2 or 0.5 to 1 is only regarded as a “little useful” and an LR of 1 as “useless.”
**D. Treatment: Magnesium Sulfate Including Doses/Regimens and Barriers to Scale-up**

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<tr>
<td><strong>Background:</strong></td>
<td>Magnesium sulfate has been identified as the drug of choice for women with eclampsia; however, evidence is required to establish its utility in managing PE.</td>
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<td><strong>Objectives/Aims:</strong></td>
<td>To examine &quot;whether women with PE, their children, or both do better if given magnesium sulfate compared to placebo, regardless of whether treatment is started before or after delivery and irrespective of any previous anticonvulsant therapy.&quot;</td>
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<td><strong>Setting:</strong></td>
<td>175 hospitals in 33 countries (Asia, Africa, North America, South America, Europe, Middle East)</td>
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<td><strong>Sample:</strong></td>
<td>10,136 women randomized to receive magnesium sulfate (n=5,068) or placebo (5,068)</td>
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<td><strong>Intervention:</strong></td>
<td>The exact regimen of magnesium sulfate (including route of maintenance dose) varied by setting. Standard magnesium sulfate treatment was a loading dose followed by 24-hour maintenance therapy—with clinicians choosing either intravenous (IV) or intramuscular (IM) administration of the maintenance doses. The loading dose was 8 mL trial treatment (4 g magnesium sulfate or placebo) given IV for 10–15 minutes. For IV maintenance, the loading dose was followed by an infusion of 2 mL/h treatment for 24 hours (1 g/h magnesium sulfate or placebo). For IM maintenance, the loading dose was combined with 20 mL treatment by IM injection, given as 10 mL trial treatment (5g magnesium sulfate or placebo) into each buttock. This was followed by 10mL treatment (5g magnesium sulfate or placebo) every four hours for 24 hours.</td>
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<td><strong>Results:</strong></td>
<td>In total, 0.8% of women allocated magnesium sulfate had eclamptic convulsions (n=40), compared to 1.9% of those allocated placebo (n=96). The effect was consistent regardless of severity of PE, stage of gestation, whether an anticonvulsant had been given before trial entry, whether the woman had delivered at trial entry, and parity. There were no clear differences between the groups in any measure of maternal morbidity, in the composite measure, or in use of maternal health services. There was no significant difference in the risk of the baby dying between trial groups, or in other outcomes of pregnancy, labor or delivery—except a 37% reduction in the risk of placental abruption in women receiving magnesium sulfate. In all, 24% of women allocated magnesium sulfate had side effects (e.g., flushing), compared with 5% allocated placebo.</td>
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<td><strong>Conclusions/Discussion:</strong></td>
<td>This large multicenter trial demonstrated that magnesium sulfate &quot;halves the risk of eclampsia, and probably reduces the risk of maternal death&quot; without evidence of substantive harmful effects in the short-term. Research is needed to determine the minimum effective dose and answer questions regarding timing and route of administration, and the association of the latter with side effects.</td>
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### Background:
Eclampsia is a rare but serious complication of pregnancy that accounts for about 10% of maternal deaths worldwide. Anticonvulsants are used to control eclamptic fits and prevent recurrence, but there has been controversy about which drug to use. Different drugs are used in different settings. While magnesium sulfate is the drug of choice in the U.S., drugs in use in other settings include diazepam, phenytoin and lytic cocktail.

### Objectives/Aims:
The objective of this review was to assess the effects of magnesium sulfate compared with diazepam when used for the care of women with eclampsia.

### Review Design:
“All known randomized trials that compare magnesium sulfate with diazepam when used for the care of women with eclampsia” were included. Quasi-random designs were excluded.

### Included Studies:
Seven trials were included (n=1441); trial locations included Bangladesh, Egypt, India, Malaysia, and Zimbabwe.

### Results:
In most trials, the magnesium sulfate regimen included a 4g loading dose, followed by 24 hours of IV or IM maintenance therapy. Magnesium sulfate is associated with a reduction in the risk of maternal death compared to diazepam (RR = 0.59, CI: 0.37 to 0.94). Magnesium sulfate is associated with a “substantial reduction” in the risk of recurrent convulsions (RR = 0.44, CI: 0.34 to 0.57). “On average, for every seven women treated with magnesium sulfate rather than diazepam, one recurrence of convulsions will be prevented.” Three trials reported on perinatal mortality; there was not a significant difference between magnesium sulfate and diazepam. There was a statistically significant reduction in Apgar scores <7 at 1 minute (RR = 0.75, CI: 0.65 to 0.87) and <7 at 5 minutes (RR = 0.72, CI: 0.55 to 0.94) with magnesium sulfate versus diazepam. There was also a statistically significant reduction in the number of liveborn babies with a length of stay in a special care baby unit >7 days (RR = 0.66, CI: 0.46 to 0.95) associated with the use of magnesium sulfate versus diazepam.

### Conclusions/Discussion:
Magnesium sulfate for women with eclampsia reduces the risk of both maternal death and further fits, compared to diazepam. The authors also discuss findings in the context of other reviews comparing magnesium sulfate to lytic cocktail and phenytoin. “There is now compelling evidence in favor of magnesium sulfate, rather than diazepam, phenytoin or lytic cocktail for the treatment of eclampsia. Magnesium sulfate is cheap and relatively easy to produce, and so making it readily available for the care of women with eclampsia in both high-income and low-income to middle-income countries should be a high priority.”

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<tr>
<td>Background:</td>
<td>Magnesium sulfate has been recognized as the drug of choice in treating eclampsia and in preventing it among women with PE. The Pritchard and Zuspan regimens for loading dose and maintenance therapy “have been evaluated in the randomized trials of anticonvulsants for women with eclampsia and PE.” Various alternative regimens have been proposed and there is “growing interest in the use of short regimens” in low-resource settings, as well as in administration of a single dose of magnesium sulfate at community or primary care level before transfer to a hospital.</td>
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<td>Objectives/ Aims:</td>
<td>“The aim of this review is to assess the comparative effects of alternative regimens for the administration of magnesium sulfate when used for the care of women with PE or eclampsia, or both.”</td>
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<tr>
<td>Review Design:</td>
<td>The review included “randomized trials comparing different regimens for administration of magnesium sulfate used for the care of women with PE and/or eclampsia, or both.” Quasi-random designs were excluded.</td>
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<td>Included Studies:</td>
<td>“Six trials (n=866) met inclusion criteria: two trials (n=451) compared regimens for women with eclampsia and 4 (415 women) for women with PE.”</td>
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<td>Results:</td>
<td>A Bangladesh trial compared a magnesium sulfate loading dose alone to a loading dose plus maintenance regimen. The loading dose was 4 g IV plus 6 g IM, and maintenance was 2.5g IM every four hours (standard doses in Bangladesh). There was no clear difference between the groups in recurrence of convulsions (RR = 1.13, CI: 0.42 to 3.05), stillbirth (RR = 1.13, CI: 0.66 to 1.92), or other outcomes. Another trial compared the Dhaka low-dose regimen to a standard dose regimen. While there were clear differences between treatment groups, this trial was too small for reliable conclusions (n=50) and confidence intervals were extremely wide (RR=3.0, CI: 0.13 to 70.30). A trial compared IV with IM maintenance regimen for the prevention of eclampsia. “Women allocated the standard IM regimen were less likely to need antenatal antihypertensive therapy than those allocated high-dose IV regimens.” The confidence intervals were extremely wide, and the trial was too small (n=17) for reliable conclusions. Three trials compared short maintenance regimens postpartum with continuing for 24 hours after the birth. “Even taken together these trials were too small for any reliable conclusions.”</td>
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<td>Conclusions/ Discussion:</td>
<td>“There is little reliable evidence... assessing the minimum effective dose, the comparative effects of alternative routes of administration (intravenous or intramuscular), or the ideal duration of therapy.”</td>
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"There is little reliable evidence... assessing the minimum effective dose, the comparative effects of alternative routes of administration (intravenous or intramuscular), or the ideal duration of therapy."

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<th><strong>Background:</strong></th>
<th>Although WHO has recommended magnesium sulfate as the “most effective, safe, and low-cost drug to treat” severe PE/E, less effective and higher-risk drugs are still widely used in developing countries.</th>
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<td><strong>Objectives/Aims:</strong></td>
<td>Engender Health convened a group of researchers, advocates and actors in the health field to “identify country-specific barriers and potential facilitating factors” related to the availability of magnesium sulfate.</td>
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<td><strong>Findings</strong></td>
<td>The group identified four main barriers to magnesium sulfate use:</td>
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<td>1. Absence of guidelines mandating magnesium sulfate use in most developing countries, and absence of magnesium sulfate on most essential drug lists.</td>
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<td>2. Existing guidelines are often not widely disseminated or mandatory.</td>
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<td>3. Health workers are often not trained or authorized to administer magnesium sulfate and its use is often restricted to higher-level facilities due to perceptions regarding the need for close monitoring.</td>
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<td>4. There are few incentives for drug companies to expand magnesium sulfate availability or improve its packaging dose for use in PE/E, because it is an inexpensive drug and these conditions affect relatively few people.</td>
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<td><strong>Conclusions/Discussion:</strong></td>
<td>Despite the evidence regarding magnesium sulfate’s efficacy, safety and cost-effectiveness, it is “unavailable in most health facilities in the settings where most deaths [due to PE/eclampsia] occur... Widespread availability and appropriate use of affordable, ready-to-use eclampsia treatment packs to give magnesium sulfate should be priorities for the reduction of the unacceptable burden of eclampsia and severe PE.” The authors call for the inclusion of magnesium sulfate on essential drug lists, the availability of appropriate treatment packs in all settings, and the training of all health professionals in the appropriate use of magnesium sulfate to treat severe PE and eclampsia.</td>
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*Widespread availability and appropriate use of affordable, ready-to-use eclampsia treatment packs to give magnesium sulfate should be priorities for the reduction of the unacceptable burden of eclampsia and severe PE.*
Background: A review of maternal deaths in the United Kingdom found that 10% were “due to a hypertensive disorder of pregnancy [that] occurred in the postpartum period.” Another review in the United Kingdom found that 1 of 15 maternal deaths “was attributed to severe hypertension that developed only postpartum in a woman with antenatal PE.” However, “there is very little information on how best to manage postpartum hypertension, regardless of type or severity, to optimize maternal safety and minimize hospital stay.”

Objectives/Aims: “To assess the relative benefits and risks of interventions to:

1. Prevent postpartum hypertension by assessing whether “routine” postpartum medical therapy is better than placebo/no treatment; and

2. Treat postpartum hypertension by assessing whether: (i) one antihypertensive therapy is better than placebo/no therapy for mild-moderate postpartum hypertension; and (ii) one antihypertensive agent offers advantages over another for mild-moderate or severe postpartum hypertension.”

Randomized controlled trials were included. Quasi-random designs were excluded.

Results: The prevention trials compared routine furosemide or nifedipine therapy to prevent postpartum hypertension with placebo or no therapy among women with antenatal PE. “Postnatal furosemide was associated with a strong trend towards reduced use of antihypertensive therapy in hospital” (RR= 0.74, CI: 0.55 to 1.00).

The treatment trials included women with antenatal PE and women who were normotensive ante- and intrapartum. The trials on treatment of mild-to-moderate hypertension compared “timolol, hydralazine (po), or nifedipine (po) with methyldopa. Use of additional antihypertensive therapy did not differ between groups (RR=0.69, CI: 0.39 to 1.21), but the trials were not consistent in their effects.”

The trials on treatment of severe hypertension compared “intravenous hydralazine with either sublingual nifedipine or intravenous labetalol... Use of additional antihypertensive therapy did not differ between groups (RR=0.43, CI 0.11 to 1.77), but the trials were not consistent in their effects.”

Conclusions/Discussion: “For women with PE, postnatal furosemide may decrease the need for postnatal antihypertensive therapy in hospital, but more data are needed on substantive outcomes before this practice can be recommended. There are no reliable data to guide management of women who are hypertensive postpartum.”

Any antihypertensive agent used should be based on a clinician’s familiarity with the drug.” As postpartum blood pressure peaks three to six days postpartum, “clinicians should be aware that peaks may occur after hospital discharge and... may be missed unless close follow up is ensured.” It is recommended that future studies include data on “postpartum analgesics, severe maternal hypertension, breastfeeding, hospital length of stay, and maternal satisfaction with care.” Future trials should also compare treatments to placebo before comparing them to each other.
**Full citation:**

**Background:**
In Bangladesh, eclampsia is a major cause of maternal mortality, estimated to account for 16% of maternal deaths. While magnesium sulfate is known to be the most effective treatment, most women with eclampsia die without hospital care. Moreover, case fatality rates are high among those that do reach care due to delays in referral and the "long interval between onset of convulsion and reaching the hospital."

**Objectives/Aims:**
"To see the role of injection magnesium sulfate in eclampsia and severe PE patients at community level in a rural set-up before referral to the hospital."

**Study Design:**
Quasi-experimental intervention study

**Setting:**
Upazilas (sub-districts) in Tanagil, Netrokona, and Jamalpur districts in Bangladesh

**Sample:**
Women with eclampsia and severe PE (n=265)

**Intervention:**
Awareness was raised about PE and eclampsia in study sites and local providers were trained. Women with convulsions were reported to field workers or traditional birth attendants by family members. Once cases were confirmed, women in the intervention group received a loading dose of magnesium sulfate at home (4g by IV and 3g IM magnesium sulfate in each buttock) before referral to the nearest hospital. Women in the control group received the loading dose of magnesium sulfate upon admission to a hospital.

**Results:**
There was a statistically significantly higher recurrence of fits in the control group (25.8%) versus the intervention group (6.0%). Control of convulsions by the loading dose was achieved in 94% of the intervention group and 74% of the control group. A longer time to regain full consciousness was observed in the control group (17.4 hours) versus the intervention group (12.0 hours). There was a statistically significant difference in maternal mortality: three deaths in intervention group (2.3%) compared to 14 in the control group (10.4%). There were also statistically significant differences in the rates of complications in the intervention group (17.3%) versus the control group (27.3%). There were 14 stillbirths (13.7%) in the intervention group versus 21 (20%) in the control group.

**Conclusions/Discussion:**
The findings of this study indicate that "earlier administration of injection magnesium sulfate in the community is superior to the administration of the drug after arrival in the hospital." Early intervention with magnesium sulfate injection in the community could result in better maternal and fetal outcomes. Introducing this intervention at the community level will require training, supply and supervision inputs, but may bring benefits in health outcomes and potentially reductions in other health care costs.
E. Expectant/Conservative Management of Severe PE


**Background:** Because pregnancies with severe PE “are associated with high rates of maternal morbidity and mortality and... potential risks for the fetus, there is... agreement that such patients should be delivered if the disease develops at >34 weeks of gestation.” When severe disease develops at <34 weeks of gestation, expectant management has been suggested as a way to prolong gestation and improve outcomes.

**Objectives/Aims:** The objective is “to review the maternal and perinatal risks of the treatment of severe PE remote from term including patients who are considered ideal candidates for this treatment and contraindications to this therapy.”

**Review Design:** Review of trials and observational studies; generation of evidence-based recommendations.

**Included Studies:** Two randomized trials and eight observational studies were included, with sample sizes ranging from 18 to 340. Six additional studies of expectant management at <25 weeks of gestation were also included.

**Results:** Among patients receiving expectant management at 24–34 weeks of gestation, the rate of perinatal deaths in included studies ranged from 0 to 16.6%. The rate of placental abruption ranged from 4.1% to 22.9%. Pooling two large studies, the combined average need for delivery due to “worsening fetal status” was 44%. The rate of small for gestational age ranged from 21.7% to 61.9%.

Regarding maternal complications, the rate of HELLP syndrome/thrombocytopenia ranged from 4.1% to 27.1%. The rate of pulmonary edema ranged from 0-8.5%. Rates of eclampsia ranged from 0 to 5.6% and rates of acute renal failure ranged from 0 to 5.5% (although both were at 1% in recent studies from the United States and Europe).

There is less data on patients receiving expectant management at <25 weeks of gestation. Among these patients, “the perinatal death rate ranged from 71% to 100%, with few newborn infants surviving without handicap.” Of the 115 patients, there was 1 maternal death (0.9%) and high rates of morbidities (27%to 71%).

**Conclusions/Discussion:** The author proposes a selection and management plan that considers “fetal gestational age, maternal and fetal status at... initial assessment, presence of labor, or rupture of fetal membranes.” The author proposes that patients at 24–33 weeks of gestation “receive individualized treatment based on their clinical response” during an initial 24-hour observation period during which magnesium sulfate is administered. If blood pressure is controlled and fetal testing is reassuring, magnesium sulfate can be discontinued, and patients can be monitored closely on an inpatient basis until 33 weeks of gestation. Patients should be delivered if any of a set of maternal or fetal indicators arises (e.g., uncontrolled hypertension). Patients with certain contraindications for expectant management (e.g., HELLP syndrome) should be delivered.

Recommendations regarding delivery method are also provided. “Expectant treatment improves perinatal outcome in a select group of women with severe PE at <33 weeks.” The authors note that this type of expectant management “should be performed only in select hospitals (with adequate maternal and neonatal intensive care facilities) and should include close... surveillance and a target gestational age for delivery and indications for delivery before the target.” The authors also note that recommendations are based on limited evidence, including only two small randomized trials.
SECTION 2: CITATIONS

A. General information about PE/E: statistics, guidelines, risks and strategies


B. PE/E Prevention: Calcium, Aspirin, Vitamin D and Anti-oxidants


C. Detection, Screening and Prediction of PE/E


D. Treatment: Magnesium Sulfate Including Doses/Regimens and Barriers to Scale-up


E. Expectant/conservative Management of Severe PE


F. Cardiovascular Disease and Body Mass Index


