

Hypertension In Pregnancy: A Review of Preeclampsia, Its Effects and Management

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ABSTRACT

Hypertension complicates 5% to 7% of all pregnancies. Pre-eclampsia is a major contributor to maternal mortality worldwide. In Africa and Asia they contribute to 9% of deaths. A subset of preeclampsia, characterized by new-onset hypertension, proteinuria, and multisystem involvement, is responsible for substantial maternal and fetal morbidity and is a marker for future cardiac and metabolic disease. It is a pregnancy-specific disease characterized by de-novo development of concurrent hypertension and proteinuria, sometimes progressing into a multi organ cluster of varying clinical features. Poor early placentation is especially associated with early onset disease. Symptomatic clinical management should be mainly directed to prevent maternal morbidity (e.g. eclampsia) and mortality. Expectant management of women with early onset disease to improve perinatal outcome should not preclude timely delivery—the only definitive cure.

KEY WORDS: *Proteinuria, Preeclampsia, Uteroplacental, Glomerular Endotheliosis.*

INTRODUCTION

Hypertension, complicating 5% to 7% of all pregnancies, is a leading cause of maternal and fetal morbidity, particularly when the elevated blood pressure (BP) is due to preeclampsia, either alone (pure) or "superimposed" on chronic vascular disease.^{1,2} Preeclampsia is a major contributor to maternal mortality worldwide. In Africa and Asia they contribute to 9% of deaths.^{3,4}

Preeclampsia is a major cause of preterm birth and an early marker for future cardiovascular and metabolic diseases, whereas preterm delivery is associated with immediate neonatal morbidity and has been linked to remote cardiovascular and metabolic disease in the newborns.^{2,5} This is diagnosed when there are two or more episodes, more than 4 hours apart, of blood pressure >140/90 mmHg at ≥ 20 weeks of gestation.⁶ Proteinuria is significant if there is ≥ 0.3 g urinary protein/24 hours, a spot protein:creatinine ratio ≥ 30 , or $\geq ++$ protein on urine dipstick, with no evidence of urinary tract infection. Pre-eclampsia is hypertension and significant proteinuria at ≥ 20 weeks of gestation with incidence of 2-8% while gestational hypertension is hypertension at ≥ 20 weeks of gestation in the absence of significant proteinuria with incidence of 4.2 -7.9%.⁷ Both gestational and essential hypertension can

progress to pre-eclampsia, which is mainly a disease of primigravidae (occurring in 4.1% of first versus 1.7% of subsequent pregnancies), although it can recur or occur for the first time in subsequent pregnancies. The lower overall risk of pre-eclampsia among parous women cannot be explained by their being fewer pregnancies among women who have had pre-eclampsia in a previous pregnancy.⁶ There is no effect of parity on women with gestational hypertension and they have a 16-50% chance of developing the disease again.⁹

Large increments in cardiac output, accompanied by marked increases in intravascular and extracellular volume, occur rapidly during the first half of pregnancy, then plateau or rise more slowly thereafter. BP falls, with decrements starting in early gestation and reaching a nadir near term.

DISCUSSION

Pathology Of Preeclampsia:

BP and the Cardiovascular System: Hypertension in preeclampsia is due primarily to marked vasoconstriction, because both cardiac output and arterial compliance are reduced.^{10, 12, 13}

Kidney: Renal hemodynamics increases markedly in normal gestation. Renal plasma flow (RPF) and GFR decrease in preeclampsia (25%); thus, values may still be above or at those measured in the non pregnant state. The decrement in RPF is attributable to vasoconstriction, whereas the fall in GFR relates both to the decrement of RPF and the development of a glomerular lesion termed glomerular endotheliosis.^{12, 14, 15}

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Placenta: Shallow and abnormal placentation is a hallmark of preeclampsia, highlighted by a failure of the normal trophoblastic invasion of the spiral arteries, these vessels failing to remodel and dilate.¹⁶ Restriction of placental blood flow leads to a relatively hypoxic uteroplacental environment, with subsequent events mediated through hypoxemia-induced genes resulting in the release of factors (e.g. antiangiogenic proteins) that enter the mother's circulation and initiate the maternal syndrome.

Brain: Studies using sophisticated imaging techniques reveal increased cerebral blood flow in preeclamptic women. Reports based on computed axial tomography and magnetic resonance imaging describe transient abnormalities consistent with localized hemorrhage or edema.¹⁷

Liver and Coagulation Abnormalities: Preeclampsia is associated with activation of the coagulation system, with thrombocytopenia (usually mild) as the most commonly detected abnormality. There is increased platelet activation and size, plus decrements in their lifespan. The hypercoagulability of normal pregnancy is accentuated (e.g., reduced antithrombin III, protein S, and protein C) even when platelet counts appear normal.^{12,18} Preeclampsia also affects the liver.^{11,12} Manifestations include elevated aspartate aminotransferase and lactic dehydrogenase levels, the increments usually small, except when the HELLP syndrome supervenes.

Prevention:

Several nutritional and non-nutritional interventions have been suggested to prevent pre-eclampsia. A recent overview of randomized trials of nutritional interventions during pregnancy reports that nutritional advice on increasing protein and energy intake generally or restricting protein or energy intake for obese women; supplementing iron, folate, magnesium, zinc, or fish oil; and restricting salt intake are unlikely to be beneficial.¹⁹ Therefore, efforts to introduce these activities for prevention of pre-eclampsia should not be a priority.

Antioxidants such as vitamin E and C have recently been demonstrated to be effective in preventing preeclampsia in a small randomized controlled trial conducted in a very high-risk population.²⁰ There are now at least three multicenter randomized controlled trials in progress or about to commence to assess the effectiveness of antioxidant supplementation in preventing pre-eclampsia among low- and high-risk women.

The idea of calcium supplementation during pregnancy to prevent pre-eclampsia is based on epidemiological observations of the link between the high incidence of pre-eclampsia and the low dietary intake of calcium.²¹ An

overview of trials evaluating the effectiveness of this approach suggests that women who are at risk of developing pre-eclampsia are those whose calcium intake is below 600 mg/day, are the group who may benefit from this intervention.¹⁹ The WHO double-blind multicenter randomized trial of 1.5 g/day of calcium supplementation recruited 8350 women and should provide conclusive evidence on the effectiveness of this intervention among low-calcium-intake women.²²

A Cochrane review of 32 randomized trials where antiplatelet agents, primarily low-dose aspirin, were administered to prevent pre-eclampsia among 29 331 women reported modest benefits from such a regimen (RR 0.85, 95% CI, 0.78–0.92).²⁵ These effects were stronger in high-risk, nulliparous women and women with poor obstetric history. Considering the advantages of low cost and reasonable reassurance about safety, the use of aspirin is primarily recommended for only these groups.^{25,26}

Clinical Presentation:

Maternal organ systems that are susceptible to excessive inflammation and endothelial damage are the CNS, lungs, liver, kidneys, systemic vasculature, coagulation, and the heart—the placenta and fetus are also at risk. The more organ systems that are affected, the more maternal and perinatal complications arise. Clinicians should take caution not to undervalue clinical signs and symptoms in (severe) pre-eclampsia because they can be non-specific (eg, nausea and vomiting). Caregivers should always remember that pre-eclampsia can potentially fulminate, and therefore they should not be given a false sense of security because mild disease has been designated. Some risks pertain to development of the HELLP syndrome of microangiopathic haemolysis and platelet consumption, and hepatocellular damage from periportal or focal parenchymal necrosis. Patients frequently (40–90%) have epigastric or right upper quadrant pain.²⁷ These clinical symptoms, along with headache, visual changes, and nausea or vomiting seem to be more predictive than are laboratory parameters for adverse maternal outcomes.²⁸

Management:

Advise women at high risk of pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby including hypertensive disease during a previous pregnancy, chronic kidney disease, autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, 1 or type 2 diabetes & chronic hypertension.

Advise women with more than one moderate risk factor for pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Factors indicating

moderate risk are: first pregnancy, age 40 years or older, pregnancy interval of more than 10 years, body mass index (BMI) of 35 kg/m² or more at first visit, family history of pre-eclampsia & multiple pregnancy.⁹

Suspicion of preeclampsia is sufficient reason to recommend hospitalization, given the disease's potential to accelerate rapidly.^{11, 12, 13, 29} This approach will minimize diagnostic error, diminish the incidence of convulsions, and improve fetal outcome. Because delivery remains the only known "cure," and maternal and fetal disease status may change rapidly, near term, induction of labor is the therapy of choice. Delivery is indicated at any stage of pregnancy if severe hypertension remains uncontrolled for 24 to 48 hours or at the appearance of certain "ominous" signs such as clotting or liver abnormalities, decreasing renal function, signs of impending convulsions (headache, epigastric pain, and hyperreflexia), or the presence of severe growth retardation or non reassuring fetal testing.³⁰

Central adrenergic inhibitor methyl dopa is the "preferred" drug of choice based on 20_ years of post marketing surveillance, several controlled trials, and the longest follow-up (7.5 years) in neonates. Adrenergic blocking agents are associated with an increased incidence of fetal growth restriction though the effects are minimal, and many clinicians use the combined beta and adrenergic blocker labetalol.^{11,31} Theoretically, there may be synergism between magnesium sulfate and calcium-channel blocking agents leading to precipitous decreases in BP and even respiratory arrest, but this has not been borne by systematic review.³² Management of eclamptic convulsions requires parenteral magnesium sulfate administration, which is shown to be superior to either diazepam or phenytoin for both prevention and treatment.^{11,12,33,34}

There are few strategies that are very effective in treating pre-eclampsia/eclampsia. Antihypertensive drugs are specifically recommended to treat severe hypertension.³⁵ The choice of antihypertensive should depend on the individual clinicians according to the clinical picture and on maternal and fetal side effects of the drugs. The effectiveness of antihypertensives in mild to moderate hypertension is still unclear.³⁶

Magnesium sulfate remains the only specific strategy recommended to prevent eclampsia, in women with pre-eclampsia and to reduce recurrence of convulsions and maternal death in women with eclampsia.^{37,38} When used for moderate to severe pre-eclampsia, magnesium sulfate reduces the risk of eclampsia by more than half compared to placebo or no anticonvulsant (six trials, 11 444 women; RR 0.41, 95% CI 0.29–0.58).³⁷ There is also a trend toward a reduction in maternal mortality when used for pre-eclampsia, although this does not

reach statistical significance (RR 0.54, 95% CI 0.26–1.10). About a quarter of women will have side effects, primarily flushing. While unpleasant, these side effects are rarely serious and cease when treatment is stopped. There is reasonable reassurance that magnesium sulfate is safe for the baby.^{37, 39} Do not use volume expansion in women with severe pre-eclampsia unless hydralazine is the antenatal antihypertensive. In women with severe pre-eclampsia, limit maintenance fluids to 80 ml/hour unless there are other ongoing fluid losses (for example, haemorrhage).⁹

When women have severe disease, issues of peripartum management of thrombocytopenia and HELLP syndrome arise.^{41,42} although routine prophylactic platelet transfusions are not recommended, ordering blood products, including platelets, should be considered when platelet counts are less than 50×10⁹ platelets per L, falling rapidly, or when coagulopathy is present. Platelet transfusion is always indicated before, during, or after either caesarean section or vaginal delivery when platelet counts are fewer than 20×10⁹/L or in case of significant bleeding (eg, ecchymosis, bleeding from gums or wound).⁴² Pre anaesthetic assessment of a woman with pre-eclampsia is essential, including an airway examination and assessment of coagulation status (such as platelet count). There is no role for tests of platelet function.^{9,40,43} Use of regional analgesia or anaesthesia, or both, is not contraindicated in women when platelet counts are higher than 75×10⁹/L in the absence of a coagulopathy, falling platelet count, or concomitant use of either an antiplatelet agent (e.g. aspirin) or anticoagulant (e.g. heparin).

Regional anaesthesia (epidural, spinal, or combined spinal-epidural) is appropriate for women taking low-dose aspirin (without either coagulopathy or platelets <75×10⁹/L), and those given low-molecular-weight heparin at least 12 h after a prophylactic dose or 24 h after a therapeutic dose.⁴⁴ Early insertion of a spinal or epidural catheter for obstetric or anaesthetic indications should be considered (in the absence of contraindications) to reduce the need for general anaesthesia in case of caesarean section. A difficult airway due to pharyngo laryngeal oedema should always be anticipated. Intubation could increase risk of severe hypertension (and subsequent cerebral events) and aspiration. Measures should be taken to avoid a speed that compromises maternal safety, even in the presence of acute fetal compromise. Central venous access or pulmonary artery catheterization should only be used for specific disorders (ie, pulmonary oedema and cardiac disease) in a high dependency setting. Ergot alkaloids should be omitted for active management of the third stage of labour if the mother is hypertensive.⁴⁵

Advice And Follow-Up Care:

Tell women who had pre-eclampsia that their risk of developing gestational hypertension in a future pregnancy ranges from about 1 in 8 (13%) pregnancies to about 1 in 2 (53%) pregnancies. Their risk of developing pre-eclampsia in a future pregnancy is up to

about 1 in 6 (16%) pregnancies while their risk of developing pre-eclampsia in a future pregnancy is about 1 in 4 (25%) pregnancies if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and about 1 in 2 (55%) pregnancies if it led to birth before 28 weeks.⁹

Table 1: Laboratory Evaluation And Its Rationale For Women In Whom Hypertension Develops After Midpregnancy⁴⁵

Test	Rationale
Hemoglobin and hematocrit	Hemoconcentration supports diagnosis of preeclampsia and is an indicator of severity. Values may be decreased, however, if hemolysis accompanies the disease
Platelet count	Platelet count Thrombocytopenia suggests severe preeclampsia
Quantification of protein excretion	Pregnancy hypertension with proteinuria should be considered preeclampsia (pure or superimposed) until it is proved otherwise
Serum creatinine level Serum creatinine level	Abnormal or rising serum creatinine levels, especially in association with oliguria, suggest severe preeclampsia.
Serum uric acid level	Increased serum uric acid levels suggest the diagnosis of preeclampsia.
Serum transaminase levels	Rising serum transaminase values suggest severe preeclampsia with hepatic involvement.
Serum albumin, lactic acid dehydrogenase	For women with severe disease, these values indicate the extent of endothelial leakage
blood smear, and coagulation profile	(hypoalbuminemia), presence of hemolysis (lactic acid dehydrogenase level increase, schizocytosis, and spherocytosis), and possible coagulopathy, including thrombocytopenia

Table 2: Management Of Pregnancy With Pre-Eclampsia⁹

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or Higher)
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol as first-line treatment to keep: diastolic blood pressure between 80-100 mmHg systolic blood pressure less than 150 mmHg	With oral labetalol as first-line treatment to keep: diastolic blood pressure between 80-100 mmHg systolic blood pressure less than 150 mmHg
Measure blood pressure	At least four times a day	At least four times a day	More than four times a day, depending on clinical circumstances
Test for proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria
Blood tests	Monitor using the following tests twice a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin

Haematological And Biochemical Monitoring:

In women who have pre-eclampsia with mild or moderate hypertension measure platelet count, transaminases and serum creatinine 48-72 hours after birth. Do not repeat platelet count, transaminases or serum creatinine measurements if results are normal at 48-72 hours.

If biochemical and haematological indices are improving but stay within the abnormal range in women with pre-eclampsia who have given birth, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated and at the postnatal review (6-8 weeks after the birth).

If biochemical and haematological indices are not improving relative to pregnancy ranges in women with pre-eclampsia who have given birth, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated.

In women with pre-eclampsia who have given birth, carry out a urinary reagent-strip test at the postnatal review

(6–8 weeks after the birth). Offer women who had pre-eclampsia and still have proteinuria (1+ or more) at the postnatal review (6–8 weeks after the birth) a further review at 3 months after the birth to assess kidney function and consider offering them a referral for specialist kidney assessment.⁹

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